Evidence Report/Technology Assessment
Number 77

Management of Treatment-Resistant Epilepsy

Volume 2. Evidence Tables

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
www.ahrq.gov

Contract No. 290-97-0020

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AHRQ Publication No. 03-0028
May 2003

Suggested Citation:
Chapell R, Reston J, Snyder D. Management of Treatment-Resistant Epilepsy. Evidence Report/Technology Assessment No. 77. (Prepared by the ECRI Evidence-based Practice Center under Contract No 290-97-0020.) AHRQ Publication No. 03-0028. Rockville, MD: Agency for Healthcare Research and Quality. May 2003.

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Contents

Volume 2

Abbreviations Used in the Evidence Tables

AED	Antiepileptic drugs
CI	95% Confidence Interval
NES	Nonepileptic seizures
ES	Epileptic seizures
NA	Not applicable
NR	Not reported
SD	Standard deviation

Question 1

What are the definitions of treatment-resistant epilepsy used in the literature?

Evidence Table 1. Definitions of treatment resistance in clinical studies

Reference	Definition
Question 2: Which methods of rediagnosing or reevaluating treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?	
Ben-Menachem (1999)	All patients refractory to available antiepileptic drugs
Handforth (1998)	Not Reported
Freeman (1998)	Not Reported
Vining (1998)	Not Reported
Salinski (1996) (Followup of Clinical Trial EO3]	Medically intractable seizures defined as a seizure frequency of ≥6 per month
Tiancai (1996)	All cases used phenytoin sodium, carbamazepine and sodium valproate to no avail.
Question 3: Is there evidence that patients with treatment-resistant epilepsy are not optimized at their current level of treatment?	
Sachdeo (2001)	Not reported
Sigler (2001)	Epilepsies which are not controlled by treatment with standard AED.
Garg (2000)	Not reported
Jozwiak (2000)	Not reported
Morrell (2000)	Not reported
El Desoky (1999)	Failure to meet their definition of "controlled cases of epilepsy" (defined as having no history of seizures for >1 year while still maintained on AEDs).
McLean (1999)	Not reported
Bruni (1998)	Not reported
Welty (1998)	Uncontrolled by standard AED therapy.
Hermanns (1996)	Seizure control not obtained despite maximum tolerable doses of at least one of the following drugs: carbamazapine (CBZ), phenytoin (PHT), or either phenobarbital (PB) or primidone (PRM).

Evidence Table 1. Definitions of treatment resistance in clinical studies (continued)

Reference	Definition
Question 4: Which drug treatment strategies lead to improved outcomes for patients with treatment-resistant epilepsy?	
Faught (2001)	Not reported
Sachdeo (2001)	Uncontrolled partial seizures while receiving carbamazepine monotherapy
Ben-Menachem (2000)	Seizures despite treatment with one AED
Betts (2000)	Not reported
Beydoun (2000)	Not reported
Cereghino (2000)	Not reported
Glauser (2000)	Partial seizures (with or without secondary generalization) that were inadequately controlled with one or two concomitant AEDs
Appleton (1999)	Not reported
Biton (1999)	Not reported
Duchowny (1999)	Epilepsy, incompletely controlled by existing therapy
Elterman (1999)	Not reported
KTSG (1999)	Not reported
Sachdeo (1999)	Not reported
Schachter (1999)	Not reported
Gilliam (1998)	Seizures, with or without secondary generalization, not adequately controlled by either carbamazepine or phenytoin monotherapy
Uthman (1998)	Not reported
Bergey (1997)	Not reported
Beydoun (1997b)	Not reported
Beydoun (1997a)	Not reported
Sachdeo (1997b)	Not reported
Ben-Menachem (1996)	Not reported
Chadwick (1996)	Medically uncontrolled generalized seizures despite treatment with one or two standard AEDs
Faught (1996)	Not reported
Privitera (1996)	Not reported
Tassinari (1996)	Not reported
Willmore (1996)	Complex partial seizures incompletely controlled by either phenytoin or carbamazepine

Evidence Table 1. Definitions of treatment resistance in clinical studies (continued)

Reference	Definition
Question 5: Which methods of nondrug treatment for epilepsy after initial treatment failure lead to improved outcomes for patients with treatment-resistant epilepsy?	
Bauer (2001)	Chronic focal epilepsy resistant to treatment with AEDs. Treatment strategy was with AED monotherapy if possible, otherwise, co-medication with two or three AEDs was established. Serum levels of AEDs were available for control of efficacy of treatment. These patients were not being considered for surgery and were selected because they had continuously documented their seizures in seizure charts.
Hennessy (2001)	Not reported
Hennessy (2001)	Not reported
Kanemoto (2001)	Not reported
Kohler (2001)	Not reported
Kwan (2001)	Not reported
Maehara (2001)	Not reported
Miranda (2001)	Not reported
Nees (2001)	Not reported
Orbach (2001)	Not reported
Schramm (2001)	A minimum one-year history of drug-resistant epilepsy and adequate trials of at least two first-line AEDs.
Wilson (2001)	Not reported
Anhoury (2000)	Not reported
Fandino-Franky (2000)	Not reported
Foldvary (2000)	Not reported
Markand (2000)	Medically refractory, all patients met the selection criteria of the presurgical evaluation set forth by the Indiana University Epilepsy Surgery Program Previous pharmacological management must have been adequate in view of the latest standards over a period of several years before medical treatment can be considered a failure. After being maintained on optimum anticonvulsant medication that does not produce unacceptable side effects, the residual seizures must be sufficiently significant to seriously disrupt normal life.
Mosewich (2000)	Not reported
Rao (2000)	Patients with 2 or more disabling complex partial seizures per month for 2 years or more and who received at least 2 trials with monotherapy and one trial with polytherapy were considered for presurgical evaluation
Westerveld (2000)	Not reported
Assaf (1999)	Not reported
Chassoux (1999)	Not reported
Eriksson (1999)	Not reported

Evidence Table 1. Definitions of treatment resistance in clinical studies (continued)

Reference	Definition
Question 5 (continued)	
Salanova (1999)	Medically refractory, all patients had frequent disabling seizures several times a month for years, despite treatment with several AEDs
Son (1999)	Not reported
Maher (1998)	Seizures refractory to at least 3 AEDs for at least 3 years
Radhakrishnan (1998)	Not reported
Ring (1998)	Not reported
Smith (1998)	Not reported
Wyllie (1998)	All of the patients had daily or weekly seizures despite multiple trials of AEDs
Ho (1997)	Not reported
McLachlan (1997)	Each patient had uncontrolled seizures for at least 3 years despite the use of three or more AEDs
Reeves (1997)	Not reported
Silander (1997)	Not reported
Smith (1997)	Not reported
Vining (1997)	Not reported
Hermanns (1996)	Resistance to an AED exists when it does not control seizures at the maximal individually tolerated dose. Prerequisite for focal epilepsy surgery is the resistance of disabling seizures to 3 major AEDs (carbamazepine, phenytoin, and either phenobarbital or primidone).
Peacock (1996)	Not reported
Rose (1996)	Not reported
Sirven (1996)	Not reported
Question 6: Which social, psychological or psychiatric services for treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?	
Sidorenko (2000)	Attacks persevered despite comprehensive drug treatments

Evidence Table 2. Definitions of treatment resistance in clinical guidelines

Reference	Definition
Tanenbaum (2000)	Not defined
French (1999)	Inadequately controlled seizures or significant side effects for whom no options had been available
Quality Standards Subcommittee of the American Academy of Neurology (1998)	Not defined

Evidence Table 3. Definitions of treatment resistance in review articles

Reference	Definition
Aldenkamp (2001)	Not defined
Benbadis (2001)	Medical intractability is a relative concept rather than an absolute one. The number of antiepileptic drugs that should be tried before a patient is deemed medically intractable is a matter of judgment. In practice, a usual medical trial may include two to four major drugs, with some used as monotherapy and at maximal tolerated dosages.
Blume (2001)	Not defined
Castillo (2001)	There is no universally accepted definition of drug-resistant, but for the purpose of this review, seizures will be considered drug-resistant if they have failed to respond to a minimum of two AEDs as monotherapy.
DeToledo (2001)	Not defined
Dlugos (2001)	Many adult epilepsy centers define medical intractability as persistent seizures despite 2 years and 2 maximally tolerated AED trials. Medical intractability is more challenging to define in children because of the tendency of many forms of pediatric epilepsy to remit with time.
Genton (2001)	Not defined
Kennedy (2001)	Not defined
Nordi (2001)	Failure to respond to three well-chosen antiepileptic medications, used alone or in combination.
Olsen (2001)	Medical intractability is established by assuring that antiepileptic medications appropriate for the child's particular epilepsy syndrome have been used and have been titrated to maximum tolerance before being deemed ineffective...There are no absolute criteria for determining when a patient has tried sufficient antiepileptic medications... There is no precisely determined time epilepsy must be present for seizures to be considered intractable.
Perucca (2001)	Not defined
Perucca (2001)	Not defined
Wisniewski (2001)	Not defined
Aarli (2000)	Not defined
Aiken (2000)	Not defined
Culy (2000)	Not defined
Davis (2000)	Not defined
Dooley (2000)	Seizures are considered refractory when they limit the patient's ability to live fully because of their frequency or severity or if they necessitate the use of medication which is effective but produces adverse effects.
Duchowny (2000)	Not defined
Glauser (2000)	Not defined
Juhasz (2000)	Not defined
Keene (2000)	Not defined
Leppik (2000)	Seizures only partially controlled at maximum tolerated doses.

Evidence Table 3. Definitions of treatment resistance in review articles (continued)

Reference	Definition
Levisohn (2000)	Not defined
McLachlan (2000)	Not defined
Nordli (2000)	Intractability should not be considered until there is a failure of three first-line antiepileptic medications.
Palmini (2000)	Not defined
Provini (2000)	Not defined
Scharfman (2000)	Not defined
Schmidt (2000)	Not satisfactorily controlled with other antiepileptic drugs
Sisodiya (2000)	Not defined
Stafstrom (2000)	Not defined
Uthman (2000)	Continue to have seizures or their seizures are controlled at the expense of intolerable side effects
Yamamoto (2000)	Not defined
Annegers (1999)	Not defined
Beydoun (1999)	Not defined
Blumcke (1999)	Not defined
Chugani (1999)	Not defined
DeFelipe (1999)	Not defined
DeToledo (1999)	Seizures are so frequent or severe that they limit the patients ability to live fully according to his or her wishes or necessitate the use of medications that, although effective, produce adverse effects.
Devinsky (1999)	Do not become completely free of seizure
Haafiz (1999)	Not defined
Lewis (1999)	Not defined
Loiseau (1999)	Not defined
Mohan (1999)	Not defined
Moran (1999)	Not defined
Regis (1999)	Not defined
Rey (1999)	Not defined
Rho (1999)	Not defined
Snodgrass (1999)	Not defined
Tamer (1999)	
Vinters (1999)	Not defined
Baxendale (1998)	Not defined

Evidence Table 3. Definitions of treatment resistance in review articles (continued)

Reference	Definition
Bazil (1998)	A definition is implied by the diagnostic and treatment guidelines: "Each drug should be pushed to the highest tolerated dose regardless of serum concentrations. Should seizures persist at this dose, or if seizure control is achieved only with unacceptable adverse effects, a second drug should be substituted as monotherapy. Should this fail, then another drug should be added that compliments the first in terms of mechanism of action and side effect profile...patients who fail two first-line anticonvulsants at maximum tolerated doses should be considered for video-EEG monitoring to rule out nonepileptic events..."
Brown (1998)	Not defined
Bruni (1998)	Not defined
Corradetti (1998)	Not defined
Emilien (1998)	Not defined
Friis (1998)	Not defined
Lalviainen (1998)	Not defined
Lesser (1998)	Not defined
Novotny (1998)	Not defined
Ozuna (1998)	Not defined
Pellock (1998)	Not defined
Sachdev (1998)	Not defined
Tallian (1998)	Unresponsive to or experience adverse effects from medications
White (1998)	Uncontrolled seizure disorders and/or experiencing significant side effects
Yagi (1998)	Not defined
Acharya (1997)	Not defined
Benbadis (1997)	Not defined
Berg (1997)	Not defined
Blume (1997)	Not defined
Chadwick (1997)	Not defined
Duncan (1997)	Not defined
Eller (1997)	Not defined
Ho (1997)	Not defined
Jallon (1997)	Persistence of true epileptic seizures with a sufficient frequency or severity in a compliant patient despite optimal therapy for a minimum of 2 years
Kaufman (1997)	Not defined
Langtry (1997)	Not defined
Meador (1977)	Not defined
Mikati (1997)	Not defined

Evidence Table 3. Definitions of treatment resistance in review articles (continued)

Reference	Definition
Ojemann (1997)	Not defined
Pellock (1997)	Not defined
Walker (1997)	Not defined
Zupane (1997)	Not defined
Duse (1996)	Not controlled after an adequate trial of first-line conventional anti-epileptic treatment
Henry (1996)	Not defined
Holmes (1996)	Seizures that either do not respond to conventional antiepileptic drugs (AEDs) or have significant adverse reactions to AEDs.
Leppik (1996)	Seizures are not controlled after usually effective levels have been attained and adverse effects are developing.
Nashef (1996)	Not defined
Neufeld (1996)	Not defined
Peacock (1996)	Patients evaluated for surgery had frequent medically intractable seizures that significantly interfered with their psychological and/or neurological development. Patients with infantile spasms had failed to respond to trials of ACTH and several antiepileptic drugs, including carbamazepine, phenytoin, Phenobarbital and valproate. As a general principle, children who were having many seizures each day required only a few months of medical therapy to determine medical intractability.
Perucca (1996)	Not defined
Reiss (1996)	Not defined
Roberts (1996)	Not defined
Trimble (1996)	Not defined
Villemure (1996)	Seizure intractability is defined as an epileptic disorder present for more than 2 years and unsuccessfully controlled with at least three anticonvulsants medications at therapeutic levels.
Wyllie (1996)	Not defined

Evidence Table 4. Inclusion/exclusion criteria implying a definition of treatment resistance

Reference	Minimum Number of AEDs Tried	Side Effects or Maximum Tolerated Dose Considered	Minimum Baseline Monthly Seizure Frequency	Minimum Duration of Symptoms	Study Purpose	Special Groups
Faught (2001)	1	No	4	Not Reported	FDA Approval	None
Sachdeo (2001)	1	No	2	Not Reported	FDA Approval	None
Beydoun (2000)	1	No	2	Not Reported	FDA Approval	None
Cereghino (2000)	2	No	4	2 years	FDA Approval	None
Glauser (2000)	1	No	4	Not Reported	FDA Approval	Pediatric
Biton (1999)	1	No	1.5	Not Reported	FDA Approval	None
Duchowny (1999)	1	No	4	Not Reported	FDA Approval	Pediatric
Elterman (1999)	1	No	3	Not Reported	FDA Approval	Pediatric
Sachdeo (1999)	1	No	60	Not Reported	FDA Approval	Lennox-Gastaut syndrome
Schachter (1999)	1	No	30	Not Reported	FDA Approval	None
Gilliam (1998)	1	No	4	Not Reported	FDA Approval	None
Uthman (1998)	1	No	2.67	Not Reported	FDA Approval	None
Bergey (1997)	1	No	3	Not Reported	FDA Approval	None
Beydoun (1997b)	1	No	2	Not Reported	FDA Approval	None
Beydoun (1997a)	1	No	2	Not Reported	FDA Approval	None
Sachdeo (1997b)	1	No	3	Not Reported	FDA Approval	None
Faught (1996)	1	Yes	4	Not Reported	FDA Approval	None
Privitera (1996)	1	No	4	Not Reported	FDA Approval	None

Evidence Table 4. Inclusion/exclusion criteria implying a definition of treatment resistance (continued)

Reference	Minimum Number of AEDs Tried	Side Effects or Maximum Tolerated Dose Considered	Minimum Baseline Monthly Seizure Frequency	Minimum Duration of Symptoms	Study Purpose	Special Groups
Willmore (1996)	1	No	4	Not Reported	FDA Approval	None
Sachdeo (2001)	1	No	2	Not Reported	Drug study	None
Sigler (2001)	NR	Yes	NR	1 year	Drug study	Pediatric (some had Lennox-Gastaut syndrome or West syndrome)
Ben-Menachem (2000)	1	No	2	1 year	Drug Study	None
Betts (2000)	1	No	0.67	Not Reported	Drug Study	None
Garg (2000)	NR	Yes	NR	Not Reported	Drug study	None
Jozwiak (2000)	1	No	1	Not Reported	Drug study	None
Morrell (2000)	1	Yes (for some but not all patients)	2	Not Reported	Drug study	None
Appleton (1999)	1	No	2.67	Not Reported	Drug Study	Pediatric
El Desoky (1999)	1	No	0.083	Not Reported	Drug study	None
KTSG (1999)	1	Yes	2	Not Reported	Drug Study	None
McLean (1999)	1	Yes (for some but not all patients)	2	Not Reported	Drug study	None
Bruni (1998)	1	No	1	1 year	Drug study	None
Welty (1998)	Not Reported	No	Not Reported	Not Reported	Drug Study	None
Ben-Menachem (1996)	1	No	4	Not Reported	Drug Study	None
Chadwick (1996)	1	No	4	Not Reported	Drug Study	None
Hermanns (1996)	1	Yes	2	6 months	Drug study	None

Evidence Table 4. Inclusion/exclusion criteria implying a definition of treatment resistance (continued)

Reference	Minimum Number of AEDs Tried	Side Effects or Maximum Tolerated Dose Considered	Minimum Baseline Monthly Seizure Frequency	Minimum Duration of Symptoms	Study Purpose	Special Groups
Tassinari (1996)	1	No	4	Not Reported	Drug Study	None
Bauer (2001)	3	No	Not Reported	Not Reported	Surgery - control patients	None
Hermanns (1996)	3	Yes	Not Reported	Not Reported	Surgery - control patients	None
Hennessy (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	Mesial temporal sclerosis
Hennessy (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	Non-MTS focal lesions
Kanemoto (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None
Kohler (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None
Miranda (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None
Nees (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None
Schramm (2001)	2	No	Not Reported	1	Surgery - Temporal lobe	None
Wilson (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None
Anhoury (2000)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None
Foldvary (2000)	Not Reported	No	Not Reported	Not Reported	Surgery - Temporal lobe	None

Evidence Table 4. Inclusion/exclusion criteria implying a definition of treatment resistance (continued)

Reference	Minimum Number of AEDs Tried	Side Effects or Maximum Tolerated Dose Considered	Minimum Baseline Monthly Seizure Frequency	Minimum Duration of Symptoms	Study Purpose	Special Groups
Markand (2000)	Not Reported	Yes	Not Reported	"Several Years"	Surgery -Temporal lobe	None
Rao (2000)	2	No	2	2	Surgery -Temporal lobe	None
Westerveld (2000)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	Pediatric
Assaf (1999)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Eriksson (1999)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Salanova (1999)	"Several"	No	"Several per month"	"Years"	Surgery -Temporal lobe	None
Son (1999)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	Mesial temporal sclerosis
Maher (1998)	3	No	Not Reported	3	Surgery -Temporal lobe	None
Radhakrishnan (1998)	Not Reported	No	Not Reported	Not reported	Surgery -Temporal lobe	None
Ring (1998)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Wyllie (1998)	Multiple	No	"Daily or weekly"	Not Reported	Surgery -Temporal lobe	None
Ho (1997)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
McLachlan (1997)	3	No	Not Reported	3	Surgery -Temporal lobe	None
Reeves (1997)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Silander (1997)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Rose (1996)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Sirven (1996)	Not Reported	No	Not Reported	Not Reported	Surgery -Temporal lobe	None
Peacock (1996)	Not Reported	No	Not Reported	Not Reported	Surgery - Hemispherectomy	None

Evidence Table 4. Inclusion/exclusion criteria implying a definition of treatment resistance (continued)

Reference	Minimum Number of AEDs Tried	Side Effects or Maximum Tolerated Dose Considered	Minimum Baseline Monthly Seizure Frequency	Minimum Duration of Symptoms	Study Purpose	Special Groups
Mosewich (2000)	Not Reported	No	Not Reported	Not Reported	Surgery -Frontal lobe resection	None
Chassoux (1999)	Not Reported	No	Not Reported	Not Reported	Surgery -Frontal lobe resection	None
Smith (1997)	Not Reported	No	Not Reported	Not Reported	Surgery -Frontal lobe resection	None
Vining (1997)	Not Reported	No	Not Reported	Not Reported	Surgery - Hemispherectomy	None
Orbach (2001)	Not Reported	No	Not Reported	Not Reported	Surgery -Multiple subpial transection	None
Smith (1998)	Not Reported	No	Not Reported	Not reported	Surgery -Multiple subpial transection	None
Fandino-Franky (2000)	Not Reported	No	Not Reported	Not Reported	Surgery - Callosotomy	None
Kwan (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Callosotomy	Lennox-Gastaut
Maehara (2001)	Not Reported	No	Not Reported	Not Reported	Surgery - Callosotomy	None
Sidorenko (2000)	2	No	Not Reported	Not Reported	Nondrug	None
Ben-Menachem (1999)	NR	No	1	Not Reported	Nondrug	None
Handforth (1998)	Not Reported	No	6	2 years	Nondrug	None
Freeman (1998)	Not Reported	No	8	Not Reported	Nondrug	Pediatric
Vining (1998)	Not Reported	No	32	Not Reported	Nondrug	Pediatric
Salinski (1996)	Not Reported	No	6	Not Reported	Nondrug	None
Tiancai (1996)	3	No	NR	2 Months	Nondrug	None

Evidence Table 5. Implied definitions from inclusion/exclusion criteria

Type of Study	Number of Studies	Number Requiring a Minimum Number of AEDs	Number Mentioning Side Effects of MTD	Number Requiring a Minimum Baseline Seizure Frequency	Number Requiring a Minimum Duration of Illness
Patients Selected					
Pediatric	8	5 (63%)	1 (13%)	6 (75%)	1 (13%)
Lennox-Gastaut Syndrome	2	1 (50%)	0	1 (50%)	0
Mesial temporal sclerosis	2	0	0	0	0
Nonmesial temporal sclerosis lesions	1	0	0	0	0
No Special Group	69	38 (55%)	8 (12%)	33 (48%)	12 (17%)
Purpose of Study					
FDA drug study	19	19 (100%)	1 (5%)	19 (100%)	1 (5%)
Non-FDA drug study	17	14 (82%)	6 (35%)	14 (82%)	4 (24%)
Nondrug treatment	7	3 (43%)	0	5 (71%)	2 (29%)
Surgery- Control patients	2	2 (100%)	1 (50%)	0	0
Surgery- Temporal lobe	27	6 (22%)	1 (4%)	2 (7%)	6 (22%)
Surgery- Hemispherectomy	2	0	0	0	0
Surgery- Frontal lobe resection	3	0	0	0	0
Surgery- Multiple subpial transection	2	0	0	0	0
Surgery- Callostomy	3	0	0	0	0
Totals					
All surgery studies	39	8 (21%)	2 (5%)	2 (5%)	6 (15%)
All studies	82	44 (54%)	9 (11%)	40 (49%)	13 (16%)

MTD Maximum tolerated dose

Question 2

Which methods of rediagnosing or reevaluating treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?

Evidence Table 6. Evidence base and important study design characteristics for Question 2A

Reference	Country	Site of Study	Total Study Size	Multicenter	Study Design	Examined Consecutive Patients
Zaidi (2000)	United Kingdom	Specialist epilepsy unit	74	Yes	Case series	Yes
Holmes (1998)	United States	Specialist neuro-electrophysiology unit	379	No	Case series	Yes
Henry (1997)	United States	Specialist neurosurgery unit	145	No	Case series	Yes
Arnold (1996)	United States	Specialist video/EEG monitoring unit	45	No	Case series	Yes
Slater (1995)	United States	Specialist video/EEG monitoring unit	101	No	Case series	Yes

Evidence Table 6. Evidence base and important study design characteristics for Question 2A (continued)

Reference	Reason For Referral (N)	Source of Referrals	Method of Original-Diagnosis	Diagnostic Reevaluation Battery	Patients Followed Up	Mean Followup Time (SD)	Who Was Followed Up
Zaidi (2000)	Refractory epilepsy (36) Diagnostic uncertainty (38)	NR	NR	Tilt Table Carotid sinus massage Continuous ECG monitoring Continuous EEG monitoring Continuous BP monitoring	Yes	10.3 (6.7) months	Only patients with NES
Holmes (1998)	Refractory epilepsy (379)	NR	NR	Clinical reevaluation vEEG	No	NA	NA
Henry (1997)	Refractory epilepsy (141)	Treating neurologist	NR	Clinical reevaluation MRI (all patients) rEEG vEEG	Yes	2.5 (0.9) years	Only patients with NES
Arnold (1996)	Refractory epilepsy (45)	NR	NR	Clinical reevaluation vEEG	Yes	NR	Only patients with confirmed epilepsy
Slater (1995)	Refractory epilepsy (101)	NR	NR	Clinical reevaluation vEEG (minimum 24 hours)	No	NA	NA

BP Blood Pressure
ECG Electrocardiogram
EEG Electroencephalogram
MRI Magnetic resonance imaging
NA Not applicable
NES Nonepileptic seizure
rEEG Routine EEG
vEEG Video EEG

Evidence Table 7. Study characteristics: Inclusion/exclusion criteria

Reference	Inclusion Criteria	Exclusion Criteria
Zaidi (2000)	Patients with clinical diagnosis of epilepsy	Patients with suspected psychogenic seizures
Holmes (1998)	Patients with intractable epilepsy Age ≥16 years	NR
Henry (1997)	Medically refractory seizures >2 years Candidates for temporal lobectomy and were referred for pre-surgical evaluation Absence of moderate or severe encephalopathy on neurologic exam EEG studies consistent with focal epilepsy Absence of generalized or extratemporal epiletiform EEG abnormality Recorded seizures considered consistent with ES	NR
Arnold (1996)	Patients with seizures refractory to AED's Age >18 years Informed consent	NR
Slater (1995)	Patients with seizures believed to be epilepsy refractory to AEDs	Refused induction procedure Mental retardation (IQ <70) Undergoing repeat hospitalization Had know psychiatric illness Incomplete medical records

NA Not applicable

Evidence Table 8. Patient characteristics for Question 2A

Reference	Total Number of Patients (N)	Number of Patients Suspected of Nonepileptic Seizures at Enrollment (%)	Mean Age (SD): Years	Age Range: Years	Mean Duration of Disease (SD): Years	Duration Range: Years
Zaidi (2000)	74	38 (51.4)	38.9 (18)	16 to 77	NR	NR
Holmes (1998)	379	0	24.2 (10.9)	≥16	NR	NR
Henry (1997)	145	0	NR	NR	20 (NR)	NR
Arnold (1996)	41	0	NR	≥18	NR	NR
Slater (1995)	101	0	NR	≥18	NR	NR

Patient characteristics for Question 2A (continued)

Reference	Percent Male	Seizure Frequency	Reported Seizure Types at Enrollment (N)	Percentage of Patients With Cognitive Deficits	Percentage of Patients With Developmental Delay	Number of AED's at Entry (Number of Patients)
Zaidi (2000)	NR	NR	NR	NR	NR	1 AED (21) 2 AED's (8) >3 AED's (7) (See footnote [b])
Holmes (1998)	40.0	NR	NR	NR	NR	NR
Henry (1997)	NR	NR	Partial seizures (145)[a]	NR	NR	NR
Arnold (1996)	NR	NR	NR	NR	NR	NR
Slater (1995)	NR	NR	NR	0.0	0.0	NR

[a] All patients were considered to have temporal lobe epilepsy. No details of the type of partial seizures was reported
[b] Only 36 of the 74 patients were taking AED's at time of investigation. These patients are the patients of interest in this section of the report.

Evidence Table 9. Rediagnosis data

Reference	Patients With Refractory Seizures	For Whom a Firm Diagnosis Could Be Made	Diagnostic Yield (%)	Patients With NES (%)	Patients With NES Only (%)	Patients With NES Plus ES (%)
Zaidi (2000)	36[b]	36	100.0	13 (36.1)	13 (36.1)	0 (0.0)
Holmes (1998)	379	338	89.2	114 (33.7)	111 (32.8)	3 (0.9)
Henry (1997)	145	145	100.0	12 (8.3)	0 (0.0)	12 (8.3)
Arnold (1996)	45	41	91.0	14 (34.1)	14 (34.1)	0 (0.0)
Slater (1995)	101	101	100.0	38 (37.6)	37 (36.7)	1 (1.0)

Rediagnosis data (continued)

Reference	Post Rediagnosis Treatment Strategies	Were Patients Followed Up?	Mean Followup Time (SD)	Patients Followed Up	Reported Outcomes
Zaidi (2000)	11/13 patients with NES stopped AED's and were treated for underlying cause of syncope. New treatments not reported	Yes	10.3 (6.7) months	13 All NES	11/13 patients seizure free
Holmes (1998)	Not reported	No	Not applicable	Not applicable	Not applicable
Henry (1997)	Psychotherapy (n = 5) Refused psychotherapy (n = 6) Lost-to-followup (n = 1)	Yes	2.48 (0.86) years	11/12 All NES	Frequency of NES: Ceased: 3/12 patients Reduced >75%: 1/12 patients No change: 6/12 Unknown 1/12[a] Lost-to-followup: 1/12
Arnold (1996)	ES Group: Resection of epileptic focus (n = 20) Medical treatment only (n = 7) NES Group: Not reported	Yes	Not reported	27	Not reported
Slater (1995)	Not reported	No	Not applicable	Not applicable	Not applicable

[a] Patient and observers were unable to distinguish true epileptic seizures from nonepileptic seizures
[b] Consists of only those patients still on antiepileptic drugs on entry to study who were not suspected of misdiagnosis (see text)

Evidence Table 10. Meta-analysis of non-epileptic seizure prevalence data

Reference	N	Effect Size (Cohen's h and CI)	P-Value	Standard Residual	Outlier by Standard Residual?	Q[a] if Study Removed	P (Q) =	Greatest Outlier By Q?
Zaidi (2000)	36	1.29 (0.83 to 1.75)	0.000000	0.13	No	0.259181	0.967513	No
Holmes (1998)	338	1.24 (1.09 t0 1.39)	0.000000	-0.45	No	0.078236	0.994315	No
Arnold (1996)	41	1.25 (0.82 to 1.68)	0.000000	-0.05	No	0.273632	0.964909	No
Slater (1995)	101	1.32 (1.04 to 1.60)	0.000000	0.49	No	0.040969	0.997821	No
Fixed Effects					Summary Effect Size (CI)		1.26 (1.14 to 1.38)	
					Transformed ES (CI)		35% (29% to 41%).	
					Q[b] =		0.28	
					p =		0.964393	
Random Effects					Summary Effect Size (CI)		1.26 (1.14 to 1.38)	
					Transformed ES (CI)		35% (29% to 41%).	

[a] Critical Q_e (p = 0.1, 2 degrees of freedom) = 4.605
[b] Critical Q_e (p = 0.1, 3 degrees of freedom)= 6.250

Evidence Table 11. Number of studies addressing each diagnostic

Reference	Country	Routine EEG	Ambulaotry EEG	Video EEG	CT	MRI	Prolactin	Creatinine kinase	Tilt table	Tongue biting	Hypnotic recall	Provocation	MMPI	SPECT	Auditory Evoked Potentials
Jedrzejczak (2001)	Poland												✓		
Shah (2001)	United States						✓								
Barry (2000)	United States											✓			
Foley (2000)	United States		✓												
Srikumar (2000)	India			✓											
Storzbach (2000)	United States	✓											✓		
Zaidi (2000)	United Kingdom								✓						
Drury (1999)	United States			✓											
Kuyk (1999)	Holland										✓				
Lusic (1999)	Croatia						✓								
Shihabuddin (1999)	United States		✓	✓											
Alving (1998)	Denmark						✓								
Ettinger (1998)	United States													✓	
Holmes (1998)	United States												✓		
Neufeld (1997)	Israel							✓							
Derry (1996)	Canada												✓		
Devinski (1996)	United States	✓	✓												
Benbadis (1995)	United States									✓					

Evidence Table 11. Number of studies addressing each diagnostic (continued)

Reference	Country	Routine EEG	Ambulaotry EEG	Video EEG	CT	MRI	Prolactin	Creatinine kinase	Tilt table	Tongue biting	Hypnotic recall	Provocation	MMPI	SPECT	Auditory Evoked Potentials
Slater (1995)	United States											✓			
Boon (1994)	Belgium			✓											
Lancman (1994)	United States											✓			
Walczak (1994)	United States											✓			
Anzola (1993)	Italy						✓								
Chayasirisobhon (1993)	United States			✓											
Drake (1993)	United States														✓
Nousiainen (1992)	Finland	✓	✓	✓											
Saygi (1992)	United States					✓									
Brown (1991)	United States												✓		
Grubb (1991)	United States								✓						
Zelnick (1991)	Israel						✓								
Mishra (1990)	India						✓								
Libman (1989)	Canada							✓							

Evidence Table 11. Number of studies addressing each diagnostic (continued)

Reference	Country	Routine EEG	Ambulaotry EEG	Video EEG	CT	MRI	Prolactin	Creatinine kinase	Tilt table	Tongue biting	Hypnotic recall	Provocation	MMPI	SPECT	Auditory Evoked Potentials
Wroe (1989)	United Kingdom						✓								
Vandervant (1986)	United States												✓		
Laxter (1985)	United States						✓								
Goodin (1984)	United States	✓													
Sivenius (1984)	Finland		✓												
Chesson (1983)	United States							✓							
Size of Evidence Base For Each Modality		**4**	**5**	**6**	**0**	**1**	**8**	**3**	**2**	**1**	**1**	**4**	**6**	**1**	**1**

✓ Study assessed the ability of this diagnostic technology to differentiate between epileptic and nonepilpetic seizures

[a] This article was published prior to 1985. Included because evidence base for diagnostic modality of interest was <5 when only articles published during or after 1985 were considered (See inclusion criteria in Volume 1)

EEG Electroencephalogram
CT Computed tomography
MRI Magnetic resonance imaging
MMPI Minnesota Multiphasic Personality Inventory
SPECT Single photon emission computed tomography

Evidence Table 12. Articles addressing blood prolactin level measurement excluded for quality reasons

Reference	Country	Reason(s) for Exclusion
Shah (2001)	United States	Independence of data violation. Mean blood prolactin levels calculated from same patients multiple times if they had multiple seizures (340 events from 89 patients). Data does not allow one to determine which patients are represented multiple times.
Alving (1998)	Denmark	Independence of data violation. All values (means, dispersions, sensitivity, specificity, positive predictive value, negative predictive value) were based on number of seizure events and not on number of patients. Data does not allow one to determine which patients are represented multiple times.
Laxer (1985)	United States	Independence of data violation. Mean blood prolactin levels calculated from blood prolactin levels taken from same pt multiple times if they had multiple seizures (85 seizures from 70 patients). Data does not allow one to determine which patients are represented multiple times. Inconsistencies in data presentation. Diagnostic performance data incorrectly presented. Authors report on data from 79 patients (37 men: 42 women) yet according to methods only 70 patients were recruited into study.

Evidence Table 13. Quality of reporting: articles describing studies of blood prolactin level measurement

Reference	Country	Refering Source of Included Patients Identified	Sampling Methodology Described	All Patients Subjected to Reference Standard	Clinical Setting in Which Diagnostic Test Evaluated Clearly Described	Inclusion/Exclusion Criteria Stated	Demographic Data For Patients Presented
Lusic (1999)	Croatia	No	No	No	Yes	Yes	No
Anzola (1993)	Italy	No	Yes	Yes	Yes	Yes	No
Zelnick (1991)	Israel	No	No	Yes	Yes	No	No
Mishra (1990)	India	No	No	Yes	Yes	No	No
Wroe (1989)	United Kingdom	No	No	Yes	Yes	No	No

Quality of reporting: articles describing studies of blood prolactin level measurement (continued)

Reference	Information on Comorbidities Presented	Information on Method of Data Collection Presented	Analytic Methods Clearly Described	Information on Sample Size Requirements Presented	Outcome Data Clearly Presented	Data Presented in Sufficient Detail For ECRI to Confirm Findings
Lusic (1999)	No	Yes	Yes	No	Yes	Yes
Anzola (1993)	No	Yes	Yes	No	Yes	Yes
Zelnick (1991)	No	Yes	Yes	No	Yes	Yes
Mishra (1990)	No	Yes	Yes	No	Yes	Yes
Wroe (1989)	No	Yes	Yes	No	Yes	Yes

Evidence Table 14. Study design characteristics in studies of blood prolactin level measurement

Reference	Setting	Study Design	Total Study Size (N)[a]	Differntial Diagnosis	Consecutive Patients
Lusic (1999)	Hospital Inpatient	Diagnostic case-control	33	CPS (n = 18) from syncopal seizures (n = 15)	Not reported
Anzola (1993)	Hospital Inpatient	Diagnostic case-control	59	GTCS (n = 40) from nonconvulsive syncope (n = 19)	No
Zelnick (1991)	Hospital Inpatient	Diagnostic case-control	27	Mix of epileptic seizure types (n = 17) from syncope (n = 10)	Not reported
Mishra (1990)	Hospital Inpatient	Diagnostic case-control	77	GTCS (n = 15), CPS (n = 11), and SPS (n = 9) from PsyS (n = 20)	Not reported
Wroe (1989)	Hospital-Inpatient	?	33	GTCS (n = 8), CPS (n = 11), and atypical seizures (n = 4) from PsyS (n = 10)	Not reported

Study design characteristics in studies of blood prolactin level measurement (continued)

Reference	Multicenter	Reference Standards	Blinded	Patients Followed Up	Reason Patients Referred
Lusic (1999)	No	ES group: Not reported Syncope group: Not reported	No	No	Patients admitted to emergency department seeking treatment for either syncopal attack or epilpetic seizure
Anzola (1993)	No	ES group: Clinical opinion with EEG support Syncope group: Clinical opinion with EEG support and in addition, cardiac	Yes	No	Patients admitted to neurological clinic due to loss of consciousness or epileptic seizure
Zelnick (1991)	No	ES group: Clinical opinion with EEG support Syncope group: Not reported	No	No	Evaluation of various seizure types
Mishra (1990)	No	ES group: Not reported PsyS group: Not reported	No	No	Not reported
Wroe (1989)	No	ES group: Clinical opinion with video-EEG support PsyS group: Clinical opinion with video-EEG support	No	No	Patients admitted to epilepsy unit for vEEG monitoring and evaluation of severe or intractable epilepsy

[a] This is the total number of patients entered into the study that suffered seizures and this number may not include all patients included in the study, some of whom are not of interest in this section of the report

PsyS Psychogenic seizures
CPS Complex partial seizures
GTCS Generalized tonic-clonic seizures
SPS Simple partial seizures

Evidence Table 15. Definitions of diagnostic groups used in studies of blood prolactin level measurement

Reference	Reference Standard Used	Criteria For Diagnosis of Epileptic Seizure	Criteria For Diagnosis of Psychogenic Seizure	Criteria For Diagnosis of Syncope
Lusic (1999)	ES group: Not reported Syncope group: Not reported	Not reported	Not applicable	Not reported
Anzola (1993)	ES group: Clinical opinion with EEG support Syncope group: Clinical opinion with EEG support and in addition, cardiac function tests	Description of witnessed seizure consistent with ES. Patient must have shown postictal confusion. Pt must have showed interictal or postictal EEG abnormalities. Corollary but non-crucial elements such as: Tongue biting Urinary incontinence Increase in serum kinase level Previous history of epilepsy	Not applicable	Loss of consciousness not accompanied by convulsions Normal EEG Negative for birth injury, cranial injury, brain infection Normal ECG Normal 24 hour ECG holter monitoring Plain chest radiograph
Zelnick (1991)	ES group: Clinical opinion with EEG support Syncope group: Not reported	Observation of seizure by clinical staff Patients with nonfebrile seizures and abnormal EEG with epileptiform features	Not applicable	Loss of tone and consciousness due to vasovagal mechisms (No more details given)
Mishra (1990)	ES group: Not reported PsyS group: Not reported	Not reported	Not reported	Not applicable
Wroe (1989)	ES group: Clinical opinion with video-EEG support PsyS group: Clinical opinion with video-EEG support	Not reported	Not reported	Not applicable

ECG Electrocardiogram
EEG Electroencephalogram
ES Epileptic seizure
GTCS Generalized tonic-clonic seizures
PsyS Psychogenic seizure
EEG Electroencephalogram

Evidence Table 16. Protocols for measurement of blood prolactin levels

Reference	Serum or Plasma	Number of Measurments	Sampling Times	Method of Measurement	Normal/Abnormal Threshold
Lusic (1999)	Serum	3	T1 = Within 60 minutes of seizure T2 = Within 60 minutes after T1 T3 = 24 hours after T1	Comercial radioimmunoassay method (Prolactin-IRMA, manufactured by IBL, Hamburg, Germany)	Normal range for lab <630 mIU/L (26 ng/ml)
Anzola (1993)	Plasma	4	T1 = Within 60 minutes of seizure T2 = 60 minutes after T1 T3 = 1 day after T1 (in morning) T4 = 2 days after T1 (in morning)	Commercial radioimmunoassay method (no more detail given)	>2 SD of mean of T2, T3, and T4 values >3 SD of mean of T2, T3, and T4 values
Zelnick (1991)	Serum	1	T1 = Within 90 minutes of seizure	Commercial radioimmunoassay method (no more detail given)	Normal ref. range for lab >15 ng/ml
Mishra (1990)	Serum	2	T1 = 15 Within 20 minutes of seizure T2 = 6-8 hours following seizure	Commercial radioimmunoassay method (no more detail given)	Mean: 278 (SD: 120.0) µIU/ml
Wroe (1989)	Serum	8	T0 = Baseline T1 = Immediately following seizure T2 = 5 minutes following seizure T3 = 10 minutes following seizure T4 = 20 minutes following seizure T5 = 30 minutes following seizure T6 = 60 minutes following seizure T7 = 90 minutes following seizure	Commercial radioimmunoassay method using rabbit antibody	>1000mU/l

Evidence Table 17. Inclusion / exclusion criteria in studies of blood prolactin level measurement

Reference	Inclusion Criteria	Exclusion Criteria
Lusic (1999)	Epilepsy group: Patients with an established diagnosis of epilepsy who had experienced a complex partial seizure Syncope group: Patients examined immediately after a typical postural vaso-vagal syncope attack	Patients with suspected or proven cardiac aetiology for syncope, or autoimmune failure, were excluded from the study
Anzola (1993)	Patients who fulfilled criteria for either generalized tonic clonic or complex partial seizure due to epilepsy Patients with noncardiac syncope	Not reported
Zelnick (1991)	Not reported	Not reported
Mishra (1990)	Not reported	Not reported
Wroe (1989)	Not reported	Not reported

Evidence Table 18. Patient characteristics in studies of blood prolactin level measurement

Reference	Study Arm	N	Age: Mean (SD)	Age Range	Percent Male	Comorbidities	Mean Prediagnostic Seizure Rate (SD)	Mean Duration of Disease (SD)	AED Usage
Lusic (1999)	ES	18	28.2 (5.8)	NR	0 (0.0)	NR	NR	NR	Carbamazepine (n = 14) Valproic acid (n = 6) Metilphenobarbitone (n = 3) Lamotrigine (n = 1) Vigabatrin (n = 1)
	Syncope	15	32.4 (5.5)	NR	0 (0.0)	NR	NR	NR	Nil
Anzola (1993)	ES	40	43.6 (17)	NR	62.5	NR	NR	NR	NR
	Syncope	19	34.8 (20)	NR	52.6	NR	NR	NR	NR
Zelnick (1991)	ES	17	7.2 (3.8)	1 to 11	76.5	NR	NR	NR	NR
	Syncope	10	6.1 (NR)	NR	NR	NR	NR	NR	NR
Mishra (1990)	GTCS	15	NR	NR	NR	NR	NR	NR	NR
	CPS	11	NR	NR	NR	NR	NR	NR	NR
	SPS	9	NR	NR	NR	NR	NR	NR	NR
	PsyS	20	NR	NR	NR	NR	NR	NR	NR
Wroe (1989)	ES	20	34.0 (NR)	NR	55.0	NR	1.7 (3.0) / day	17.4 (12.0)	NR
	PsyS	40	33.9 (NR)	NR	10.0	NR	0.6 (0.51)	6.3 (7.9)	NR
	PsyS + ES	8	NR	NR	NR	NR	NR	NR	NR

ES Epileptic seizure
GTCS Generalized tonic clonic seizure
PsyS Psychogenic seizure
SPS Simple partial seizure

Evidence Table 19. Dichotomous diagnostic performance data: definitions

Reported Outcome	Definition
Prevalence	The proportion of subjects in the sample of interest who suffer from epileptic seizures alone
True Positive (TP)	A subject who suffers from true epileptic seizures (alone) who was correctly identified by the test of interest as suffering from epileptic seizures (alone)
False Positive (FP)	A subject who suffers from non-epileptic seizures (either alone or in combination with true epileptic seizures) who was incorrectly identified by the test of interest as suffering from true epileptic seizures (alone) by the test
True Negative (TN)	A subject who suffers from non- epileptic seizures (alone or in combination with true epileptic seizures) who was correctly identified by the test of interest as having nonepileptic seizures (either alone or in combination with true epileptic seizures)
False Negative (FN)	A subject who suffers from true epileptic seizures (alone) who was incorrectly identified by the test of interest as having nonepileptic seizures by the test.
Sensitivity	The proportion of individuals suffering from true epileptic seizures (alone) who were correctly identified by the test of interest as having true epileptic seizures (alone) Sensitivity = TP/(TP + FN)
Specificity	The proportion of individuals suffering from nonepileptic seizures (either alone or in combination with true epileptic seizures) who were correctly identified by the test of interest as not having true epileptic seizures (alone) Specificity = TN/(TN + FP)
Positive Predictive Value (PPV)	The proportion of individuals identified by the test of interest as suffering from true epileptic seizures (alone) who actually suffered from true epileptic seizures (alone) PPV = TP/(TP + FP)
Negative Predictive Value (NPV)	The proportion of individuals identified by the test of interest as suffering from non-epileptic seizures (either alone or in combination with true-epileptic seizures) who actually did suffer from nonepileptic seizures (either alone or in combination with true epileptic seizures) NPV = TN/(TN + FN)

Evidence Table 20. Dichotomous diagnostic performance data in studies of blood prolactin level measurement

Reference	Differentiation	Time	Threshold	Prevalence of Epileptic Seizures (%)	True Positive[a]	False Positive[b]	True Negative[c]	False Negative[d]
Lusic (1999)	Complex partial seizure from syncopal seizures	<60 minutes after seizure	≥630 mIU/ml	54.5	14	9	6	4
Anzola (1993)	Epileptic seizure from syncopal seizures	<60 minutes after seizure	≥2 SD above mean of next three readings	64.9	17	4	9	7
	Epileptic seizure from syncopal seizures	<60 minutes after seizure	≥3 SD above mean of next three readings	64.9	17	2	11	7
Wroe (1989)	Generalized tonic clonic seizure and complex partial seizure from psychogenic seizure	10 minutes after seizure	>1000 mU/l	65.5	11	0	10	8

Prevalence based on findings of Question 2A

[a] True Positive = Number of patients with ES correctly identified by test as having ES

[b] False Positive = Number of patients with NES incorrectly identified by test as having ES

[c] True Negative = Number of patients with NES correctly identified by test as having NES

[d] False Negative = Number of patients with ES incorrectly identified by test as having NES

Evidence Table 20. Dichotomous diagnostic performance data in studies of blood prolactin level measurement (continued)

Reference	Differentiation	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)	ECRI Calculated Data			
						S[e]	D[e]	Standardized Effect Size, d (CI)[f]	Cohen's h (CI)
Lusic (1999)	Complex partial seizure from syncopal seizures	77.8 (54.7 to 90.8)	40.0 (20.0 to 64.2)	69.0 (40.8 to 77.7)	60.0 (31.3 to 83.0)	1.658	0.847	0.47 (-0.37 to 1.30)	0.39 (-0.30 to 1.07)
Anzola (1993)	Epileptic seizure from syncopal seizures	70.8 (50.8 to 84.9)	69.2 (42.3 to 87.1)	81.0 (59.9 to 92.1)	56.3 (33.3 to 76.8)	0.076	1.698	**0.94 (0.13 to 1.75)**	**0.79 (0.14 to 1.44)**
	Epileptic seizure from syncopal seizures	70.8 (50.8 to 84.9)	84.6 (57.6 to 95.4)	89.5 (68.4 to 76.8)	61.1 (38.6 to 79.6)	-0.817	2.592	**1.43 (0.47 to 2.39)**	**1.13 (0.49 to 1.78)**
Wroe (1989)	Generalized tonic clonic seizure and complex partial seizure from psychogenic seizure	57.9 (36.3 to 76.7)	100.0 (71.7 to 100.0)	100.0 (73.6 to 100.0)	55.6 (33.8 to 75.3)	-2.742	3.347	**1.85 (0.21 to 3.48)**	**1.68 (0.93 to 2.43)**

Bolded effect size data indicate a statistically significant difference.

[e] Calculated using methodology of Littenburg and Moses

[f] Calculated using methodology of Hasselblad and Hedges (NB. D, which is the Ln of the odds ratio, can be converted to d by multiplying D by $\sqrt{3}/\pi$)

Evidence Table 21. Continuous diagnostic performance data in studies of blood prolactin level measurement

Reference	Serum Prolactin Levels Normal Range For Lab Sample Time(s)	Study Arm	N	Mean (SD)	P = (Author Reported)	Prevalence of ES (%)	Calculated By ECRI		
							Power to Detect Difference	Between Groups Effect Size Hedges' d (CI)	P
Zelnick (1991)	>15 ng/ml T1 = Within 90 mins of seizure	ES (Mixed)	17	26.5 (SE: 3.3)	<0.01	62.9	0.9989	**1.69 (0.79 to 2.59)**	0.000240
		Syncope	10	7.3 (SE: 0.9)					
Mishra (1990)	Mean: 278 (SD: 120.0) µIU/ml T1 = Within 20 mins of seizure	ES (combined)	35	1584 (876)	NR	63.6	1.0000	**1.66 (1.03 to 2.29)**	0.000000
		PsyS	20	405 (19)					
		GTCS	15	2230 (966)	<0.001	42.8	0.9999	**2.83 (1.89 to 3.78)**	0.000000
		PsyS	20	405 (19)					
		CPS	11	1757 (1044)	<0.01	35.5	0.9699	**2.15 (1.24 to 3.06)**	0.000000
		PsyS	20	405 (19)					
		SPS	9	400 (28)	NS	45.0	0.0686	-0.22 (-1.01 to 0.57)	0.583966
		PsyS	20	405 (19)					
	T2 = Approx. 6 to 8 hours post-seizure	ES (combined)	35	332 (84)	NR	63.6	0.8645	-0.69 (-1.25 to -0.25)	0.017282
		PsyS	20	380 (26)					
		GTCS	15	291 (68.0)	<0.01	42.8	0.9928	-1.79 (-2.58 to -1.00)	0.000009
		PsyS	20	380 (26)					
		CPS	11	360 (119)	NS	35.5	0.0729	-0.27 (-1.01 to 0.47)	0.478861
		PsyS	20	380 (26)					
		SPS	9	365 (47)	NS	31.0	0.1146	-0.43 (-1.23 to 0.36)	0.284746
		PsyS	20	380 (26)					

ES Epileptic seizures
CPS Complex partial seizures
GTCS Generalized tonic clonic seizures
PsyS Psychogenic seizure

Evidence Table 22. Articles addressing Minnesota Multiphasic Personality Inventory excluded for quality reasons

Reference	Country	Reason(s) for Exclusion
Holmes (1998)	United States	Study in which MMPI data were collected from a total of 347 patients. Authors presented data in graphical form only. These data did not include dispersion (i.e SD, SEM) data. Nor did they present the results of a statistical analysis of the data beyond indicating that significant differnces existed across four diagnostic groups. Data from this study do not allow one to draw independent conclusions about the clinical utility of the MMPI in differentiating patients with epileptic seizures from patients with nonepileptic seizures.
Brown (1991)	United States	Diagnostic case-control study in which MMPI (and other neuropsychological) data were collected from 23 patients with confirmed nonepileptic seizures and 25 patients with EEG confirmed epileptic seizures. Authors presented MMPI data in graphical form only. These data did not include dispersion (i.e. SD, SEM) data. Presentation of findings of statistical analysis of data was incomplete. Data from this study do not allow one to draw independent conclusions about the clinical utility of the MMPI in differentiating patients with epileptic seizures from patients with nonepileptic seizures.

Evidence Table 23. Articles addressing video EEG excluded for quality reasons

Reference	Country	Reason(s) for Exclusion
Drury (1999)	United States	Case series in which only 10 of 18 patients (55.0%) that entered study were followed up (4 of 8 patients with epileptic seizures and 6 of 10 patients with nonepileptic seizures). As a consequence of the large attrition rate (45.0 %) we are precluded from drawing valid conclusions pertaining the effectiveness of this diagnostic combination in improving patient outcomes. Follow-up data poorly described making conclusions about value of diagnostic in improving patient outcome impossible to draw.
Shihabuddin (1999)	United States	Case series in which only 64 of 125 patients (51.2 %) that entered study were followed up. As a consequence of the large attrition rate (48.8 %) we are precluded from drawing valid conclusions pertaining the effectiveness of this diagnostic combination in improving patient outcomes.

Evidence Table 24. Articles addressing ambulatory EEG excluded for quality reasons

Reference	Country	Reason(s) for Exclusion
Shihabuddin (1999)	United States	Case series in which only 64 of 125 patients (51.2 %) that entered study were followed up. As a consequence of the large attrition rate (48.8 %) we are precluded from drawing valid conclusions pertaining the effectiveness of this diagnostic combination in improving patient outcomes.
Sivenius (1984)	Finland	Uninterpretable presentation of data.

Evidence Table 25. Articles included in previous technology assessments of utility of video-EEG

Technology Assessment	References Forming Database	Reason Article Not Included in Current Report (If Applicable)
AHCPR (1990)	Pierelli (1989)	Study reports on diagnostic yield and diagnoses made as a consequence of using vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Rowan (1987)	Study reports on diagnostic yield and diagnoses made as a consequence of using vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Willmer (1986)	Study reports on diagnostic yield and changes in diagnosis made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Egli (1985)	Study reports on diagnostic yield and diagnoses made as a consequence of using vEEG. No reference standard was used so no diagnostic performance data were presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Wada (1985)	Retrospective study that reports on diagnostic yield and diagnoses made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Followed data were only presented for a few (15 of 136) patients making it impossible to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Perry (1983)	Retrospective study reports on diagnostic yield and diagnoses made as a consequence of using vEEG and rEEG. No reference standard was used so diagnostic performance data not presented. Patients were not followed up to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Sutula (1981)	Study reports on diagnostic yield and diagnoses made as a consequence of using vEEG and rEEG. No reference standard was used so no diagnostic performance data were presented. Patients were followed but data on changes in seizure frequency data were presented for the study population as a whole and not by diagnosis. As a consequence data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Holmes (1980)	This study utilized vEEG in conjunction with clinical opinion to characterize patients into patients with ES and patients with psychogencic seizures. The characteristics of both the patients and the seizures that they suffered were then compared. Thus this study is not a study of the effectiveness of vEEG in differentiating epileptic seizures from nonepileptic seizures and its data. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.

Evidence Table 25. Articles included in previous technology assessments of utility of video- EEG (continued)

Technology Assessment	References Forming Database	Reason Article Not Included in Current Report (If Applicable)
AHRQ (2001)	Shihabuddin (1999)	Study met general and question specific inclusion criteria for this report. However, study was excluded from current report for reasons of quality.
	Mohan (1996)	Study reports on diagnostic yield and diagnoses made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Chen (1995)	Retrospective study that reports on diagnostic yield and differential diagnoses made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Foley (1995)	Study reports on diagnostic yield and changes in diagnosis made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Bye (1990)	Study reports on diagnostic yield and diagnoses made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Duchowny (1988)	Study reports on diagnostic yield and diagnoses made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed up to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.
	Roberts (1985)	Study reports on diagnostic yield and diagnoses made as a consequence of using outpatient vEEG. No reference standard was used so no diagnostic performance data presented. Patients were not followed to confirm accuracy of diagnoses. Thus, data from this study cannot be used to determine the efficacy of vEEG in the differential diagnosis of epileptic seizures from nonepileptic seizures.

Question 3

Is there evidence that patients with treatment-resistant epilepsy are not optimized at their current level of treatment?

Evidence Table 26. Studies that provided evidence indicating that not all patients were optimized prior to study entry

Reference	Patient Population	N	Assessed Medical Intractability or Optimization	Required Compliance With Prescribed Drug Regimen	Reported Patients Not in The Therapeutic Range	Reported Patients Not in The Upper End of The Therapeutic Range	Reported Patients Who Had Not Been Titrated	Reported Patients Whose Drug Regimen Produced Side Effects
Studies conducted in the United States								
McCabe (2001)	Adult	21	No	No	No	Yes	NR	NR
Sachdeo (2001)	Mixed adult and pediatric	143	No	Yes	No	Yes	NR	NR
Morris (1995)	Mixed adult and pediatric	100	No	No	NR	NR	NR	Yes
Gilman (1994)	Pediatric	72	Yes	No	NR	NR	Yes	NR
Leppik (1991)	Adult	67	No	Yes	Yes	Yes	NR	NR
Theodore (1991)	Adult	47	No	No	Yes	Yes	NR	NR
Lesser (1984)	Adult	28	No	No	Yes	Yes	Yes	Yes

Evidence Table 26. Studies that provided evidence indicating that not all patients were optimized prior to study entry (continued)

Reference	Patient Population	N	Assessed Medical Intractability or Optimization	Required Compliance With Prescribed Drug Regimen	Reported Patients Not in The Therapeutic Range	Reported Patients Not in The Upper End of The Therapeutic Range	Reported Patients Who Had Not Been Titrated	Reported Patients Whose Drug Regimen Produced Side Effects
Studies conducted in other countries								
Jozwiak (2000)	Mixed adult and pediatric	126	No	No	No	Yes	NR	NR
El Desoky (1999)	Mixed adult and pediatric	227	Yes	No	Yes	NR	NR	NR
Bruni (1998)	Adult	141	No	No	Yes	Yes	NR	NR
Hermanns (1996)	Mixed adult and pediatric	74	Yes	No	No	Yes	Yes	NR
Semah (1994)	Adult	18	No	No	No	Yes	NR	NR
Bittencourt (1993)	Mixed adult and pediatric	51	No	No	No	NR	NR	Yes
Karande (1992)	NR	54	Yes	No	Yes	Yes	Yes	NR
Jawad (1989)	Adult	24	No	Yes	No	Yes	NR	NR
Cornaggia (1985)	Adult	66	No	Yes	No	Yes	NR	NR
Callaghan (1984)	Mixed adult and pediatric	35	No	No	Yes	Yes	NR	NR
Schmidt (1983)	Adult	35	No	No	Yes	Yes	Yes	NR
Milano Collaborative Group for Studies on Epilepsy (1977)	Mixed adult and pediatric	60	Yes	No	Yes	Yes	Yes	Yes
Shorvon (1977)	Adult	50	Yes	No	Yes	Yes	NR	NR

Question 4

Which drug treatment strategy, 1) sequential monotherapy, 2) polytherapy, or 3) optimized current therapy leads to improved outcomes for patients with treatment-resistant epilepsy, and what are the relative improvements obtained with each strategy?

Evidence Table 27. General information for studies of sequential monotherapy

Reference	Author Affiliation	Patients	Multicenter
Sachdeo (2001)	New Jersey Comprehensive Epilepsy Center, University of Medicine & Dentistry of New Jersey, New Brunswick, USA.	Uncontrolled partial seizures while receiving carbamazepine monotherapy	Yes
Beydoun (2000)	University of Michigan Medical Center, Ann Arbor, MI 48109, USA.	Inadequately controlled partial seizures, with or without secondary generalization	Yes
Kanner (2000)	Department of Neurological Sciences, Rush Medical College, Rush Epilepsy Center and Rush-Presbyterian Saint Luke's Medical Center, Chicago, Illinois 60612, USA. akanner@rush.edu	Partial seizures that had failed to respond to monotherapy trials	No
Schachter (1999)	Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02215, USA.	Refractory partial seizures with or without secondary generalization	Yes
Gilliam (1998)	University of Alabama at Birmingham, 35294-0021, USA.	Partial seizures, with or without secondary generalization, not adequately controlled by either carbamazepine or phenytoin monotherapy	Yes
Bergey (1997)	Department of Neurology, University of Maryland Medical Center, Baltimore, USA.	Refractory complex partial seizures or secondarily generalized seizures	Yes
Beydoun (1997a)	Department of Neurology, University of Michigan Medical Center, Ann Arbor 48109, USA.	Poorly controlled partial epilepsy, with or without secondary generalization	Yes
Beydoun (1997b)	Department of Neurology, University of Michigan Medical Center, Ann Arbor, USA.	Refractory complex partial seizures or secondarily generalized seizures	Yes
Sachdeo (1997a)	University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, New Brunswick 08903-0019, USA.	Uncontrolled partial onset seizures, with or without secondary generalization	No
Devinsky (1995)	NYU School of Medicine, Hospital for Joint Diseases, New York 10003, USA.	Medically intractable partial seizures	Yes
Schachter (1995)	Comprehensive Epilepsy Center, Beth Israel Hospital, Boston, Massachusetts, USA.	Partial seizures, with or without secondary generalized seizures, inadequately controlled with a single AED	Yes
Theodore (1995)	National Institutes of Health, Bethesda, Maryland 20892, USA.	Partial and secondarily generalized seizures, not controlled by a combination of carbamazepine and phenytoin	No
Faught (1993)	Department of Neurology, University of Alabama School of Medicine, Birmingham. USA	Uncontrolled partial-onset seizures with or without secondary generalization	Yes

Evidence Table 27. General information for studies of sequential monotherapy (continued)

Reference	For-Profit Funding	Minimum Number of AEDs	Minimum Monthly Seizure Frequency	Minimum Duration of Condition	Were Side Effects in The Definition of Treatment-Resistant Epilepsy
Sachdeo (2001)	Yes	1	2	NR	No
Beydoun (2000)	Yes	1	2	NR	No
Kanner (2000)	No	1	NR	NR	No
Schachter (1999)	Yes	1	30	NR	No
Gilliam (1998)	Yes	1	4	NR	No
Bergey (1997)	Yes	1	3	NR	No
Beydoun (1997a)	Yes	1	2	NR	No
Beydoun (1997b)	Yes	1	2	NR	No
Sachdeo (1997a)	Yes	1	4	NR	No
Devinsky (1995)	Yes	2	NR	NR	No
Schachter (1995)	Yes	1	NR	NR	No
Theodore (1995)	No	2	NR	NR	No
Faught (1993)	Yes	1	4	NR	No

Evidence Table 28. Design characteristics in studies of sequential monotherapy

Reference	Reported Maximum Tolerable Dose of Prior Drugs	Required Good Compliance to Prior Drugs	All Patients Seen During Presurgical Evaluation	Patients Continue to Take Their Prestudy Drugs	Prospective	Randomized	Type of Control
Sachdeo (2001)	No	Yes	No	No	Yes	Yes	Different dose
Beydoun (2000)	No	Yes	No	No	Yes	Yes	Different dose
Kanner (2000)	Yes	No	No	No	Yes	No	None
Schachter (1999)	No	Yes	Yes	No	Yes	Yes	Placebo
Gilliam (1998)	No	No	No	Yes	Yes	Yes	Different drug
Bergey (1997)	No	No	Yes	No	Yes	Yes	Different dose
Beydoun (1997a)	No	Yes	No	No	Yes	Yes	Different dose
Beydoun (1997b)	No	No	No	No	Yes	Yes	Different dose
Sachdeo (1997a)	No	Yes	No	No	Yes	Yes	Different dose
Devinsky (1995)	No	Yes	Yes	No	Yes	Yes	Placebo
Schachter (1995)	No	No	No	No	Yes	Yes	Different dose
Theodore (1995)	No	No	Yes	No	Yes	Yes	Placebo
Faught (1993)	No	Yes	No	No	Yes	Yes	Different drug

Evidence Table 28. Design characteristics in studies of sequential monotherapy (continued)

Reference	Patients Receiveed a Placebo During The Baseline	Patients Blinded	Observers Blinded	Length of Baseline (Weeks)	Length of Titration Period (Weeks)	Length of Maintenance Period (Weeks)	Plasma Levels Monitored
Sachdeo (2001)	No	Yes	Yes	8	4 or 10	12 or 18	Yes
Beydoun (2000)	No	Yes	Yes	7	2	112 days	Yes
Kanner (2000)	No	No	No	NR	5-10 days	3 months	Yes
Schachter (1999)	No	Yes	Yes	NR	2 days	8 days	Yes
Gilliam (1998)	No	Yes	Yes	8	8	12	Yes
Bergey (1997)	No	Yes	Yes	12	0	8 days	Yes
Beydoun (1997a)	No	Yes	Yes	8 or 12	8	16	Yes
Beydoun (1997b)	No	Yes	Yes	8	10	16	Yes
Sachdeo (1997a)	No	Yes	Yes	8	5	11	Yes
Devinsky (1995)	No	Yes	Yes	4	2 days	8 days	Yes
Schachter (1995)	No	Yes	Yes	8	6	12	No
Theodore (1995)	No	Yes	Yes	6 days	4 days	2	Yes
Faught (1993)	No	Yes	Yes	8	4	12	Yes

Evidence Table 29. Reporting characteristics in trials of sequential monotherapy

Reference	Seizure Types	Used Seizure Diaries	Reported							
			Individual Patient Data	Baseline Seizure Frequency	Seizure Frequency	Adverse Effects	Quality of Life	Functional Status/Ability	Return to Work	Return to School
Sachdeo (2001)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Beydoun (2000)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Kanner (2000)	Partial	Yes	No	No	Yes	Yes	No	No	No	No
Schachter (1999)	Partial	No	No	Yes	Yes	Yes	No	No	No	No
Gilliam (1998)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Bergey (1997)	Partial	No	No	Yes	Yes	Yes	No	No	No	No
Beydoun (1997a)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Beydoun (1997b)	Partial	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Sachdeo (1997a)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Devinsky (1995)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Schachter (1995)	Partial	Not reported	No	Yes	Yes	Yes	Yes	Yes	No	No
Theodore (1995)	Partial	No	No	Yes	Yes	Yes	Yes	No	No	No
Faught (1993)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No

Evidence Table 30. Drug characteristics in studies of sequential monotherapy

Reference	Name of Drug Given to This Group of Patients	Mechanism(s) of Action[a]	Minimum Dose (mg/day)	Maximum Dose (mg/day)
Sachdeo (2001)	Oxcarbazepine	Sodium	NR	2400
Beydoun (2000)	Oxcarbazepine	Sodium	1800	2400
Kanner (2000)	Primidone	GABA	50	750
Schachter (1999)	Oxcarbazepine	Sodium	NR	2400
Gilliam (1998)	Lamotrigine	Sodium	300	500
Bergey (1997)	Gabapentin	Inhibitory	3000	3600
Beydoun (1997a)	Valproate	Inhibitory	80 µg/mL	150 µg/mL
Beydoun (1997b)	Gabapentin	Inhibitory	NR	2400
Sachdeo (1997a)	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	1000
Devinsky (1995)	Felbamate	Sodium, Inhibitory, Excitatory	NR	3600
Schachter (1995)	Tiagabine	Inhibitory	NR	36
Theodore (1995)	Felbamate	Sodium, Inhibitory, Excitatory	NR	3600
Faught (1993)	Felbamate	Sodium, Inhibitory, Excitatory	NR	3600

[a] The mechanism(s) of drug action were based on Table 3 of Brodie (2002).
µg/mL Micrograms per milliliter

Evidence Table 31. Numbers of patients and attrition in studies of sequential monotherapy

Reference	Drug And Dose (mg/day)	Characteristics Reported For Patients Who Started or Completed The Study	Number of Patients					
			Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics
Sachdeo (2001)	Oxcarbazepine 2400	Neither	51	30	0	5	16	49
Beydoun (2000)	Oxcarbazepine 2400	Started	41	14	6	1	20	41
Kanner (2000)	Primidone 750	Started	30	2	7	0	21	30
Schachter (1999)	Oxcarbazepine 2400	Started	51	24	2[a]	1[a]	24	51
Gilliam (1998)	Lamotrigine 500	Started	76	22[a]	15[a]	11[a]	28	76
Bergey (1997)	Gabapentin 3600	Started	40	18	0	1	21	40
Beydoun (1997a)	Valproate 150 µg/mL	Neither	131	12[a]	31[a]	35[a]	53[a]	96
Beydoun (1997b)	Gabapentin 2400	Started	91	66	4	4	17	91
Sachdeo (1997a)	Topiramate 1000	Started	24	9	1	1	13	24
Devinsky (1995)	Felbamate 3600	Started	25	11[a]	0	5	9	25
Schachter (1995)	Tiagabine 36	Started	96	58[a]	0	0	38[a]	96
Theodore (1995)	Felbamate 3600	Started	21	2	6	0	13	21
Faught (1993)	Felbamate 3600	Started	56	18	6	5	27	56

[a] Calculated by ECRI based on reported information
µg/mL Micrograms per milliliter

Evidence Table 32. Age, gender, and duration of condition of patients in studies of sequential monotherapy

Reference	Drug And Dose (mg/day)	Age Mean	Age SD	Minimum Age	Maximum Age	Number of Males	Number of Females	Mean Duration of Epilepsy	Duration SD	Median Duration of Epilepsy
Sachdeo (2001)	Oxcarbazepine 2400	35.6	NR	12	65	22	27	NR	NR	NR
Beydoun (2000)	Oxcarbazepine 2400	35.1	NR	13	59	15	26	NR	NR	NR
Kanner (2000)	Primidone 750	35.7	14	4	73	11	19	23.3	15.2	NR
Schachter (1999)	Oxcarbazepine 2400	33	NR	NR	NR	31	20	NR	NR	NR
Gilliam (1998)	Lamotrigine 500	37	NR	13	73	33	43	NR	NR	NR
Bergey (1997)	Gabapentin 3600	36.1	10.2	19	61	19	21	19.8	12.8	NR
Beydoun (1997a)	Valproate 150 µg/mL	34	NR	10	70	43	53	NR	NR	NR
Beydoun (1997b)	Gabapentin 2400	37.1	12.2	14	64	35	56	NR	NR	20
Sachdeo (1997a)	Topiramate 1000	39.3	11.0	NR	NR	9	15	22	12.5	NR
Devinsky (1995)	Felbamate 3600	33.7	NR	20	60	11	14	NR	NR	NR
Schachter (1995)	Tiagabine 36	NR	NR	NR	NR	NR	NR	NR	NR	NR
Theodore (1995)	Felbamate 3600	34.1[a,b]	9.2[a,b]	14 [a]	55 [a]	10 [a,b]	11 [a,b]	23.4 [a,b]	11.5 [a,b]	NR
Faught (1993)	Felbamate 3600	33.4	NR	16.3	71.7	32	24	NR	NR	NR

[a] Reported only for the entire patient group, not separately for different groups.
[b] Information reported by a secondary publication.
µg/mL Micrograms per milliliter

Evidence Table 33. Baseline seizure frequencies and specific types of partial seizures in studies of sequential monotherapy

Reference	Drug And Dose (mg/day)	Seizure Frequency					
		Type of Baseline Seizure	Mean Baseline	SD of Baseline	Median Baseline	Minimum Monthly	Maximum Monthly
Sachdeo (2001)	Oxcarbazepine 2400	Partial	NR	NR	NR	NR	NR
Beydoun (2000)	Oxcarbazepine 2400	Partial	NR	NR	10.5	NR	NR
Kanner (2000)	Primidone 750	NR	NR	NR	NR	NR	NR
Schachter (1999)	Oxcarbazepine 2400	Partial	74.5[a]	NR	74.5[a]	NR	NR
Gilliam (1998)	Lamotrigine 500	Partial	NR	NR	9	1	737
Bergey (1997)	Gabapentin 3600	Partial	NR	NR	5.8	3	285
Beydoun (1997a)	Valproate 150 µg/mL	Complex partial	NR	NR	6.7[c]	NR	NR
Beydoun (1997b)	Gabapentin 2400	Partial	8.6	7	6.5	NR	NR
Sachdeo (1997a)	Topiramate 1000	Partial	17.9	42.5	6.5	NR	NR
Devinsky (1995)	Felbamate 3600	Partial	18.3	NR	NR	NR	NR
Schachter (1995)	Tiagabine 36	Complex partial	NR	NR	7.3	NR	NR
Theodore (1995)	Felbamate 3600	Complex partial	6.4[b]	8.2[b]	NR	NR	NR
Faught (1993)	Felbamate 3600	Partial	12.4	NR	NR	3.7	49.1

[a] Study did not report whether the reported value was a mean or median
[b] Information obtained from a secondary publication.
[c] Calculated by ECRI based on reported information
µg/mL Micrograms per milliliter

Evidence Table 33. Baseline seizure frequencies and specific types of partial seizures in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients With			
		Partial Seizures	Complex Partial Seizures	Simple Partial Seizures	Secondarily Generalized Seizures
Sachdeo (2001)	Oxcarbazepine 2400	49	43	26	31
Beydoun (2000)	Oxcarbazepine 2400	41	NR	NR	NR
Kanner (2000)	Primidone 750	30	30	NR	16
Schachter (1999)	Oxcarbazepine 2400	51	NR	NR	NR
Gilliam (1998)	Lamotrigine 500	76	64	31	38
Bergey (1997)	Gabapentin 3600	40	NR	NR	37
Beydoun (1997a)	Valproate 150 µg/mL	96	96	32	59
Beydoun (1997b)	Gabapentin 2400	91	83	61	31
Sachdeo (1997a)	Topiramate 1000	24	23	2	4
Devinsky (1995)	Felbamate 3600	25	NR	NR	NR
Schachter (1995)	Tiagabine 36	96	96	NR	NR
Theodore (1995)	Felbamate 3600	21	NR	NR	NR
Faught (1993)	Felbamate 3600	56	NR	NR	NR

µg/mL Micrograms per milliliter

Evidence Table 34. Known etiology and prior drugs in studies of sequential monotherapy

Reference	Drug And Dose (mg/day)	Number of Patients			
		With Known Etiology	On One AED Prior to The Study	On Two AEDs Prior to The Study	On Three or More AEDs Prior to The Study
Sachdeo (2001)	Oxcarbazepine 2400	NR	49	0	0
Beydoun (2000)	Oxcarbazepine 2400	NR	NR	NR	0
Kanner (2000)	Primidone 750	NR	30	0	0
Schachter (1999)	Oxcarbazepine 2400	NR	NR	NR	NR
Gilliam (1998)	Lamotrigine 500	NR	76	0	0
Bergey (1997)	Gabapentin 3600	NR	23	16	1
Beydoun (1997a)	Valproate 150 µg/mL	NR	96	0	0
Beydoun (1997b)	Gabapentin 2400	53	57	34	0
Sachdeo (1997a)	Topiramate 1000	NR	20	4	0
Devinsky (1995)	Felbamate 3600	NR	0	NR	NR
Schachter (1995)	Tiagabine 36	NR	96	0	0
Theodore (1995)	Felbamate 3600	NR	0	21	0
Faught (1993)	Felbamate 3600	NR	56	0	0

µg/mL Micrograms per milliliter

Evidence Table 34. Known etiology and prior drugs in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients Receiving Specific Prior Drugs								
		Carbamazepine	Felbamate	Gabapentin	Lamotrigine	Lorazepam	Phenytoin	Phenobarbital	Primidone	Valproate
Sachdeo (2001)	Oxcarbazepine 2400	49	0	0	0	0	0	0	0	0
Beydoun (2000)	Oxcarbazepine 2400	22	NR	4	5	NR	8	NR	NR	6
Kanner (2000)	Primidone 750	>0	0	0	0	0	>0	7	0	>0
Schachter (1999)	Oxcarbazepine 2400	NR	NR	NR	NR	45	NR	NR	NR	NR
Gilliam (1998)	Lamotrigine 500	48	0	0	0	0	28	0	0	0
Bergey (1997)	Gabapentin 3600	18	7	NR	NR	NR	14	0	NR	14
Beydoun (1997a)	Valproate 150 µg/mL	>0	NR	NR	NR	NR	>0	>0	>0	NR
Beydoun (1997b)	Gabapentin 2400	67	8	NR	NR	NR	26	NR	NR	26
Sachdeo (1997a)	Topiramate 1000	10	6	2	0	0	4	2	0	4
Devinsky (1995)	Felbamate 3600	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schachter (1995)	Tiagabine 36	NR	NR	NR	NR	NR	NR	NR	NR	NR
Theodore (1995)	Felbamate 3600	21	0	0	0	0	21	0	0	0
Faught (1993)	Felbamate 3600	NR	NR	NR	NR	NR	NR	NR	NR	NR

µg/mL Micrograms per milliliter
>0 At least one patient had received the drug, but the study did not report the exact number of patients who received the drug.

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Sachdeo (2001)	Oxcarbazepine 2400	PAR	PAR	Median time to exit	49	51	68 days
				Number of patients who completed 18 weeks of monotherapy	49	51	16
				Number of patients who exited due to a new-onset tonic-clonic seizure	49	51	5
				Number of patients who exited due to any of four exit criteria	49	51	30
				Number of patients who exited due to doubling of monthly seizure frequency	49	51	15
				Number of patients who exited due to doubling of two-day seizure frequency	49	51	7
				Number of patients who exited due to prolongation of a tonic-clonic seizure	49	51	3
Beydoun (2000)	Oxcarbazepine 2400	PAR	PAR	Number of patients with 50% or more seizure reduction	41	41	17c
				Median time to exit	34	41	Median not yet reached
				Number of patients who exited due to a new-onset secondarily generalized seizure	34	41	5
				Number of patients who exited due to any of four exit criteria	34	41	14
				Number of patients who exited due to doubling of monthly seizure frequency	34	41	6

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Beydoun (2000) continued	Oxcarbazepine 2400	PAR	PAR	Number of patients who exited due to doubling of two-day seizure frequency	34	41	3
				Number of patients who exited due to prolongation of secondarily generalized seizures	34	41	0
				Number of patients seizure free	41	41	5[c]
Kanner (2000)	Primidone 750	PAR	PAR	Mean time on monotherapy	30	30	16 months SD 21.6 months
				Median time on monotherapy	30	30	7.5 months range 0.5-80
				Number of patients seizure free and no side effects for at least 12 months	30	30	4
				Number of patients seizure free and no side effects for at least 3 months	30	30	15
				Number of patients seizure free and no side effects for at least 6 months	30	30	9
				Number of patients who completed at least 12 months of monotherapy	30	30	9
				Number of patients who completed at least 3 months of monotherapy	30	30	25
				Number of patients who completed at least 6 months of monotherapy	30	30	21

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Schachter (1999)	Oxcarbazepine 2400	PAR	PAR	Median monthly seizure frequency	51	51	6.8[c]
				Number of patients who exited due to a fourth seizure	51	51	24
				Number of patients who exited due to a new-onset secondarily generalized seizure	51	51	0
				Number of patients who exited due to any of three exit criteria	51	51	24
				Number of patients who exited due to doubling of monthly seizure frequency	51	51	0
				Number of patients who exited due to serial seizures	51	51	0
				Number of patients who exited due to status epilepticus	51	51	0
				Number of patients seizure free	51	51	13
				Risk ratio of time to exit	102	102	0.2 (CI: 0.11 to 0.38)
Gilliam (1998)	Lamotrigine 500	PAR	PAR	Median time to exit	50	50	168 days
				Number of patients who completed 12 weeks of monotherapy	76	76	28
				Number of patients who exited due to any of four exit criteria	76	76	22c

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Bergey (1997)	Gabapentin 3600	PAR	PAR	Mean time on monotherapy	40	40	151 hours
				Number of patients who exited due to a continued intolerance to study medication following dose reduction	40	40	0
				Number of patients who exited due to a fourth seizure	40	40	17
				Number of patients who exited due to a new-onset secondarily generalized seizure	40	40	0
				Number of patients who exited due to any of six exit criteria	40	40	19
				Number of patients who exited due to other lack of efficacy	40	40	0
				Number of patients who exited due to prolongation of secondarily generalized seizures	40	40	1
				Number of patients who exited due to status epilepticus	40	40	0
				Number of patients seizure free	40	40	11
Beydoun (1997a)	Valproate 150 µg/mL	PAR	CPS	Number of patients with 50% or more seizure reduction	96	96	36[c]
			SPS	Number of patients with 50% or more seizure reduction	30	32	11[c]
			SG	Number of patients with 50% or more seizure reduction	30	59	17[c]

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Beydoun (1997a) continued	Valproate 150 µg/mL	PAR	CPS	Number of patients with 75% or more seizure reduction	96	96	22[c]
			CPS	Number of patients with any reduction in seizure frequency	96	96	66[c]
			SPS	Number of patients with any reduction in seizure frequency	30	32	23[c]
			SG	Number of patients with any reduction in seizure frequency	30	59	20[c]
			CPS	Median % reduction from baseline in seizure frequency	96	96	30
			SG	Median % reduction from baseline in seizure frequency	30	59	70
			CPS	Median difference from baseline in seizure frequency	96	96	2.8
			SPS	Median difference from baseline in seizure frequency	30	32	4.9
			SG	Median difference from baseline in seizure frequency	30	59	1.9
			PAR	Number of patients who completed 16 weeks of monotherapy	96	96	84
			CPS	Number of patients seizure free	96	96	9[c]

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Beydoun (1997b)	Gabapentin 2400	PAR	CPS SG	Mean time on monotherapy	91	91	61 days
			CPS SG	Median time to exit	91	91	75 days
			CPS SG	Number of patients who exited due to a new-onset secondarily generalized seizure	91	91	11
			CPS SG	Number of patients who exited due to any of five exit criteria	91	91	66
			CPS SG	Number of patients who exited due to clinical judgment of lack of efficacy	91	91	21
			CPS SG	Number of patients who exited due to doubling of monthly seizure frequency	91	91	12
			CPS SG	Number of patients who exited due to doubling of two-day seizure frequency	91	91	21
			CPS SG	Number of patients who exited due to status epilepticus	91	91	1
Sachdeo (1997a)	Topiramate 1000	PAR	PAR	Number of patients with 50% or more seizure reduction	24	24	11
				Number of patients with 75% or more seizure reduction	24	24	6
				Number of patients who exited due to a new-onset secondarily generalized seizure	24	24	3
				Number of patients who exited due to any of four exit criteria	24	24	9

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Sachdeo (1997a) continued	Topiramate 1000	PAR	PAR	Number of patients who exited due to doubling of monthly seizure frequency	24	24	4
				Number of patients who exited due to doubling of two-day seizure frequency	24	24	1
				Number of patients who exited due to prolongation of secondarily generalized seizures	24	24	4
				Number of patients seizure free	24	24	3
				Risk ratio of time to exit	48	48	0.336 (CI: 0.149 to 0.757)
Devinsky (1995)	Felbamate 3600	ALL	ALL	Mean rank of daily seizure frequency	25	25	21.6
				Median time to fourth seizure	25	25	6.26 days
				Number of patients who exited due to a fourth seizure	25	25	11c
Schachter (1995)	Tiagabine 36	PAR	CPS	Number of patients with 50% or more seizure reduction	96	96	30
			PAR	Mean time on monotherapy	96	96	62.9 days
			CPS	Median monthly seizure frequency	96	96	5.0c
Theodore (1995)	Felbamate 3600	PAR	CPS	Mean monthly seizure frequency	21	21	24.4[c]
			SPS	Mean monthly seizure frequency	21	21	0.9[c]
			SG	Mean monthly seizure frequency	21	21	2.4[c]

Evidence Table 35. Seizure frequency outcomes in studies of sequential monotherapy (continued)

Reference	Patient Group Drug And Dose (mg/day)	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcomes	N	Number of Patients Using Intent-to-Treat	Outcome[b]
Theodore (1995) continued	Felbamate 3600	ALL	ALL	Mean monthly seizure frequency	21	21	27.8 [c]
				Number of patients who exited due to exit criteria	21	21	8
				Number of patients who exited due to status epilepticus	21	21	0
		PAR	PAR	Mean monthly seizure frequency	21	21	25.3 [c]
Faught (1993)	Felbamate 3600	PAR	PAR	Number of patients who exited due to a new-onset tonic-clonic seizure	45	45	4
			PAR	Number of patients who exited due to any of four exit criteria	45	45	18
			SG	Number of patients who exited due to any of four exit criteria	18	18	4
			PAR	Number of patients who exited due to doubling of monthly seizure frequency	45	45	4
			PAR	Number of patients who exited due to doubling of two-day seizure frequency	45	45	6
			PAR	Number of patients who exited due to prolongation of a tonic-clonic seizure	45	45	7

[a] The following abbreviations for seizure types have been used in Evidence Table 35
ALL all seizures
CPS complex partial seizures
PAR partial seizures
SG secondarily generalized seizures
SPS simple partial seizures

[b] In the outcome column, a positive value for either median % reduction from baseline or median difference from baseline represents a beneficial reduction in seizures. This conforms to the convention in the epilepsy literature.

[c] Calculated by ECRI based on published information

µg/mL micrograms per milliliter

Evidence Table 36. Adverse effects in studies of sequential monotherapy

Reference	Drug And Dose (mg/day)	Description of Adverse Effect	Severity of Adverse Effect	Number With This Effect / Number of Patients in The Group	Percentage
Sachdeo (2001)	Oxcarbazepine 2400	Dizziness		3/45	7%
		Headache		5/45	11%
		Increase in seizures	Severe	2/45	4%
		Nausea		1/45	2%
Beydoun (2000)	Oxcarbazepine 2400	Abnormal vision		7/41	17%
		Accidental injury	Severe	1/41	2%
		Angina	Severe	1/41	2%
		Any	Severe	2/41	5%
		Diplopia		8/41	20%
		Dizziness		19/41	46%
		Fatigue		16/41	39%
		Headache		9/41	22%
		Nausea		12/41	29%
		Rash		5/41	12%
		Somnolence		12/41	29%
		Vomiting		9/41	22%
Kanner (2000)	Primidone 750	Any	Any	16/30	53%
		Attention		1/30	3%
		Dizziness	Severe	3/30	10%
		Dizziness	Withdrawal	1/30	3%
		Dysthymic disorder		4/30	13%
		Irritability		11/30	37%
		Mood lability		11/30	37%
		Poor frustration tolerance		11/30	37%
		Sedation		5/30	17%
		Sexual impotence		2/30	7%

Evidence Table 36. Adverse effects in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Description of Adverse Effect	Severity of Adverse Effect	Number With This Effect / Number of Patients in The Group	Percentage
Schachter (1999)	Oxcarbazepine 2400	Any	Mild / moderate	46/51	91%
		Any	Any	38/51	75%
		Body as a whole		7/51	14%
		Diplopia		6/51	12%
		Dizziness		9/51	18%
		Fatigue		5/51	10%
		Gastrointestinal system		21/51	41%
		Headache		10/51	20%
		Nausea		10/51	20%
		Nervous system		23/51	45%
		Pruritus		9/51	18%
		Skin		12/51	24%
		Somnolence		8/51	16%
		Special senses		8/51	16%
		Vomiting		5/51	10%
Gilliam (1998)	Lamotrigine 500	Any		57/76	75%
		Asthenia		9/76	12%
		Coordination abnormalities		9/76	12%
		Dizziness		15/76	20%
		Dyspepsia		0/76	0%
		Headache		10/76	13%
		Nausea		12/76	16%
		Rash		8/76	11%
		Somnolence		6/76	8%
		Tremor		5/76	7%
		Vomiting		8/76	11%
		Rash	Withdrawal	6/76	8%
		Vomiting/Dizziness	Withdrawal	1/76	1%
		Dizziness	Withdrawal	1/76	1%
		Myalgia	Withdrawal	1/76	1%

Evidence Table 36. Adverse effects in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Description of Adverse Effect	Severity of Adverse Effect	Number With This Effect / Number of Patients in The Group	Percentage
Gilliam (1998) continued		Personality disorder	Withdrawal	1/76	1%
		Alopecia	Withdrawal	1/76	1%
		Anxiety	Withdrawal	2/76	2%
		Ataxia	Withdrawal	1/76	1%
		Chest pain	Withdrawal	1/76	1%
Bergey (1997)	Gabapentin 3600	Anorexia		2/40	5%
		Any	Any	29/40	73%
		Ataxia	Severe	1/40	3%
		Ataxia		8/40	20%
		Death	Severe	0/40	0%
		Dizziness		7/40	18%
		Dysarthria		5/40	13%
		Fatigue		4/40	10%
		Headache	Severe	1/40	3%
		Headache		3/40	8%
		Myalgia		3/40	8%
		Nystagmus		5/40	13%
		Paresthesia		4/40	10%
		Somnolence		6/40	15%
		Tremor		3/40	8%
Beydoun (1997a)	Valproate 150 µg/mL	Alopecia		2/47	4%
		Anorexia		0/47	0%
		Asthenia		0/47	0%
		Death	Severe	1/47	2%
		Diarrhea		2/47	4%
		Headache		15/47	32%
		Thrombocytopenia		0/47	0%
		Tremor		3/47	6%
		Vomiting		0/47	0%
		Weight gain		2/47	4%

Evidence Table 36. Adverse effects in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Description of Adverse Effect	Severity of Adverse Effect	Number With This Effect / Number of Patients in The Group	Percentage
Beydoun (1997b)	Gabapentin 2400	Any		80/91	88%
		Ataxia		12/91	13%
		Death	Severe	0/91	0%
		Dizziness		23/91	25%
		Fatigue		13/91	14%
		Headache		9/91	10%
		Insomnia		7/91	8%
		Nausea and/or vomiting		4/91	4%
		Organic delusional disorder	Severe	1/91	1%
		Purpura		7/91	8%
		Sedation	Severe	1/90	1%
		Somnolence		15/91	16%
		Upper respiratory tract infection		9/91	10%
Sachdeo (1997a)	Topiramate 1000	Anorexia		10/24	42%
		Confusion		3/24	13%
		Death	Severe	0/24	0%
		Dizziness		6/24	25%
		Facial edema	Withdrawal	1/24	4%
		Fatigue		11/24	46%
		Headache		6/24	25%
		Insomnia		4/24	17%
		Nausea		4/24	17%
		Paresthesia		14/24	58%
		Renal stones		1/24	4%
		Upper respiratory tract infection		5/24	21%
Devinsky (1995)	Placebo	Hypoesthesia	Withdrawal	1/27	4%

Evidence Table 36. Adverse effects in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Description of Adverse Effect	Severity of Adverse Effect	Number With This Effect / Number of Patients in The Group	Percentage
Schachter (1995)	Tiagabine 36	Accidental injury		20/96	21%
		Amnesia		8/96	8%
		Any	Any	91/96	95%
		Asthenia		12/96	13%
		Dizziness		34/96	35%
		Headache		8/96	8%
		Impaired concentration		22/96	23%
		Insomnia		10/96	10%
		Nervousness		15/96	16%
		Paresthesia		19/96	20%
		Somnolence		24/96	25%
Theodore (1995)	Felbamate 3600	Abdominal pain	Withdrawal	1/21	5%
		Anxiety	Withdrawal	2/21	10%
		Increase in seizures	Withdrawal	2/21	10%
		Insomnia	Withdrawal	1/21	5%
		Orobuccal dyskinesias	Withdrawal	1/21	5%
		Psychosis	Withdrawal	1/21	5%
Faught (1993)	Felbamate 3600	Abdominal pain		1/56	2%
		Anorexia		6/56	11%
		Diarrhea		2/56	4%
		Diplopia		3/56	5%
		Dizziness		9/56	16%
		Dyspepsia		8/56	14%
		Fatigue		3/56	5%
		Headache		19/56	34%
		Insomnia		2/56	4%
		Nausea		17/56	30%
		Nausea and/or vomiting	Withdrawal	5/56	9%
		Nervousness		4/56	7%
		Rash	Withdrawal	1/56	2%

Evidence Table 36. Adverse effects in studies of sequential monotherapy (continued)

Reference	Drug And Dose (mg/day)	Description of Adverse Effect	Severity of Adverse Effect	Number With This Effect / Number of Patients in The Group	Percentage
Faught (1993) contineud	Felbamate 3600	Somnolence		10/56	18%
		Tremor		3/56	5%
		Upper respiratory tract infection		3/56	5%
		Vomiting		8/56	14%
		Weight loss		2/56	4%

µg/mL micrograms per milliliter

Evidence Table 37. Quality of life outcomes and mood outcomes in studies of sequential monotherapy

Primary Efficacy Study Study Reporting Quality of Life	Drug And Dose (mg/day)	Quality of Life Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Beydoun (1997b) Dodrill (1999)	Gabapentin 2400	Profile of Mood States	Tension-anxiety	Worse	No
			Depression-dejection	Worse	No
			Anger-hostility	Better	No
			Vigor-activity	Worse	No
			Fatigue-inertia	Worse	No
			Confusion-bewilderment	Worse	No
			Total mood disturbance	Worse	No
		Washington Psychosocial Seizure Inventory	Family background	Worse	No
			Emotional adjustment	Better	No
			Interpersonal adjustment	Better	No
			Vocational adjustment	Better	No
			Financial status	Better	No
			Adjustment to seizures	Better	No
			Medicine & medical management	Better	No
			Overall functioning	Better	No
			Lie Scale	Worse	No
			Rare Items	Worse	No
		Mood Rating Scale	Mood Rating Scale	Worse	No

Evidence Table 37. Quality of life outcomes and mood outcomes in studies of sequential monotherapy (continued)

Primary Efficacy Study Study Reporting Quality of Life	Drug And Dose (mg/day)	Quality of Life Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Schachter (1995) Dodrill (1998)	Tiagabine 6 or 36	Profile of Mood States	Tension-anxiety	Worse	No
			Depression-dejection	Better	No
			Anger-hostility	Better	No
			Vigor-activity	Worse	Yes
			Fatigue-inertia	Worse	No
			Confusion-bewilderment	Worse	No
			Total mood disturbance	Worse	No
		Washington Psychosocial Seizure Inventory	Family background	Better	No
			Emotional adjustment	Better	No
			Interpersonal adjustment	Better	No
			Vocational adjustment	Better	No
			Financial status	Better	No
			Adjustment to seizures	Better	No
			Medicine & medical management	Better	No
			Overall functioning	Better	No
			Lie Scale	Worse	No
			Rare Items	Better	No
		Mood Rating Scale	Mood Rating Scale	Worse	No

Evidence Table 37. Quality of life outcomes and mood outcomes in studies of sequential monotherapy (continued)

Primary Efficacy Study Study Reporting Quality of Life	Drug And Dose (mg/day)	Quality of Life Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Theodore (1995) Ketter (1996)	Patients on no AEDs	Zung Anxiety	Zung Anxiety	Worse	Yes
		Hamilton Depression	Hamilton Depression	Worse	Yes
		Young mania	Young mania	Worse	No
		Brief Psychiatric Rating Scale	Brief Psychiatric Rating Scale	Worse	Yes
		Clinical Global Impression	Clinical Global Impression	Worse	Yes
		Bunney-Hamburg anxiety	Bunney-Hamburg anxiety	Worse	Yes
		Bunney-Hamburg depression	Bunney-Hamburg depression	Worse	Yes
		Bunney-Hamburg mania	Bunney-Hamburg mania	Worse	No
		Bunney-Hamburg psychosis	Bunney-Hamburg psychosis	Same	No
		Bunney-Hamburg obsessive compulsive	Bunney-Hamburg obsessive compulsive	Same	No
		Bunney-Hamburg global impairment	Bunney-Hamburg global impairment	Worse	Yes
	Felbamate 3600 week 1	Zung Anxiety	Zung Anxiety	Worse	Yes
		Hamilton Depression	Hamilton Depression	Worse	Yes
		Young mania	Young mania	Worse	No
		Brief Psychiatric Rating Scale	Brief Psychiatric Rating Scale	Worse	Yes
		Clinical Global Impression	Clinical Global Impression	Worse	Yes
		Bunney-Hamburg anxiety	Bunney-Hamburg anxiety	Worse	Yes
		Bunney-Hamburg depression	Bunney-Hamburg depression	Worse	Yes

Evidence Table 37. Quality of life outcomes and mood outcomes in studies of sequential monotherapy (continued)

Primary Efficacy Study Study Reporting Quality of Life	Drug And Dose (mg/day)	Quality of Life Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Theodore (1995) Ketter (1996) continued	Felbamate 3600 week 1	Bunney-Hamburg mania	Bunney-Hamburg mania	Worse	No
		Bunney-Hamburg psychosis	Bunney-Hamburg psychosis	Worse	No
		Bunney-Hamburg obsessive compulsive	Bunney-Hamburg obsessive compulsive	Same	No
		Bunney-Hamburg global impairment	Bunney-Hamburg global impairment	Worse	Yes
	Felbamate 3600 week 2	Zung Anxiety	Zung Anxiety	Worse	Yes
		Hamilton Depression	Hamilton Depression	Worse	Yes
		Young mania	Young mania	Worse	No
		Brief Psychiatric Rating Scale	Brief Psychiatric Rating Scale	Worse	Yes
		Clinical Global Impression	Clinical Global Impression	Worse	Yes
		Bunney-Hamburg anxiety	Bunney-Hamburg anxiety	Worse	Yes
		Bunney-Hamburg depression	Bunney-Hamburg depression	Worse	Yes
		Bunney-Hamburg mania	Bunney-Hamburg mania	Worse	No
		Bunney-Hamburg psychosis	Bunney-Hamburg psychosis	Worse	No
		Bunney-Hamburg obsessive compulsive	Bunney-Hamburg obsessive compulsive	Worse	No
		Bunney-Hamburg global impairment	Bunney-Hamburg global impairment	Worse	Yes

Evidence Table 38. Cognitive function outcomes in studies of sequential monotherapy

Primary Efficacy Study Study Reporting Quality of Life	Drug And Dose (mg/day)	Functional Status / Ability Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Beydoun (1997b) Dodrill (1999)	Gabapentin 2400	Lafayette Grooved Pegboard	Preferred hand	Better	No
		Lafayette Grooved Pegboard	Nonpreferred hand	Better	No
		Stroop Test	Reading speed	Worse	No
		Stroop Test	Reading speed, errors	Better	No
		Stroop Test	Interference	Better	No
		Stroop Test	Interference, errors	Better	No
		Benton Visual Retention Test	Form F	Better	No
		Benton Visual Retention Test	Form G	Better	No
		Controlled Oral Word Association Test	Controlled Oral Word Association Test	Better	No
		Symbol Digit Modalities Test	Symbol Digit Modalities Test	Better	No
		Rey Auditory Verbal Learning Test	Trial 1-5, first list recall	Better	No
		Rey Auditory Verbal Learning Test	Trial 6, second list recall	Worse	No
		Rey Auditory Verbal Learning Test	Trial 7, first list recall	Better	No
		Rey Auditory Verbal Learning Test	Trial 8, first delay recall	Better	No
		Rey Auditory Verbal Learning Test	Trial 9, first delay recognition	Worse	No
		Wonderlic Personnel Test	Items correct	Worse	No
		Wonderlic Personnel Test	items wrong	Worse	No
		Digit Cancellation	Number right	Better	No
		Digit Cancellation	Number omitted	Worse	No

Evidence Table 38. Cognitive function outcomes in studies of sequential monotherapy (continued)

Primary Efficacy Study Study Reporting Quality of Life	Drug And Dose (mg/day)	Functional Status / Ability Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Schachter (1995) Dodrill (1998)	Tiagabine 6 or 36	Lafayette Grooved Pegboard	Preferred hand	Better	Yes
		Lafayette Grooved Pegboard	Nonpreferred hand	Better	No
		Stroop Test	Reading speed	Same	No
		Stroop Test	Reading speed, errors	Better	Yes
		Stroop Test	Interference	Better	No
		Stroop Test	Interference, errors	Better	Yes
		Benton Visual Retention Test	Form F	Better	No
		Benton Visual Retention Test	Form G	Worse	No
		Controlled Oral Word Association Test	Controlled Oral Word Association Test	Better	Yes
		Symbol Digit Modalities Test	Symbol Digit Modalities Test	Better	No
		Rey Auditory Verbal Learning Test	Trial 1-5, first list recall	Worse	No
		Rey Auditory Verbal Learning Test	Trial 6, second list recall	Worse	No
		Rey Auditory Verbal Learning Test	Trial 7, first list recall	Worse	No
		Rey Auditory Verbal Learning Test	Trial 8, first delay recall	Worse	No
		Rey Auditory Verbal Learning Test	Trial 9, first delay recognition	Better	No
		Wonderlic Personnel Test	Items correct	Better	No
		Wonderlic Personnel Test	Items wrong	Worse	No
		Digit Cancellation	Number right	Worse	No
		Digit Cancellation	Number omitted	Worse	No

Evidence Table 39. Scales used to measure quality of life in trials of sequential monotherapy

Reference	Corresponding Primary Efficacy Trial	Trial Drug	Scales Used to Measure Quality of Life	Total Number of Subscales
Dodrill (1999)	Beydoun (1997)	Gabapentin	Washington Psychosocial Seizure Inventory Family background Emotional adjustment Interpersonal adjustment Vocational adjustment Financial status Adjustment to seizures Medicine and medical management Overall functioning Lie scale Rare items	10
Dodrill (1998)	Schachter (1995)	Tiagabine	Same as above	10

Evidence Table 40. Scales used to measure mood in trials of sequential monotherapy

Reference	Corresponding Primary Efficacy Trial	Trial Drug	Scales Used to Measure Mood	Total Number of Subscales
Dodrill (1999)	Beydoun (1997)	Gabapentin	Profile of Mood States: Tension-anxiety Depression-dejection Anger-hostility Vigor-activity Fatigue-inertia Confusion-bewilderment Total mood disturbance Mood Rating Scale	8
Dodrill (1998)	Schachter (1995)	Tiagabine	Same as Dodrill (1999)	8
Ketter (1996)	Theodore (1995)	Felbamate	Zung Anxiety Hamilton Depression Young Mania Brief Psychiatric Rating Scale Clinical Global Impression Bunney-Hamburg ratings: Bunney-Hamburg Anxiety Bunney-Hamburg Depression Bunney-Hamburg Mania Bunney-Hamburg Psychosis Bunney-Hamburg Obsessive compulsive Bunney-Hamburg Global impairment	11

Evidence Table 41. Scales used to measure cognitive function in trials of sequential monotherapy

Reference	Corresponding Primary Efficacy Trial	Trial Drug	Scales Used to Measure Cognitive Function	Total Number of Subscales
Dodrill (1999)	Beydoun (1997)	Gabapentin	Lafayette Grooved Pegboard: Preferred hand Nonpreferred hand Stroop Test: Reading speed Reading speed, errors Interference Interference, errors Benton Visual Retention Test: Form F Form G Controlled Oral Word Association Test Symbol Digit Modalities Test Rey Auditory Verbal Learning Test: Trial 1-5, first list recall Trial 6, second list recall Trial 7, first list recall Trial 8, first delay recall Trial 9, first delay recognition Wonderlic Personnel Test: Items correct items wrong Digit Cancellatio: Number right Number omitted	19
Dodrill (1998)	Schachter (1995)	Tiagabine	Same as above (Dodrill (1999))	19

Evidence Table 42. Mortality in trials of sequential monotherapy

Reference	Drug	Dose (mg/day)	Number of Patients Who Died During The Trial	Percentage
Sachdeo (2001)	Oxcarbazepine	300	1/51	2%
Bergey (1997)	Gabapentin	300	0/42	0%
Bergey (1997)	Gabapentin	3600	0/40	0%
Beydoun (1997a)	Valproate	50 µG/mL	1/47	2%
Beydoun (1997b)	Gabapentin	600	0/94	0%
Beydoun (1997b)	Gabapentin	1200	0/90	0%
Beydoun (1997b)	Gabapentin	2400	0/91	0%
Sachdeo (1997a)	Topiramate	100	0/24	0%
Sachdeo (1997a)	Topiramate	1000	0/24	0%

mg/day Milligrams per day
µG/mL Micrograms per milliliter

Evidence Table 43. General information on studies of polytherapy

Reference	Author Affiliation	Patients	Country	Multicenter
Faught (2001)	University of Alabama School of Medicine, Birmingham, USA	Refractory partial-onset seizures (complex partial or simple partial with an observable motor component, with or without secondary generalization to tonic-clonic seizures)	United States	Yes
Ben-Menachem (2000)	Dr. E. Ben-Menachem, Department of Clinical Neuroscience, Section of Neurology, Sahlgren University Hospital, 413 45 Goteborg, Sweden	Partial seizures despite treatment with one AED	Sweden, Belgium, Czech Republic, Denmark, France, Germany, Hungary, The Netherlands, Norway, Poland, Switzerland, UK	Yes
Betts (2000)	Birmingham University Seizure Clinic, UK	Well-characterized refractory epilepsy and any seizure type	UK, Belgium	Yes
Cereghino (2000)	Oregon Health Sciences University, Portland, OR USA	Uncontrolled partial seizures with or without becoming secondarily generalized	United States	Yes
Glauser (2000)	Children's Hospital, Department of Neurology, Cincinnati, OH 45229, USA	Partial seizures (with or without secondary generalization) that were inadequately controlled with one or two concomitant AEDs	United States, Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel	Yes
Appleton (1999)	Department of Neurology, Alder Hey Children's Hospital, Liverpool, England, UK	History of medically uncontrolled partial seizures with or without secondary generalization	UK, The Netherlands, France, South Africa, Ireland, Italy, Germany, Spain, Switzerland, United States, Hungary, Yugoslavia, Finland, Czech Republic	Yes
Biton (1999)	Arkansas Epilepsy Program, Little Rock 72205, USA	Uncontrolled primary generalized tonic-clonic seizures	United States	Yes
Duchowny (1999)	Miami Children's Hospital, FL 33155-4079, USA	Confirmed diagnosis of partial epilepsy, incompletely controlled by existing therapy	United States, France	Yes
Elterman (1999)	Dallas Pediatric Neurology Associates, TX 75230, USA	Uncontrolled partial onset seizures with or without secondary generalized tonic-clonic seizures in children	United States	Yes
KTSG (1999)	Department of Neurology, Yonsei University College of Medicine, Severance Hospital, CPO Box 8044, Seoul, Korea	Well-established partial epilepsy, medically intractable	Korea	Yes

Evidence Table 43. General information on studies of polytherapy (continued)

Reference	Author Affiliation	Patients	Country	Multicenter
Sachdeo (1999)	Department of Neurology, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick 08903-0019, USA	Lennox-Gastaut syndrome	United States	Yes
Uthman (1998)	Veterans Affairs Medical Center, and the Department of Neurology and Brain Institute, University of Florida College of Medicine, Gainesville 32608, USA	Intractable complex partial seizures, medically refractory	United States	Yes
Sachdeo (1997b)	Department of Neurology, University of Medicine and Dentistry of New Jersey, New Brunswick 08901-2160, USA	Complex partial seizures that are refractory to other treatment	United States	Yes
Ben-Menachem (1996)	Sahlgren University Hospital, Goteborg, Sweden	Patients with refractory partial seizures, with or without secondary generalized seizures	Sweden, Norway, Denmark, Germany	Yes
Chadwick (1996)	Department of Medical and Surgical Neurology, Walton Hospital, Liverpool, UK	Medically uncontrolled generalized seizures despite treatment with one or two standard AEDs	UK, Australia, Sweden	Yes
Faught (1996)	Department of Neurology, University of Alabama School of Medicine, Birmingham 35294-0021, USA	Unequivocal history of partial onset seizures with or without secondary generalized seizures	United States	Yes
Privitera (1996)	Department of Neurology (525), University of Cincinnati Medical Center, OH 45267-0525, USA	History of refractory partial epilepsy with or without secondary generalized seizures	United States	Yes
Sharief (1996)	Institute of Neurology, London, UK	Unequivocal history of partial onset seizures with or without secondary generalized seizures	Sweden, Spain, UK, France	Yes
Tassinari (1996)	Institute of Clinical Neurology, Bellaria Hospital, Bologna, Italy	Documented history of partial seizures with or without secondary generalized seizures	UK, Italy, France, Norway, Denmark	Yes
Willmore (1996)	Department of Neurology, University of Texas, Houston 77030, USA	Complex partial seizures incompletely controlled by either phenytoin or carbamazepine	United States, Canada	Yes
Anhut (1994)	Parke-Davis Pharmaceutical Research, Freiburg, Germany	Partial seizures that failed to respond to standard AED therapy	Australia, France, Canada, Austria, Belgium, Denmark, Finland, South Africa, UK	Yes

Evidence Table 43. General information on studies of polytherapy (continued)

Reference	Author Affiliation	Patients	Country	Multicenter
Messenheimer (1994)	Department of Neurology, University of North Carolina at Chapel Hill 27599	Patients receiving a stable regimen fo AEDs that did not control their partial seizures adequately	United States	Yes
Bourgeois (1993)	Cleveland Clinic Foundation, OH 44195-5221	Refractory partial-onset seizures	United States	Yes
FSG (1993)	Minnesota Epilepsy Group, 310 N. Smith Avenue, Suite 300, St. Paul, MN 55102	Lennox-Gastaut syndrome resistant to standard AEDs	United States	Yes
Matsuo (1993)	Department of Neurology, University of Utah, Salt Lake City 84132	Partial seizures that were refractory to currently marketed AEDs	United States	Yes
McLean (1993)	Department of Neurology, 352 Medical Center South, Vanderbilt University, 2100 Pierce Avenue, Nashville, TN 37212	Documented partial seizures refractory to treatment with currently available AEDs	United States	Yes
Schmidt (1993)	Epilepsy Research Group, Universitatsklinikum Rudolf Virchow, Berlin, Germany.	Refractory partial epilepsy in spite of therapeutic plasma concentrations of standard AEDs	Germany, France, Austria, Switzerland,	Yes
Sivenius (1991)	Department of Neurology, University of Kuopio, Finland	Patients with AED-resistant partial or secondarily generalized epilepsy	Finland	No
UKGSG (1990)	University Department of Neuroscience, Walton Hospital, Liverpool L9 1AE, UK	Partial epilepsy resistant to treatment with one or two standard AEDs	UK	Yes
Jawad (1989)	Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff	Partial seizures uncontrolled by optimal therapy with standard AED therapy	UK	No

Evidence Table 43. General information on studies of polytherapy (continued)

Reference	For-Profit Funding	Minimum Number of AEDs	Minimum Monthly Seizure Frequency	Minimum Duration of Condition	Were Side Effects in The Definition of Treatment-Resistant Epilepsy
Faught (2001)	Yes	1	4	NR	No
Ben-Menachem (2000)	Yes	1	2	1 year	No
Betts (2000)	Yes	1	0.67	NR	No
Cereghino (2000)	Yes	2	4	2 years	No
Glauser (2000)	Yes	1	4	NR	No
Appleton (1999)	Yes	1	2.67	NR	No
Biton (1999)	Yes	1	1.5	NR	No
Duchowny (1999)	Yes	1	4	NR	No
Elterman (1999)	Yes	1	3	NR	No
KTSG (1999)	Yes	1	2	NR	No
Sachdeo (1999)	Yes	1	60	NR	No
Uthman (1998)	Yes	1	2.67	NR	No
Sachdeo (1997b)	Yes	1	3	NR	No
Ben-Menachem (1996)	Yes	1	4	NR	No
Chadwick (1996)	Yes	1	4	NR	No
Faught (1996)	Yes	1	4	NR	No
Privitera (1996)	Yes	1	4	NR	No
Sharief (1996)	Yes	1	4	NR	No
Tassinari (1996)	Yes	1	4	NR	No
Willmore (1996)	Yes	1	4	NR	No
Anhut (1994)	Yes	1	4	NR	No
Messenheimer (1994)	Yes	1	4	32 weeks	No
Bourgeois (1993)	Yes	1	28	NR	No
FSG (1993)	Yes	1	90	NR	No
Matsuo (1993)	No	1	4	NR	No
McLean (1993)	Yes	1	4	NR	No
Schmidt (1993)	No	1	4	NR	No
Sivenius (1991)	No	1	4	NR	No
UKGSG (1990)	Yes	1	4	NR	No
Jawad (1989)	Yes	1	4	NR	No

Evidence Table 44. Design characteristics of studies of polytherapy

Reference	Prospective	Randomized	Type of Control	Study Reported Maximum Tolerable Dose of Prior Drugs	Required Good Compliance to Prior Drugs	All Patients Seen During Presurgical Evaluation	Patients Continued to Take Their Pre-Study Drugs
Faught (2001)	Yes	Yes	Placebo	No	No	No	Yes
Ben-Menachem (2000)	Yes	Yes	Placebo	No	Yes	No	Yes
Betts (2000)	Yes	Yes	Placebo	No	No	No	Yes
Cereghino (2000)	Yes	Yes	Placebo	No	No	No	Yes
Glauser (2000)	Yes	Yes	Placebo	No	Yes	No	Yes
Appleton (1999)	Yes	Yes	Placebo	No	No	No	Yes
Biton (1999)	Yes	Yes	Placebo	No	No	No	Yes
Duchowny (1999)	Yes	Yes	Placebo	No	Yes	No	Yes
Elterman (1999)	Yes	Yes	Placebo	No	No	No	Yes
KTSG (1999)	Yes	Yes	Placebo	Yes	Yes	No	Yes
Sachdeo (1999)	Yes	Yes	Placebo	No	Yes	No	Yes
Uthman (1998)	Yes	Yes	Placebo	No	No	No	Yes
Sachdeo (1997b)	Yes	Yes	Placebo	No	No	No	Yes
Ben-Menachem (1996)	Yes	Yes	Placebo	No	Yes	No	Yes
Chadwick (1996)	Yes	Yes	Placebo	No	No	No	Yes
Faught (1996)	Yes	Yes	Placebo	Yes	Yes	No	Yes
Privitera (1996)	Yes	Yes	Placebo	No	Yes	No	Yes
Sharief (1996)	Yes	Yes	Placebo	No	No	No	Yes
Tassinari (1996)	Yes	Yes	Placebo	No	No	No	Yes
Willmore (1996)	Yes	Yes	Placebo	No	Yes	No	Yes
Anhut (1994)	Yes	Yes	Placebo	Yes	No	No	Yes
Messenheimer (1994)	Yes	Yes	Placebo	No	Yes	No	Yes
Bourgeois (1993)	Yes	Yes	Placebo	No	Yes	Yes	No

Evidence Table 44. Design characteristics of studies of polytherapy (continued)

Reference	Prospective	Randomized	Type of Control	Study Reported Maximum Tolerable Dose of Prior Drugs	Required Good Compliance to Prior Drugs	All Patients Seen During Presurgical Evaluation	Patients Continued to Take Their Pre-Study Drugs
FSG (1993)	Yes	Yes	Placebo	No	Yes	No	Yes
Matsuo (1993)	Yes	Yes	Placebo	No	Yes	No	Yes
McLean (1993)	Yes	Yes	Placebo	No	No	No	Yes
Schmidt (1993)	Yes	Yes	Placebo	No	No	No	Yes
Sivenius (1991)	Yes	Yes	Placebo	No	Yes	No	Yes
UKGSG (1990)	Yes	Yes	Placebo	No	No	No	Yes
Jawad (1989)	Yes	Yes	Placebo	No	Yes	No	Yes

Evidence Table 44. Design characteristics of studies of polytherapy (continued)

Reference	Patients Received a Placebo During The Baseline	Patients Blinded	Observers Blinded	Length of Baseline (Weeks)	Length of Titration Period (Weeks)	Length of Maintenance Period (Weeks)	Plasma Levels Monitored
Faught (2001)	Yes	Yes	Yes	4	7	5	Yes
Ben-Menachem (2000)	No	Yes	Yes	12	4	12	Yes
Betts (2000)	No	Yes	Yes	1 to 4	0	24	Yes
Cereghino (2000)	Yes	Yes	Yes	12	4	14	Yes
Glauser (2000)	No	Yes	Yes	8	2	14	Yes
Appleton (1999)	No	Yes	Yes	6	3 days	11	Yes
Biton (1999)	No	Yes	Yes	8	8	12	Yes
Duchowny (1999)	No	Yes	Yes	8	6	12	Yes
Elterman (1999)	No	Yes	Yes	8	8	8	Yes
KTSG (1999)	No	Yes	Yes	12	10	8	Yes
Sachdeo (1999)	No	Yes	Yes	4	3	8	Yes
Uthman (1998)	No	Yes	Yes	12	4	12	Yes
Sachdeo (1997b)	No	Yes	Yes	8	4	8	Yes
Ben-Menachem (1996)	No	Yes	Yes	8	5	8	Yes
Chadwick (1996)	No	Yes	Yes	12	2	12	Yes
Faught (1996)	No	Yes	Yes	12	4	12	Yes
Privitera (1996)	No	Yes	Yes	12	6	12	Yes
Sharief (1996)	No	Yes	Yes	8	3	8	Yes
Tassinari (1996)	No	Yes	Yes	8	4	8	Yes
Willmore (1996)	Yes	Yes	Yes	16	8	8	Yes
Anhut (1994)	No	Yes	Yes	12	2 days	12	Yes
Messenheimer (1994)	No	Yes	Yes	8	4	10	Yes
Bourgeois (1993)	No	Yes	Yes	4	1 day	4	Yes
FSG (1993)	No	Yes	Yes	4	2	8	Yes
Matsuo (1993)	No	Yes	Yes	12	3 to 5	19 to 21	Yes

Evidence Table 44. Design characteristics of studies of polytherapy (continued)

Reference	Patients Received a Placebo During The Baseline	Patients Blinded	Observers Blinded	Length of Baseline (Weeks)	Length of Titration Period (Weeks)	Length of Maintenance Period (Weeks)	Plasma Levels Monitored
McLean (1993)	No	Yes	Yes	12	2 or 3 days	12	Yes
Schmidt (1993)	No	Yes	Yes	8 to 12	4	8	Yes
Sivenius (1991)	No	Yes	Yes	13	2 days	13	Yes
UKGSG (1990)	No	Yes	Yes	13	2	12	Yes
Jawad (1989)	No	Yes	Yes	8	4	8	Yes

Evidence Table 45. Reporting characteristics of trials of polytherapy

Reference	Seizure Types	Seizure Diaries Used	Reporting							
			Individual Patient Data	Baseline Seizure Freq.	Seizure Freq.	Adverse Effects	Quality of Life	Functional Status / Ability	Return to Work	Return to School
Faught (2001)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Ben-Menachem (2000)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Betts (2000)	Generalized and partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Cereghino (2000)	Partial	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Glauser (2000)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Appleton (1999)	Generalized and partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Biton (1999)	Generalized	Yes	No	Yes	Yes	Yes	No	No	No	No
Duchowny (1999)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Elterman (1999)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
KTSG (1999)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Sachdeo (1999)	Generalized	Yes	No	Yes	Yes	Yes	No	No	No	No
Uthman (1998)	Partial	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
Sachdeo (1997b)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Ben-Menachem (1996)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Chadwick (1996)	Generalized	Yes	No	Yes	Yes	Yes	No	No	No	No
Faught (1996)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No

Evidence Table 45. Reporting characteristics of trials of polytherapy (continued)

Reference	Seizure Types	Seizure Diaries Used	Reporting							
			Individual Patient Data	Baseline Seizure Freq.	Seizure Freq.	Adverse Effects	Quality of Life	Functional Status / Ability	Return to Work	Return to School
Privitera (1996)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Sharief (1996)	Generalized and partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Tassinari (1996)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Willmore (1996)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Anhut (1994)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Messenheimer (1994)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Bourgeois (1993)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
FSG (1993)	Generalized	Yes	No	Yes	Yes	Yes	No	No	No	No
Matsuo (1993)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
McLean (1993)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Schmidt (1993)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Sivenius (1991)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
UKGSG (1990)	Partial	Yes	No	Yes	Yes	Yes	No	No	No	No
Jawad (1989)	Partial	Yes	Yes	No	Yes	No	No	No	No	No

Freq. Frequency

Evidence Table 46. Drug characteristics in studies of polytherapy

Reference	Name of Drug Given to This Group of Patients	Mechanism(s) of Action[a]	Minimum Dose (mg/day)	Maximum Dose (mg/day)	Highest Dose in The Study	Lowest Dose in The Study
Faught (2001)	Placebo	NA	NA	NA	Yes	Yes
	Zonisamide	Sodium, Calcium	NR	400	Yes	Yes
Ben-Menachem (2000)	Placebo	NA	NA	NA	Yes	Yes
	Levetiracetam	Unknown	3000	3000	Yes	Yes
Betts (2000)	Placebo	NA	NA	NA	Yes	Yes
	Levetiracetam	Unknown	2000	2000	No	Yes
	Levetiracetam	Unknown	4000	4000	Yes	No
Cereghino (2000)	Placebo	NA	NA	NA	Yes	Yes
	Levetiracetam	Unknown	1000	1000	No	Yes
	Levetiracetam	Unknown	3000	3000	Yes	No
Glauser (2000)	Placebo	NA	NA	NA	Yes	Yes
	Oxcarbazepine	Sodium	900	1800	Yes	Yes
Appleton (1999)	Placebo	NA	NA	NA	Yes	Yes
	Gabapentin	Inhibitory	600	1800	Yes	Yes
Biton (1999)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	150	400	Yes	Yes
Duchowny (1999)	Placebo	NA	NA	NA	Yes	Yes
	Lamotrigine	Sodium	150	750	Yes	Yes
Elterman (1999)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	125	400	Yes	Yes
KTSG (1999)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	200	600	Yes	Yes

Evidence Table 46. Drug characteristics in studies of polytherapy (continued)

Reference	Name of Drug Given to This Group of Patients	Mechanism(s) of Action[a]	Minimum Dose (mg/day)	Maximum Dose (mg/day)	Highest Dose in The Study	Lowest Dose in The Study
Sachdeo (1999)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	600	Yes	Yes
	Placebo	NA	NA	NA	Yes	Yes
	Tiagabine	Inhibitory	16	16	No	Yes
	Tiagabine	Inhibitory	32	32	No	No
	Tiagabine	Inhibitory	56	56	Yes	No
Sachdeo (1997b)	Placebo	NA	NA	NA	Yes	Yes
	Tiagabine	Inhibitory	24	32	No	Yes
	Tiagabine	Inhibitory	24	32	Yes	No
Ben-Menachem (1996)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	800	Yes	Yes
Chadwick (1996)	Placebo	NA	NA	NA	Yes	Yes
	Gabapentin	Inhibitory	1200	1200	Yes	Yes
Faught (1996)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	200	200	No	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	400	No	No
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	600	Yes	No
Privitera (1996)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	600	No	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	800	No	No
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	1000	Yes	No
Sharief (1996)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	400	Yes	Yes

Evidence Table 46. Drug characteristics in studies of polytherapy (continued)

Reference	Name of Drug Given to This Group of Patients	Mechanism(s) of Action[a]	Minimum Dose (mg/day)	Maximum Dose (mg/day)	Highest Dose in The Study	Lowest Dose in The Study
Tassinari (1996)	Placebo	NA	NA	NA	Yes	Yes
	Topiramate	Sodium, Calcium, Inhibitory, Excitatory	NR	600	Yes	Yes
Willmore (1996)	Placebo	NA	NA	NA	Yes	Yes
	Valproate	Inhibitory	NR	90 mg/kg	Yes	Yes
Anhut (1994)	Placebo	NA	NA	NA	Yes	Yes
	Gabapentin	Inhibitory	900	900	No	Yes
	Gabapentin	Inhibitory	1200	1200	Yes	No
Messenheimer (1994)	Placebo	NA	NA	NA	Yes	Yes
	Lamotrigine	Sodium	100	400	Yes	Yes
Bourgeois (1993)	Placebo	NA	NA	NA	Yes	Yes
	Felbamate	Sodium, Inhibitory, Excitatory	NR	3600	Yes	Yes
FSG (1993)	Placebo	NA	NA	NA	Yes	Yes
	Felbamate	Sodium, Inhibitory, Excitatory	NR	3600	Yes	Yes
Matsuo (1993)	Placebo	NA	NA	NA	Yes	Yes
	Lamotrigine	Sodium	200	300	No	Yes
	Lamotrigine	Sodium	400	500	Yes	No
McLean (1993)	Placebo	NA	NA	NA	Yes	Yes
	Gabapentin	Inhibitory	NR	600	No	Yes
	Gabapentin	Inhibitory	NR	1200	No	No
	Gabapentin	Inhibitory	NR	1800	Yes	No
Schmidt (1993)	Placebo	NA	NA	NA	Yes	Yes
	Zonisamide	Sodium, Calcium	1.5 mg/kg	20 mg/kg	Yes	Yes
Sivenius (1991)	Placebo	NA	NA	NA	Yes	Yes
	Gabapentin	Inhibitory	900	900	Yes	Yes
UKGSG (1990)	Placebo	NA	NA	NA	Yes	Yes
	Gabapentin	Inhibitory	1200	1200	Yes	Yes
Jawad (1989)	Placebo	NA	NA	NA	Yes	Yes
	Lamotrigine	Sodium	75	400	Yes	Yes

[a] The mechanism(s) of drug action were based on Table 3 of Gilliam (2002).
mg/kg Milligrams per kilogram
NA Not applicable

Evidence Table 47. Numbers of patients and attrition in studies of polytherapy

Reference	Drug And Dose (mg/day)	Number of Patients						Patient Characteristics Reported For Those Who Started or Completed The Study
		Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics	
Faught (2001)	Placebo	85	NR	7	NR	72[a]	85	Started
	Zonisamide 400	118	NR	14	NR	85[a]	118	Started
Ben-Menachem (2000)	Placebo	105	1	9	5[a]	90	105	Started
	Levetiracetam 3000	181	3	17	12[a]	149	181	Started
Betts (2000)	Placebo	39	NR	6	NR	29	39	Started
	Levetiracetam 2000	42	NR	11	NR	28	42	Started
	Levetiracetam 4000	38	NR	5	NR	29	38	Started
Cereghino (2000)	Placebo	95	NR	5	NR	89	95	Started
	Levetiracetam 1000	98	NR	6	NR	86	98	Started
	Levetiracetam 3000	101	NR	7	NR	93	101	Started
Glauser (2000)	Placebo	129	4	4	2[a]	119	129	Started
	Oxcarbazepine 1800	138	0	14	4	117	138	Started
Appleton (1999)	Placebo	128	19	3	6[a]	100	128	Started
	Gabapentin 1800	119	11	6	4[a]	98	119	Started
Biton (1999)	Placebo	41	NR	1	NR	38	41	Started
	Topiramate 400	39	NR	1	NR	34	39	Started
Duchowny (1999)	Placebo	101	8	6	4[a]	83	101	Started
	Lamotrigine 750	98	6	5	2	84	98	Started
Elterman (1999)	Placebo	45	NR	1	NR	43	45	Started
	Topiramate 400	41	0	0	0	41	41	Started

Evidence Table 47. Numbers of patients and attrition in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients						Patient Characteristics Reported For Those Who Started or Completed The Study
		Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics	
KTSG (1999)	Placebo	86	NR	3	NR	77	86	Started
	Topiramate 600	91	NR	7	NR	76	91	Started
Sachdeo (1999)	Placebo	50	0	0	0	50	50	Started
	Topiramate 600	48	NR	0	NR	47	48	Started
Uthman (1998)	Placebo	91	6	7	0	78	91	Started
	Tiagabine 16	61	2	4	0	55	61	Started
	Tiagabine 32	88	1	13	4[a]	70	88	Started
	Tiagabine 56	57	5	9	3[a]	40	57	Started
Sachdeo (1997b)	Placebo	107	1	7	2[a]	97	107	Started
	Tiagabine 32	105	1	8	12[a]	84	105	Started
	Tiagabine 32	106	1	13	2[a]	90	106	Started
Ben-Menachem (1996)	Placebo	28	0	0	0	28	28	Started
	Topiramate 800	28	0	6	0	22	28	Started
Chadwick (1996)	Placebo	71	0	6	0	65	71	Started
	Gabapentin 1200	58	0	4	0	54	58	Started
Faught (1996)	Placebo	45	0	7	0	38[a]	45	Started
	Topiramate 200	45	0	4	0	41[a]	45	Started
	Topiramate 400	45	0	9	0	36[a]	45	Started
	Topiramate 600	46	0	13	0	33[a]	46	Started

Evidence Table 47. Numbers of patients and attrition in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients						Patient Characteristics Reported For Those Who Started or Completed The Study
		Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics	
Privitera (1996)	Placebo	47	0	1	0	46[a]	47	Started
	Topiramate 600	48	0	10	0	38[a]	48	Started
	Topiramate 800	48	0	5	0	43[a]	48	Started
	Topiramate 1000	47	0	8	0	39[a]	47	Started
Sharief (1996)	Placebo	24	NR	1	NR	22	24	Started
	Topiramate 400	23	0	6	0	17	23	Started
Tassinari (1996)	Placebo	30	0	1	1[a]	28	30	Started
	Topiramate 600	30	1	3	1[a]	25	30	Started
Willmore (1996)	Placebo	70	3	1	6[a]	60	70	Started
	Valproate 90 mg/kg	77	0	5	4[a]	68	77	Started
Anhut (1994)	Placebo	109	2	4	4[a]	99	109	Started
	Gabapentin 900	111	1	9	5[a]	96	111	Started
	Gabapentin 1200	52	0	2	0	50	52	Started
Messenheimer (1994)	Placebo	48	2	1	1[a]	44	44	Completed
	Lamotrigine 400	50	NR	5	NR	44	44	Completed
Bourgeois (1993)	Placebo	34	0	0	1[a]	33	34	Started
	Felbamate 3600	30	0	2	0	28	30	Started
FSG (1993)	Placebo	36	0	1	0	35	36	Started
	Felbamate 3600	37	0	1	0	36	37	Started

Evidence Table 47. Numbers of patients and attrition in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients						Patient Characteristics Reported For Those Who Started or Completed The Study
		Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics	
Matsuo (1993)	Placebo	73	NR	1	NR	67	73	Started
	Lamotrigine 300	71	NR	3	NR	65	71	Started
	Lamotrigine 500	72	NR	10	NR	59	72	Started
McLean (1993)	Placebo	98	NR	1	NR	95	98	Started
	Gabapentin 600	53	NR	3	NR	49	53	Started
	Gabapentin 1200	101	NR	2	NR	91	101	Started
	Gabapentin 1800	54	0	2	0	52	54	Started
Schmidt (1993)	Placebo	68	0	0	4[a]	64	68	Started
	Zonisamide 20 mg/kg	71	1	1	2[a]	67	71	Started
Sivenius (1991)	Placebo	18	0	0	0	18	18	Started
	Gabapentin 900	16	0	0	0	16	16	Started
UKGSG (1990)	Placebo	66	1	3	1[a]	61	66	Started
	Gabapentin 1200	61	1	6	2[a]	52	61	Started
Jawad (1989)	Placebo	12	0	1	0	11	11	Completed
	Lamotrigine 400	12	NR	1	NR	10	10	Completed

[a] Calculated by ECRI based on reported information
mg/kg Milligrams per kilogram

Evidence Table 48. Age, gender, and duration of condition of patients in studies of polytherapy

Reference	Drug And Dose (mg/day)	Age Mean	Age SD	Age Minimum	Age Maximum	Number of Males	Number of Females	Mean Duration of Epilepsy	SD Duration	Median Duration of Epilepsy
Faught (2001)	Placebo	34.2[a]	11.4	14	67	35	50	22[a]	11.8[a]	NR
	Zonisamide 400	34.7[a]	11.3[a]	13	68	69	49	22.2[a]	10.8[a]	NR
Ben-Menachem (2000)	Placebo	36	12	NR	NR	51	54	19	12	NR
	Levetiracetam 3000	37	12	NR	NR	87	94	19	11	NR
Betts (2000)	Placebo	35	12	NR	NR	24	15	26	13.2	NR
	Levetiracetam 2000	39	13	NR	NR	29	13	21.1	14.4	NR
	Levetiracetam 4000	40	12	NR	NR	20	18	24.6	15.6	NR
Cereghino (2000)	Placebo	38	11	NR	NR	50	45	24.6[b]	12.0[b]	NR
	Levetiracetam 1000	38	11	NR	NR	62	36	23.8[b]	12.7[b]	NR
	Levetiracetam 3000	38	11	NR	NR	66	35	24.9[b]	12.1[b]	NR
Glauser (2000)	Placebo	11	NR	3	17	71	58	NR	NR	NR
	Oxcarbazepine 1800	11	NR	3	17	70	68	NR	NR	NR
Appleton (1999)	Placebo	8.4	2.5	3	12	75	53	5.4	3.1	NR
	Gabapentin 1800	8.5	2.6	3	12	59	60	5.7	3.0	NR
Biton (1999)	Placebo	25.6	13.4	3	50	21	20	NR	NR	NR
	Topiramate 400	26.8	12.8	5	59	24	15	NR	NR	NR
Duchowny (1999)	Placebo	7.6[d]	NR	NR	NR	56	45	NR	NR	NR
	Lamotrigine 750	8.2[d]	NR	NR	NR	47	51	NR	NR	NR
Elterman (1999)	Placebo	9	3.4	2	16	25	20	NR	NR	NR
	Topiramate 400	8.8	3.6	2	16	23	18	NR	NR	NR

Evidence Table 48. Age, gender, and duration of condition of patients in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Age Mean	Age SD	Age Minimum	Age Maximum	Number of Males	Number of Females	Mean Duration of Epilepsy	SD Duration	Median Duration of Epilepsy
KTSG (1999)	Placebo	29.8	8.71	NR	NR	48	38	17.5	8.2	NR
	Topiramate 600	29.6	7.8	NR	NR	47	44	15	8.8	NR
Sachdeo (1999)	Placebo	11.2	7.7	2	42	25	25	NR	NR	NR
	Topiramate 600	11.2	6.2	2	29	28	20	NR	NR	NR
Uthman (1998)	Placebo	34[c]	NR	12[c]	77[c]	53[c]	38[c]	NR	NR	22.9[c]
	Tiagabine 16	34[c]	NR	12[c]	77[c]	35[c]	26[c]	NR	NR	22.9[c]
	Tiagabine 32	34[c]	NR	12[c]	77[c]	51[c]	37[c]	NR	NR	22.9[c]
	Tiagabine 56	34[c]	NR	12[c]	77[c]	33[c]	24[c]	NR	NR	22.9[c]
Sachdeo (1997b)	Placebo	35.3	NR	NR	NR	54	53	24	NR	NR
	Tiagabine 32	32.6	NR	NR	NR	60	45	22	NR	NR
	Tiagabine 32	33.4	NR	NR	NR	65	41	18	NR	NR
Ben-Menachem (1996)	Placebo	37.2[c]	NR	18[c]	65[c]	24[c]	4[c]	NR	NR	NR
	Topiramate 800	37.2[c]	NR	18[c]	65[c]	24[c]	4[c]	NR	NR	NR
Chadwick (1996)	Placebo	29	NR	13	61	28	43	20	NR	NR
	Gabapentin 1200	30	NR	16	62	27	31	22	NR	NR
Faught (1996)	Placebo	36.2	NR	19	68	36	9	NR	NR	NR
	Topiramate 200	38.6	NR	19	67	29	19	NR	NR	NR
	Topiramate 400	38.9	NR	19	61	39	6	NR	NR	NR
	Topiramate 600	33.8	NR	20	58	39	7	NR	NR	NR

Evidence Table 48. Age, gender, and duration of condition of patients in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Age Mean	Age SD	Age Minimum	Age Maximum	Number of Males	Number of Females	Mean Duration of Epilepsy	SD Duration	Median Duration of Epilepsy
Privitera (1996)	Placebo	35	NR	18	68	33	14	NR	NR	NR
	Topiramate 600	35.6	NR	18	57	38	10	NR	NR	NR
	Topiramate 800	34.3	NR	18	67	41	7	NR	NR	NR
	Topiramate 1000	36.3	NR	18	64	40	7	NR	NR	NR
Sharief (1996)	Placebo	32.6	11.1	NR	NR	19	5	NR	NR	NR
	Topiramate 400	35.4	14	NR	NR	21	2	NR	NR	NR
Tassinari (1996)	Placebo	32.9[c]	NR	18[c]	65[c]	20[c]	10[c]	NR	NR	NR
	Topiramate 600	32.9[c]	NR	18[c]	65[c]	20[c]	10[c]	NR	NR	NR
Willmore (1996)	Placebo	32[c]	NR	NR	NR	29[c]	41[c]	19[c]	NR	NR
	Valproate 90 mg/kg	32[c]	NR	NR	NR	32[c]	45[c]	19[c]	NR	NR
Anhut (1994)	Placebo	32[c]	NR	12[c]	67[c]	61[c]	48[c]	NR	NR	19
	Gabapentin 900	32[c]	NR	12[c]	67[c]	62[c]	49[c]	NR	NR	19
	Gabapentin 1200	32[c]	NR	12[c]	67[c]	29[c]	23[c]	NR	NR	22
Messenheimer (1994)	Placebo	35	NR	18	64	20	24	24	NR	NR
	Lamotrigine 400	35	NR	18	58	21	23	22.3	NR	NR
Bourgeois (1993)	Placebo	33.3	NR	17	49	20	14	NR	NR	NR
	Felbamate 3600	33.3	NR	18	51	18	12	NR	NR	NR
FSG (1993)	Placebo	14	NR	4	36	24	12	NR	NR	NR
	Felbamate 3600	12	NR	4	24	27	10	NR	NR	NR
Matsuo (1993)	Placebo	34	NR	18	63	22	51	21.5	NR	NR
	Lamotrigine 300	33	NR	20	57	30	41	22.4	NR	NR
	Lamotrigine 500	32	NR	18	59	15	57	21.8	NR	NR

Evidence Table 48. Age, gender, and duration of condition of patients in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Age Mean	Age SD	Age Minimum	Age Maximum	Number of Males	Number of Females	Mean Duration of Epilepsy	SD Duration	Median Duration of Epilepsy
McLean (1993)	Placebo	34	NR	17	66	69	29	NR	NR	22
	Gabapentin 600	34	NR	16	67	36	17	NR	NR	20
	Gabapentin 1200	35	NR	19	65	60	41	NR	NR	21
	Gabapentin 1800	35	NR	18	70	37	17	NR	NR	21
Schmidt (1993)	Placebo	33.4	NR	NR	NR	40	28	20.9	NR	NR
	Zonisamide 20 mg/kg	36.2	NR	NR	NR	41	30	23.5	NR	NR
Sivenius (1991)	Placebo	39[c]	NR	16[c]	59[c]	8[c]	10[c]	NR	NR	23[c]
	Gabapentin 900	39[c]	NR	16[c]	59[c]	7[c]	9[c]	NR	NR	23[c]
UKGSG (1990)	Placebo	31	NR	14	73	29	37	NR	NR	19
	Gabapentin 1200	30	NR	15	62	24	37	NR	NR	17
Jawad (1989)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Lamotrigine 400	NR	NR	NR	NR	NR	NR	NR	NR	NR

[a] Calculated by ECRI based on reported information
[b] Information obtained from a secondary publication.
[c] Reported only for the entire patient group, not separately for different groups.
[d] Estimated by ECRI using the method of Chene.
mg/kg milligrams per kilogram

Evidence Table 49. Baseline seizure frequencies in studies of polytherapy

Reference	Drug And Dose (mg/day)	Baseline Seizure Frequency					
		Seizure Type	Mean	SD	Median	Minimum	Maximum
Faught (2001)	Placebo	Partial	NR	NR	13	NR	NR
	Zonisamide 400	Partial	NR	NR	12.1[a]	NR	NR
Ben-Menachem (2000)	Placebo	Partial	NR	NR	7.5	NR	NR
	Levetiracetam 3000	Partial	NR	NR	7.3	NR	NR
Betts (2000)	Placebo	Partial	NR	NR	5.4[a]	NR	NR
	Levetiracetam 2000	Partial	NR	NR	5.3[a]	NR	NR
	Levetiracetam 4000	Partial	NR	NR	5.8[a]	NR	NR
Cereghino (2000)	Placebo	Partial	5.7[b] week	18.8[b] week	7.6[a]	NR	NR
	Levetiracetam 1000	Partial	7.6[b] week	14[b] week	10.9[a]	NR	NR
	Levetiracetam 3000	Partial	5.2[b] week	15.6[b] week	8.9[a]	NR	NR
Glauser (2000)	Placebo	Partial	NR	NR	13	2	554
	Oxcarbazepine 1800	Partial	NR	NR	12	3	1470
Appleton (1999)	Placebo	Partial	63.3	103.8	28	1.3	698
	Gabapentin 1800	Partial	74.5	268.3	24.1	2.7	2893
Biton (1999)	Placebo	Generalized	NR	NR	17.5	2	79,109
	Topiramate 400	Generalized	NR	NR	15.3	1	1134
Duchowny (1999)	Placebo	Partial	NR	NR	10	NR	NR
	Lamotrigine 750	Partial	NR	NR	7.5	NR	NR
Elterman (1999)	Placebo	Partial	NR	NR	19	2	1133
	Topiramate 400	Partial	NR	NR	22	2	232
KTSG (1999)	Placebo	Partial	11.5	2.4	5.6	NR	NR
	Topiramate 600	Partial	9.4	14.8	5.6	NR	NR
Sachdeo (1999)	Placebo	Generalized and partial	NR	NR	244	7	4324
	Topiramate 600	Generalized and partial	NR	NR	267	13	3795

Evidence Table 49. Baseline seizure frequencies in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Baseline Seizure Frequency					
		Seizure Type	Mean	SD	Median	Minimum	Maximum
Uthman (1998)	Placebo	Complex partial	NR	NR	7.4	2.8	109
	Tiagabine 16	Complex partial	NR	NR	8.5	2.6	170
	Tiagabine 32	Complex partial	NR	NR	9.6	2.2	401
	Tiagabine 56	Complex partial	NR	NR	9.1	2.1	209
Sachdeo (1997b)	Placebo	Complex partial	NR	NR	8[a]	NR	NR
	Tiagabine 32	Complex partial	NR	NR	8[a]	NR	NR
	Tiagabine 32	Complex partial	NR	NR	8.5[a]	NR	NR
Ben-Menachem (1996)	Placebo	Partial	NR	NR	11.4	NR	NR
	Topiramate 800	Partial	NR	NR	14.2	NR	NR
Chadwick (1996)	Placebo	Generalized tonic-clonic	7.3	NR	3.3	0	103.3
	Gabapentin 1200	Generalized tonic-clonic	7.4	NR	3.9	0	54.3
Faught (1996)	Placebo	Partial	16	NR	10	NR	NR
	Topiramate 200	Partial	31.3	NR	11.5	NR	NR
	Topiramate 400	Partial	33	NR	11	NR	NR
	Topiramate 600	Partial	23.6	NR	11.2	NR	NR
Privitera (1996)	Placebo	Partial	18.2	NR	9.3	NR	NR
	Topiramate 600	Partial	23.5	NR	10	NR	NR
	Topiramate 800	Partial	39.8	NR	16.2	NR	NR
	Topiramate 1000	Partial	24.7	NR	11.7	NR	NR
Sharief (1996)	Placebo	Partial	23.6	34.5	10	NR	NR
	Topiramate 400	Partial	33.4	52.6	18	NR	NR
Tassinari (1996)	Placebo	Partial	NR	NR	15	4	925
	Topiramate 600	Partial	NR	NR	16.8	4	230
Willmore (1996)	Placebo	Complex partial	29.4	32.8	16	NR	NR
	Valproate 90 mg/kg	Complex partial	27.1	40.4	15.2	NR	NR
Anhut (1994)	Placebo	Partial	NR	NR	9.3	NR	NR
	Gabapentin 900	Partial	NR	NR	10.3	NR	NR
	Gabapentin 1200	Partial	NR	NR	9.8	NR	NR
Messenheimer (1994)	Placebo	Partial	NR	NR	12.3	NR	NR
	Lamotrigine 400	Partial	NR	NR	13.3	NR	NR

Evidence Table 49. Baseline seizure frequencies in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Baseline Seizure Frequency					
		Seizure Type	Mean	SD	Median	Minimum	Maximum
Bourgeois (1993)	Placebo	Partial	13.8	NR	NR	NR	NR
	Felbamate 3600	Partial	19.4	NR	NR	NR	NR
FSG (1993)	Placebo	Generalized	19.9	NR	NR	NR	NR
	Felbamate 3600	Generalized	43.7	NR	NR	NR	NR
Matsuo (1993)	Placebo	Partial	NR	NR	12.7	NR	NR
	Lamotrigine 300	Partial	NR	NR	12	NR	NR
	Lamotrigine 500	Partial	NR	NR	12.7	NR	NR
McLean (1993)	Placebo	Partial	31.1	NR	10.7	2.3	455
	Gabapentin 600	Partial	21.7	NR	10	2	271.7
	Gabapentin 1200	Partial	51.7	NR	11	2.3	1092.7
	Gabapentin 1800	Partial	31.5	NR	12.7	3.7	207.8
Schmidt (1993)	Placebo	Complex partial	9.7	NR	NR	NR	NR
	Zonisamide 20 mg/kg	Complex partial	10	NR	NR	NR	NR
Sivenius (1991)	Placebo	Partial	NR	NR	36	NR	NR
	Gabapentin 900	Partial	NR	NR	26	NR	NR
UKGSG (1990)	Placebo	Partial	NR	NR	13	1	216
	Gabapentin 1200	Partial	NR	NR	13	3	368
Jawad (1989)	Placebo	NR	NR	NR	NR	NR	NR
	Lamotrigine 400	NR	NR	NR	NR	NR	NR

[a] Calculated by ECRI based on reported information
[b] Information obtained from a secondary publication.
mg/kg milligrams per kilogram

Evidence Table 50. Specific types of generalized seizures in studies of polytherapy

Reference	Drug And Dose (mg/day)	Any Generalized Seizures	Numbers of Patients With Specific Types of Generalized Seizures									
			Tonic-Clonic	Tonic	Atonic	Myoclonic	Absence	Atypical Absence	Lennox-Gastaut Syndrome	Clonic	West Syndrome	Other Generalized Seizures
Faught (2001)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Zonisamide 400	0	0	0	0	0	0	0	0	0	0	0
Ben-Menachem (2000)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Levetiracetam 3000	0	0	0	0	0	0	0	0	0	0	0
Betts (2000)	Placebo	16	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Levetiracetam 2000	17	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Levetiracetam 4000	17	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cereghino (2000)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Levetiracetam 1000	0	0	0	0	0	0	0	0	0	0	0
	Levetiracetam 3000	0	0	0	0	0	0	0	0	0	0	0
Glauser (2000)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Oxcarbazepine 1800	0	0	0	0	0	0	0	0	0	0	0
Appleton (1999)	Placebo	0	13	11	9	12	2	7	0	2	0	0
	Gabapentin 1800	0	15	8	8	16	0	7	0	2	0	0
Biton (1999)	Placebo	41	40	10	0	8	16	4	0	1	0	0
	Topiramate 400	39	39	9	0	8	16	2	0	1	0	0
Duchowny (1999)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Lamotrigine 750	0	0	0	0	0	0	0	0	0	0	0
Elterman (1999)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 400	0	0	0	0	0	0	0	0	0	0	0

Evidence Table 50. Specific types of generalized seizures in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Any Generalized Seizures	Numbers of Patients With Specific Types of Generalized Seizures									
			Tonic-Clonic	Tonic	Atonic	Myoclonic	Absence	Atypical Absence	Lennox-Gastaut Syndrome	Clonic	West Syndrome	Other Generalized Seizures
KTSG (1999)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 600	0	0	0	0	0	0	0	0	0	0	0
Sachdeo (1999)	Placebo	50	0	0	0	0	0	0	50	0	0	0
	Topiramate 600	48	0	0	0	0	0	0	48	0	0	0
Uthman (1998)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Tiagabine 16	0	0	0	0	0	0	0	0	0	0	0
	Tiagabine 32	0	0	0	0	0	0	0	0	0	0	0
	Tiagabine 56	0	0	0	0	0	0	0	0	0	0	0
Sachdeo (1997b)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Tiagabine 32	0	0	0	0	0	0	0	0	0	0	0
	Tiagabine 32	0	0	0	0	0	0	0	0	0	0	0
Ben-Menachem (1996)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 800	0	0	0	0	0	0	0	0	0	0	0
Chadwick (1996)	Placebo	71	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Gabapentin 1200	58	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Faught (1996)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 200	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 400	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 600	0	0	0	0	0	0	0	0	0	0	0

Evidence Table 50. Specific types of generalized seizures in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Any Generalized Seizures	Numbers of Patients With Specific Types of Generalized Seizures									
			Tonic-Clonic	Tonic	Atonic	Myoclonic	Absence	Atypical Absence	Lennox-Gastaut Syndrome	Clonic	West Syndrome	Other Generalized Seizures
Privitera (1996)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 600	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 800	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 1000	1	1	0	0	0	0	0	0	0	0	0
Sharief (1996)	Placebo	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topiramate 400	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tassinari (1996)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Topiramate 600	0	0	0	0	0	0	0	0	0	0	0
Willmore (1996)	Placebo	0	51[b]	0	0	NR	4[b]	0	0	0	0	0
	Valproate 90 mg/kg	0	56[b]	0	0	NR	5[b]	0	0	0	0	0
Anhut (1994)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 900	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 1200	0	0	0	0	0	0	0	0	0	0	0
Messenheimer (1994)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Lamotrigine 400	0	0	0	0	0	0	0	0	0	0	0
Bourgeois (1993)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Felbamate 3600	0	0	0	0	0	0	0	0	0	0	0
FSG (1993)	Placebo	36	13	0	22	0	0	0	36	0	0	0
	Felbamate 3600	37	16	0	28	0	0	0	37	0	0	0

Evidence Table 50. Specific types of generalized seizures in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Any Generalized Seizures	Numbers of Patients With Specific Types of Generalized Seizures									
			Tonic-Clonic	Tonic	Atonic	Myoclonic	Absence	Atypical Absence	Lennox-Gastaut Syndrome	Clonic	West Syndrome	Other Generalized Seizures
Matsuo (1993)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Lamotrigine 300	0	0	0	0	0	0	0	0	0	0	0
	Lamotrigine 500	0	0	0	0	0	0	0	0	0	0	0
McLean (1993)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 600	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 1200	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 1800	0	0	0	0	0	0	0	0	0	0	0
Schmidt (1993)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Zonisamide 20 mg/kg	0	0	0	0	0	0	0	0	0	0	0
Sivenius (1991)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 900	0	0	0	0	0	0	0	0	0	0	0
UKGSG (1990)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Gabapentin 1200	0	0	0	0	0	0	0	0	0	0	0
Jawad (1989)	Placebo	0	0	0	0	0	0	0	0	0	0	0
	Lamotrigine 400	0	0	0	0	0	0	0	0	0	0	0

[a] Calculated by ECRI based on reported information
[b] Reported only for the entire patient group, not separately for different groups.
mg/kg Milligrams per kilogram

Evidence Table 51. Specific types of partial seizures seizures in studies of polytherapy

Reference	Drug And Dose (mg/day)	Any Partial Seizures	Numbers of Patients With Specific Types of Partial Seizures		
			Complex Partial	Simple Partial	Secondarily Generalized
Faught (2001)	Placebo	85	81	4	20
	Zonisamide 400	118	114[a]	4[a]	26[a]
Ben-Menachem (2000)	Placebo	105	105	NR	NR
	Levetiracetam 3000	181	181	NR	NR
Betts (2000)	Placebo	19	NR	NR	NR
	Levetiracetam 2000	20	NR	NR	NR
	Levetiracetam 4000	19	NR	NR	NR
Cereghino (2000)	Placebo	95	NR	NR	NR
	Levetiracetam 1000	98	NR	NR	NR
	Levetiracetam 3000	101	NR	NR	NR
Glauser (2000)	Placebo	129	NR	NR	57
	Oxcarbazepine 1800	138	NR	NR	50
Appleton (1999)	Placebo	128	112	58	70
	Gabapentin 1800	119	99	54	73
Biton (1999)	Placebo	0	0	0	0
	Topiramate 400	0	0	0	0
Duchowny (1999)	Placebo	101	NR	NR	NR
	Lamotrigine 750	98	NR	NR	NR
Elterman (1999)	Placebo	45	37	12	17
	Topiramate 400	41	31	11	17
KTSG (1999)	Placebo	86	72	5	39
	Topiramate 600	91	70	11	31
Sachdeo (1999)	Placebo	0	0	0	0
	Topiramate 600	0	0	0	0
Uthman (1998)	Placebo	91	90	51	38[a]
	Tiagabine 16	61	61	39	32[a]
	Tiagabine 32	88	86	49	37[a]
	Tiagabine 56	57	55	33	29[a]

Evidence Table 51. Specific types of partial seizures in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Any Partial Seizures	Numbers of Patients With Specific Types of Partial Seizures		
			Complex Partial	Simple Partial	Secondarily Generalized
Sachdeo (1997b)	Placebo	107	107	NR	NR
	Tiagabine 32	105	105	NR	NR
	Tiagabine 32	106	106	NR	NR
Ben-Menachem (1996)	Placebo	28	NR	NR	NR
	Topiramate 800	28	NR	NR	NR
Chadwick (1996)	Placebo	0	0	0	0
	Gabapentin 1200	0	0	0	0
Faught (1996)	Placebo	45	39	20	34
	Topiramate 200	45	42	18	27
	Topiramate 400	45	43	21	26
	Topiramate 600	46	43	26	32
Privitera (1996)	Placebo	47	44	19	36
	Topiramate 600	48	46	22	29
	Topiramate 800	48	42	22	33
	Topiramate 1000	47	45	27	21
Sharief (1996)	Placebo	24	23	7	16
	Topiramate 400	23	20	9	19
Tassinari (1996)	Placebo	30	NR	NR	NR
	Topiramate 600	30	NR	NR	NR
Willmore (1996)	Placebo	70	70	33[b]	NR
	Valproate 90 mg/kg	77	77	36[b]	NR
Anhut (1994)	Placebo	109	98	40	58
	Gabapentin 900	111	99	42	61
	Gabapentin 1200	52	48	23	31
Messenheimer (1994)	Placebo	44	NR	NR	NR
	Lamotrigine 400	44	NR	NR	NR
Bourgeois (1993)	Placebo	34	NR	NR	NR
	Felbamate 3600	30	NR	NR	NR

Evidence Table 51. Specific types of partial seizures in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Any Partial Seizures	Numbers of Patients With Specific Types of Partial Seizures		
			Complex Partial	Simple Partial	Secondarily Generalized
FSG (1993)	Placebo	0	0	0	0
	Felbamate 3600	0	0	0	0
Matsuo (1993)	Placebo	73	NR	NR	NR
	Lamotrigine 300	71	NR	NR	NR
	Lamotrigine 500	72	NR	NR	NR
McLean (1993)	Placebo	98	NR	NR	NR
	Gabapentin 600	53	NR	NR	NR
	Gabapentin 1200	101	NR	NR	NR
	Gabapentin 1800	54	NR	NR	NR
Schmidt (1993)	Placebo	68	NR	NR	NR
	Zonisamide 20 mg/kg	71	NR	NR	NR
Sivenius (1991)	Placebo	18	17	0	8
	Gabapentin 900	16	15	1	9
UKGSG (1990)	Placebo	66	NR	NR	NR
	Gabapentin 1200	61	NR	NR	NR
Jawad (1989)	Placebo	11[a]	8[a]	0[a]	10[a]
	Lamotrigine 400	10[a]	9[a]	1[a]	5[a]

[a] Calculated by ECRI based on reported information
[b] Reported only for the entire patient group, not separately for different groups.
mg/kg Milligrams per kilogram

Evidence Table 52. Known etiology and prior AEDs use in studies of polytherapy

Reference	Drug And Dose (mg/day)	Number of Patients			
		Known Etiology	One AED Prior to The Study	Two AEDs Prior to The Study	Three or More AEDs Prior to The Study
Faught (2001)	Placebo	NR	NR	NR	0
	Zonisamide 400	NR	NR	NR	0
Ben-Menachem (2000)	Placebo	52	105	0	0
	Levetiracetam 3000	74	181	0	0
Betts (2000)	Placebo	15	NR	NR	NR
	Levetiracetam 2000	13	NR	NR	NR
	Levetiracetam 4000	18	NR	NR	NR
Cereghino (2000)	Placebo	NR	25	67	3
	Levetiracetam 1000	NR	35	57	6
	Levetiracetam 3000	NR	36	59	6
Glauser (2000)	Placebo	NR	NR	NR	NR
	Oxcarbazepine 1800	NR	NR	NR	NR
Appleton (1999)	Placebo	NR	44	57	27
	Gabapentin 1800	NR	31	58	30
Biton (1999)	Placebo	NR	NR	NR	NR
	Topiramate 400	NR	NR	NR	NR
Duchowny (1999)	Placebo	60	NR	NR	0
	Lamotrigine 750	61	NR	NR	0
Elterman (1999)	Placebo	NR	25	20	1
	Topiramate 400	NR	15	25	1
KTSG (1999)	Placebo	NR	16	70	0
	Topiramate 600	NR	22	69	0
Sachdeo (1999)	Placebo	NR	20	29	1
	Topiramate 600	NR	19	27	2
Uthman (1998)	Placebo	NR	NR	NR	NR
	Tiagabine 16	NR	NR	NR	NR
	Tiagabine 32	NR	NR	NR	NR
	Tiagabine 56	NR	NR	NR	NR

Evidence Table 52. Known etiology and prior AEDs use in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients			
		Known Etiology	One AED Prior to The Study	Two AEDs Prior to The Study	Three or More AEDs Prior to The Study
Sachdeo (1997b)	Placebo	NR	NR	NR	NR
	Tiagabine 32	NR	NR	NR	NR
	Tiagabine 32	NR	NR	NR	NR
Ben-Menachem (1996)	Placebo	NR	11[b]	17[b]	0
	Topiramate 800	NR	11[b]	17[b]	0
Chadwick (1996)	Placebo	NR	15	37	18
	Gabapentin 1200	NR	11	36	11
Faught (1996)	Placebo	NR	16	29	0
	Topiramate 200	NR	15	30	0
	Topiramate 400	NR	16	29	0
	Topiramate 600	NR	16	30	0
Privitera (1996)	Placebo	NR	25	22	0
	Topiramate 600	NR	23	25	0
	Topiramate 800	NR	22	26	0
	Topiramate 1000	NR	16	31	0
Sharief (1996)	Placebo	NR	NR	NR	NR
	Topiramate 400	NR	NR	NR	NR
Tassinari (1996)	Placebo	NR	NR	NR	NR
	Topiramate 600	NR	NR	NR	NR
Willmore (1996)	Placebo	NR	70	0	0
	Valproate 90 mg/kg	NR	77	0	0
Anhut (1994)	Placebo	NR	26[b]	74[b]	9[b]
	Gabapentin 900	NR	27[b]	75[b]	9[b]
	Gabapentin 1200	NR	12[b]	35[b]	5[b]
Messenheimer (1994)	Placebo	NR	16	27	1
	Lamotrigine 400	NR	20	23	1
Bourgeois (1993)	Placebo	NR	NR	NR	NR
	Felbamate 3600	NR	NR	NR	NR
FSG (1993)	Placebo	NR	NR	NR	NR
	Felbamate 3600	NR	NR	NR	NR

Evidence Table 52. Known etiology and prior AEDs use in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients			
		Known Etiology	One AED Prior to The Study	Two AEDs Prior to The Study	Three or More AEDs Prior to The Study
Matsuo (1993)	Placebo	NR	36	33	4
	Lamotrigine 300	NR	21	45	5
	Lamotrigine 500	NR	29	36	7
McLean (1993)	Placebo	NR	30	68	0
	Gabapentin 600	NR	21	32	0
	Gabapentin 1200	NR	34	66	1
	Gabapentin 1800	NR	28	26	0
Schmidt (1993)	Placebo	NR	NR	NR	NR
	Zonisamide 20 mg/kg	NR	NR	NR	NR
Sivenius (1991)	Placebo	9[b]	9[b]	9[b]	0
	Gabapentin 900	8[b]	8[b]	8[b]	0
UKGSG (1990)	Placebo	NR	21	43	2
	Gabapentin 1200	NR	20	38	2
Jawad (1989)	Placebo	NR	1[a]	10[a]	0[a]
	Lamotrigine 400	NR	3[a]	7[a]	0[a]

[a] Calculated by ECRI based on reported information
[b] Reported only for the entire patient group, not separately for different groups.
>0 At least one patient had received the drug, but study did not report the number of patients who received the drug.
mg/kg milligrams per kilogram

Evidence Table 53. Prior drugs in studies of polytherapy

Reference	Drug And Dose (mg/day)	Number of Patients Receiving Specific Prior Drugs								
		Carbamazepine	Clonzaepam	Felbamate	Gabapentin	Lamotrigine	Phenytoin	Phenobarbital	Primidone	Valproate
Faught (2001)	Placebo	>0	NR	NR	NR	NR	>0	>0	>0	>0
	Zonisamide 400	>0	NR	NR	NR	NR	>0	>0	>0	>0
Ben-Menachem (2000)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Levetiracetam 3000	NR	NR	NR	NR	NR	NR	NR	NR	NR
Betts (2000)	Placebo	>0	NR	NR	NR	NR	>0	>0	NR	>0
	Levetiracetam 2000	>0	NR	NR	NR	NR	>0	>0	NR	>0
	Levetiracetam 4000	>0	NR	NR	NR	NR	>0	>0	NR	>0
Cereghino (2000)	Placebo	59	3	0	24	4	29	7	9	28
	Levetiracetam 1000	52	1	0	35	3	37	9	2	24
	Levetiracetam 3000	56	2	0	24	5	36	10	9	26
Glauser (2000)	Placebo	55	NR	NR	NR	29	22	NR	NR	31
	Oxcarbazepine 1800	27	NR	NR	NR	22	21	NR	NR	23
Appleton (1999)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Gabapentin 1800	NR	NR	NR	NR	NR	NR	NR	NR	NR
Biton (1999)	Placebo	9	6	0	0	0	13	3	6	20
	Topiramate 400	11	6	0	0	0	12	8	0	19
Duchowny (1999)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Lamotrigine 750	NR	NR	NR	NR	NR	NR	NR	NR	NR
Elterman (1999)	Placebo	26	0	0	0	0	9	0	0	10
	Topiramate 400	25	0	0	0	0	6	0	0	10
KTSG (1999)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topiramate 600	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sachdeo (1999)	Placebo	NR	NR	8	NR	NR	NR	NR	NR	NR
	Topiramate 600	NR	NR	7	NR	NR	NR	NR	NR	NR
Uthman (1998)	Placebo	61	0	0	0	0	19	8	9	21
	Tiagabine 16	36	0	0	0	0	24	7	6	13
	Tiagabine 32	55	0	0	0	0	18	13	12	24
	Tiagabine 56	28	0	0	0	0	19	3	10	9

Evidence Table 53. Prior drugs in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients Receiving Specific Prior Drugs								
		Carbamazepine	Clonzaepam	Felbamate	Gabapentin	Lamotrigine	Phenytoin	Phenobarbital	Primidone	Valproate
Sachdeo (1997b)	Placebo	68	NR	NR	NR	NR	31	NR	NR	34
	Tiagabine 32	62	NR	NR	NR	NR	33	NR	NR	41
	Tiagabine 32	69	NR	NR	NR	NR	34	NR	NR	30
Ben-Menachem (1996)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topiramate 800	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chadwick (1996)	Placebo	>0	NR	NR	NR	NR	>0	NR	NR	>0
	Gabapentin 1200	>0	NR	NR	NR	NR	>0	NR	NR	>0
Faught (1996)	Placebo	36	NR	NR	NR	NR	16	NR	NR	NR
	Topiramate 200	33	NR	NR	NR	NR	16	NR	NR	NR
	Topiramate 400	30	NR	NR	NR	NR	17	NR	NR	NR
	Topiramate 600	36	NR	NR	NR	NR	19	NR	NR	NR
Privitera (1996)	Placebo	30	NR	NR	NR	NR	17	NR	NR	NR
	Topiramate 600	36	NR	NR	NR	NR	15	NR	NR	NR
	Topiramate 800	33	NR	NR	NR	NR	13	NR	NR	NR
	Topiramate 1000	35	NR	NR	NR	NR	21	NR	NR	NR
Sharief (1996)	Placebo	16	1	0	0	0	10	5	2	4
	Topiramate 400	16	1	0	0	0	8	6	3	3
Tassinari (1996)	Placebo	21	0	0	0	0	5	10	3	1
	Topiramate 600	20	0	0	0	0	11	8	5	2
Willmore (1996)	Placebo	53[b]	0	0	0	0	17[b]	0	0	0
	Valproate 90 mg/kg	59[b]	0	0	0	0	18[b]	0	0	0
Anhut (1994)	Placebo	82[b]	NR	NR	NR	NR	31[b]	>0	NR	34[b]
	Gabapentin 900	83[b]	NR	NR	NR	NR	31[b]	>0	NR	34[b]
	Gabapentin 1200	39[b]	NR	NR	NR	NR	15[b]	>0	NR	16[b]
Messenheimer (1994)	Placebo	33	NR	NR	NR	NR	22	NR	NR	NR
	Lamotrigine 400	33	NR	NR	NR	NR	23	NR	NR	NR
Bourgeois (1993)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Felbamate 3600	NR	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 53. Prior drugs in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Number of Patients Receiving Specific Prior Drugs								
		Carbamazepine	Clonzaepam	Felbamate	Gabapentin	Lamotrigine	Phenytoin	Phenobarbital	Primidone	Valproate
FSG (1993)	Placebo	NR	NR	NR	NR	NR	>0	NR	NR	>0
	Felbamate 3600	NR	NR	NR	NR	NR	>0	NR	NR	>0
Matsuo (1993)	Placebo	61	NR	NR	NR	NR	21	NR	NR	NR
	Lamotrigine 300	50	NR	NR	NR	NR	32	NR	NR	NR
	Lamotrigine 500	55	NR	NR	NR	NR	24	NR	NR	NR
McLean (1993)	Placebo	79	NR	NR	NR	NR	40	NR	NR	21
	Gabapentin 600	39	NR	NR	NR	NR	23	NR	NR	8
	Gabapentin 1200	79	NR	NR	NR	NR	36	NR	NR	21
	Gabapentin 1800	41	NR	NR	NR	NR	18	NR	NR	13
Schmidt (1993)	Placebo	>0	0	0	0	0	>0	>0	>0	>0
	Zonisamide 20 mg/kg	>0	0	0	0	0	>0	>0	>0	>0
Sivenius (1991)	Placebo	16[b]	6[b]	0	0	0	1[b]	0	0	3[b]
	Gabapentin 900	14[b]	5[b]	0	0	0	1[b]	0	0	3[b]
UKGSG (1990)	Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Gabapentin 1200	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jawad (1989)	Placebo	10[a]	0	0	0	0	5[a]	1[a]	5[a]	0
	Lamotrigine 400	8[a]	0	0	0	0	2[a]	0	6[a]	1[a]

[a] Calculated by ECRI based on reported information
[b] Reported only for the entire patient group, not separately for different groups.
>0 At least one patient had received the drug, but study did not report the number of patients who received the drug.
mg/kg milligrams per kilogram

Evidence Table 54. Tests of potential selection bias in studies of polytherapy

Reference	Mean Age		Proportion Female		Duration of Condition		Baseline Seizure Frequency		Proportion With					
									Partial Seizures		Known Etiology		1,2 or 3 Prior AEDs	
	Test	p	Test	p	Test	p	Test	p	Test	p	Test	p	Test	p
Faught (2001)	t(201) = 0.04	0.96	$\chi^2(1)$ = 5.917	0.015	t(201) = 0.018	0.99	NC	NC	NC	NC	NC	NC	NC	NC
Ben-Menachem (2000)	t(284) = 0.08	0.93	$\chi^2(1)$ = 0.007	0.93	t(284) = 0	1	NC	NC	NC	NC	$\chi^2(1)$ = 2.012	0.16	NC	NC
Betts (2000)	F(2, 116) = 1.78	0.17	$\chi^2(2)$ = 2.268	0.32	F(2, 116) = 1.250	0.29	NC	NC	$\chi^2(2)$ = 0.019	0.99	$\chi^2(2)$ = 2.268	0.32	NC	NC
Cereghino (2000)	F(2, 291) = 0	1	$\chi^2(2)$ = 3.769	0.15	F(2, 291) = 0.212	0.81	NC	NC	NC	NC	NC	NC	$\chi^2(4)$ = 4.316	0.37
Glauser (2000)	NC	NC	$\chi^2(1)$ = 0.498	0.48	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Appleton (1999)	t(245) = 0.04	0.97	$\chi^2(1)$ = 2.019	0.16	t(245) = 0.098	0.92	t(245) = 0.056	0.96	NC	NC	NC	NC	$\chi^2(2)$ = 2.095	0.35
Biton (1999)	t(78) = 0.09	0.93	$\chi^2(1)$ = 0.865	0.35	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Duchowny (1999)	NC	NC	$\chi^2(1)$ = 1.116	0.29	NC	NC	NC	NC	NC	NC	$\chi^2(1)$ = 0.168	0.68	NC	NC
Elterman (1999)	t(84) = 0.06	0.95	$\chi^2(1)$ = 0.003	0.96	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(2)$ = 2.78	0.25
KTSG (1999)	t(175) = 0.02	0.98	$\chi^2(1)$ = 0.309	0.58	t(175) = 0.294	0.77	t(175) = 0.195	0.85	NC	NC	NC	NC	$\chi^2(1)$ = 0.814	0.37
Sachdeo (1999)	t(96) = 0	1	$\chi^2(1)$ = 0.685	0.41	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(2)$ = 0.390	0.82

Evidence Table 54. Tests of potential selection bias in studies of polytherapy (continued)

Reference	Mean Age		Proportion Female		Duration of Condition		Baseline Seizure Frequency		Proportion With					
									Partial Seizures		Known Etiology		1,2 or 3 Prior AEDs	
	Test	p	Test	p	Test	p	Test	p	Test	p	Test	p	Test	p
Uthman (1998)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Sachdeo (1997b)	NC	NC	$\chi^2(2) = 2.596$	0.27	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Ben-Menachem (1996)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Chadwick (1996)	NC	NC	$\chi^2(1) = 0.661$	0.42	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(2) = 1.204$	0.55
Faught (1996)	NC	NC	NC[a]	NC[a]	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(3) = 0.065$	0.99
Privitera (1996)	NC	NC	$\chi^2(3) = 4.481$	0.21	NC	NC	NC	NC	$\chi^2(3) = 2.995$	0.39	NC	NC	$\chi^2(3) = 3.724$	0.29
Sharief (1996)	$t(45) = 0.22$	0.83	$\chi^2(1) = 1.365$	0.24	NC	NC	$t(45) = 0.221$	0.83	$\chi^2(1) = 0.503$	0.48	NC	NC	NC	NC
Tassinari (1996)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Willmore (1996)	NC	NC	NC	NC	NC	NC	$t(145) = 0.062$	0.95	NC	NC	NC	NC	NC	NC
Anhut (1994)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
FSG (1993)	NC	NC	$\chi^2(1) = 0.345$	0.56	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Matsuo (1993)	NC	NC	$\chi^2(2) = 7.706$	0.021	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(4) = 6.838$	0.15
McLean (1993)	NC	NC	$\chi^2(3) = 3.046$	0.38	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(6) = 9.42$	0.15

Evidence Table 54. Tests of potential selection bias in studies of polytherapy (continued)

Reference	Mean Age		Proportion Female		Duration of Condition		Baseline Seizure Frequency		Proportion With					
									Partial Seizures		Known Etiology		1,2 or 3 Prior AEDs	
	Test	p	Test	p	Test	p	Test	p	Test	p	Test	p	Test	p
Schmidt (1993)	NC	NC	$\chi^2(1) = 0.017$	0.90	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Sivenius (1991)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
UKGSG (1990)	NC	NC	$\chi^2(1) = 0.275$	0.60	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(2) = 0.047$	0.98
Messenheimer (1994)	NC	NC	$\chi^2(1) = 0.046$	0.83	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(2) = 0.764$	0.68
Bourgeois (1993)	NC	NC	$\chi^2(1) = 0.009$	0.92	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC
Jawad (1989)	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	NC	$\chi^2(1) = 1.485$	0.22

[a] There was an error in the publication by Faught (1996) with respect to the numbers of males and females in the group that received topiramate 200 mg/day, thus we could not test for potential gender selection bias in that study.
NC Not calculable

Evidence Table 55. Overall test of age selection bias in trials of polytherapy

Reference	N	Summary Effect Size Hedges' d (CI)[a]	p-value	Standardized Residual	Outlier by Standard Residual	Greatest Outlier by Q
Faught (2001)	203	-0.04 (-0.32 to 0.23)	0.76	0.08	No	NA
Ben-Menachem (2000)	286	-0.08 (-0.32 to 0.16)	0.5	-0.25	No	NA
Betts (2000)	119	-0.36 (-0.75 to 0.03)	0.07	-1.6	No	NA
Cereghino (2000)	294	0 (-0.24 to 0.24)	1	0.48	No	NA
Appleton (1999)	247	-0.04 (-0.29 to 0.21)	0.76	0.14	No	NA
Biton (1999)	80	-0.09 (-0.53 to 0.35)	0.69	-0.16	No	NA
Elterman (1999)	86	0.06 (-0.37 to 0.48)	0.79	0.53	No	NA
KTSG (1999)	177	0.02 (-0.27 to 0.32)	0.87	0.56	No	NA
Sachdeo (1999)	98	0 (-0.4 to 0.4)	1	0.28	No	NA
Sharief (1996)	47	-0.22 (-0.79 to 0.36)	0.46	-0.57	No	NA
Fixed Effects Summary Effect Size (Hedges' d)		**-0.06 (-0.15 to 0.04)**	**0.277**			
Test of Homogeneity[b]		**Q=3.62**	**0.935**			
Random Effects Summary Effect Size (Hedges' d)		**-0.06 (-0.15 to 0.04)**	**0.277**			

[a] A positive effect size indicates that the mean age of patients in the add-on placebo group(s) was higher than the mean age of patients in the add-on drug group(s). The finding that the summary effect size was not different from zero indicates that there was no age bias in assignment of patients to groups.
[b] Critical Q = 14.68 (df = 9)
NA Not applicable

Evidence Table 56. Overall test of gender selection bias in studies of polytherapy

Reference	N	Summary Effect Size Hedges' d (CI)[a]	p-value	Standardized Residual	Outlier by Standard Residual	Greatest Outlier by Q
Faught (2001)	203	0.35 (0.07 to 0.63)	0.01	2.21	Yes	NA
Ben-Menachem (2000)	286	-0.01 (-0.25 to 0.23)	0.93	-0.44	No	NA
Betts (2000)	119	-0.01 (-0.39 to 0.38)	0.98	-0.25	No	NA
Cereghino (2000)	294	0.24 (-0.01 to 0.48)	0.06	1.63	No	NA
Glauser (2000)	267	-0.09 (-0.33 to 0.15)	0.48	-1.09	No	NA
Appleton (1999)	247	-0.18 (-0.43 to 0.07)	0.15	-1.81	No	NA
Biton (1999)	80	0.21 (-0.23 to 0.65)	0.35	0.75	No	NA
Duchowny (1999)	199	-0.15 (-0.43 to 0.13)	0.29	-1.39	No	NA
Elterman (1999)	86	0.01 (-0.41 to 0.43)	0.96	-0.14	No	NA
KTSG (1999)	177	-0.08 (-0.38 to 0.21)	0.58	-0.85	No	NA
Sachdeo (1999)	98	0.17 (-0.23 to 0.56)	0.41	0.63	No	NA
Sachdeo (1997b)	318	0.18 (-0.06 to 0.41)	0.14	1.19	No	NA
Chadwick (1996)	129	0.14 (-0.2 to 0.49)	0.42	0.59	No	NA
Privitera (1996)	190	0.31 (-0.02 to 0.64)	0.06	1.63	No	NA
Sharief (1996)	47	0.35 (-0.22 to 0.92)	0.23	1.06	No	NA
Messenheimer (1994)	88	0.05 (-0.37 to 0.46)	0.83	0.02	No	NA
Bourgeois (1993)	64	0.02 (-0.47 to 0.51)	0.92	-0.07	No	NA
FSG (1993)	73	0.14 (-0.32 to 0.6)	0.56	0.41	No	NA
Matsuo (1993)	216	0.03 (-0.25 to 0.31)	0.84	-0.09	No	NA
McLean (1993)	306	-0.14 (-0.38 to 0.1)	0.26	-1.52	No	NA
Schmidt (1993)	139	-0.02 (-0.35 to 0.31)	0.9	-0.38	No	NA
UKGSG (1990)	127	-0.09 (-0.44 to 0.25)	0.6	-0.77	No	NA
Fixed Effects Summary Effect Size (Hedges' d)		**0.04 (-0.03 to 0.11)**	**0.217**			
Test of Homogeneity[b]		**Q = 23.32**	**0.327**			
Random Effects Summary Effect Size (Hedges' d)		**0.04 (-0.03 to 0.11)**	**0.229**			

[a] A positive effect size indicates that the proportion of females was greater in the placebo group than in the drug groups. The finding that the summary effect size was not different from zero indicates that there was no gender bias in assignment of patients to groups.
[b] Critical Q = 32.7 (df = 21)
NA Not applicable

Evidence Table 57. Overall test of duration of condition selection bias in trials of polytherapy

Reference	N	Summary Effect Size Hedges' d (CI)[a]	p-value	Standardized Residual	Outlier by Standard Residual	Greatest Outlier by Q
Faught (2001)	203	-0.02 (-0.3 to 0.26)	0.9	-0.45	No	NA
Ben-Menachem (2000)	286	0 (-0.24 to 0.24)	1	-0.38	No	NA
Betts (2000)	119	0.22 (-0.16 to 0.61)	0.25	0.97	No	NA
Cereghino (2000)	294	0.02 (-0.22 to 0.26)	0.88	-0.2	No	NA
Appleton (1999)	247	-0.1 (-0.35 to 0.15)	0.44	-1.22	No	NA
KTSG (1999)	177	0.29 (0 to 0.59)	0.05	1.79	No	NA
Fixed Effects Summary Effect Size (Hedges' d)		**0.04 (-0.07 to 0.15)**	**0.463**			
Test of Homogeneity[b]		**Q = 5.13**	**0.400**			
Random Effects Summary Effect Size (Hedges' d)		**0.04 (-0.07 to 0.15)**	**0.463**			

[a] A positive effect size indicates that the mean duration of condition of patients in the add-on placebo group(s) was higher than the mean duration of condition of patients in the add-on drug group(s). The finding that the summary effect size was not different from zero indicates that there was no duration of condition bias in assignment of patients to groups.
[b] Critical Q = 9.24 (df = 5)
NA Not applicable

Evidence Table 58. Overall test of prior drug selection bias in trials of polytherapy

Reference	N	Summary Effect Size Hedges' d (CI)[a]	p-value	Standardized Residual	Outlier by Standard Residual	Greatest Outlier by Q
Cereghino (2000)	294	0.2 (-0.04 to 0.45)	0.1	1.81	No	NA
Appleton (1999)	247	-0.18 (-0.43 to 0.07)	0.15	-1.47	No	NA
Elterman (1999)	87	-0.36 (-0.78 to 0.06)	0.09	-1.68	No	NA
KTSG (1999)	177	0.14 (-0.16 to 0.43)	0.37	1	No	NA
Sachdeo (1999)	98	-0.01 (-0.4 to 0.39)	0.97	-0.01	No	NA
Chadwick (1996)	128	-0.06 (-0.41 to 0.29)	0.73	-0.32	No	NA
Faught (1996)	181	-0.02 (-0.36 to 0.32)	0.9	-0.08	No	NA
Privitera (1996)	190	-0.21 (-0.54 to 0.12)	0.21	-1.26	No	NA
Messenheimer (1994)	88	0.19 (-0.23 to 0.6)	0.39	0.92	No	NA
Matsuo (1993)	216	-0.29 (-0.57 to -0.01)	0.04	-2.09	Yes	NA
McLean (1993)	306	0.19 (-0.05 to 0.44)	0.11	1.77	No	NA
UKGSG (1990)	126	0.03 (-0.32 to 0.38)	0.86	0.23	No	NA
Jawad (1989)	21	0.55 (-0.31 to 1.4)	0.21	1.27	No	NA
Fixed Effects Summary Effect Size (Hedges' d)		**-0.01 (-0.10 to 0.08)**	**0.878**			
Test of Homogeneity[b]		**Q=18.98**	**0.089**			
Random Effects Summary Effect Size (Hedges' d)		**-0.01 (-0.13 to 0.10)**	**0.839**			

[a] A positive effect size indicates that the mean age of patients in the add-on placebo group(s) was higher than the mean age of patients in the add-on drug group(s). The finding that the summary effect size was not different from zero indicates that there was no prior-drug bias in assignment of patients to groups.
[b] Critical Q = 18.55 (df = 12)
NA Not applicable

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Faught (2001)	Placebo	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	72	85	16
	Zonisamide 400	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	98	118	41
	Placebo	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	72	85	7[c]
	Zonisamide 400	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	98	118	20[c]
	Placebo	MTN	PAR	PAR	Number of patients seizure free	72	85	2
	Zonisamide 400	MTN	PAR	PAR	Number of patients seizure free	98	118	6
	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	72	85	9
	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	85	85	5.6
	Zonisamide 400	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	118	118	32.3
	Zonisamide 400	Subset of MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	98	118	40.5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Ben-Menachem (2000)	Placebo	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	102	105	17[c]
	Levetiracetam 3000	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	171	181	72[c]
	Placebo	MTN	PAR	PAR	Number of patients seizure free	102	105	1
	Levetiracetam 3000	MTN	PAR	PAR	Number of patients seizure free	171	181	14
	Placebo	MTN	PAR	PAR	Median monthly seizure frequency	102	105	7.5[c]
	Levetiracetam 3000	MTN	PAR	PAR	Median monthly seizure frequency	171	181	4.6[c]
	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	102	105	7.2
	Levetiracetam 3000	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	171	181	39.9
	Placebo	MTN	PAR	PAR	Number needed to treat to yield one patient with 50% reduction	102	105	3.9 CI: 2.8-6.6
	Levetiracetam 3000	MTN	PAR	PAR	Number needed to treat to yield one patient with 50% reduction	171	181	3.9 CI: 2.8-6.6
	Placebo	MTN	PAR	PAR	Number needed to treat to yield one patient seizure free	102	105	13.9 CI: 8.5-37.4
	Levetiracetam 3000	MTN	PAR	PAR	Number needed to treat to yield one patient seizure free	171	181	13.9 CI: 8.5-37.4

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Betts (2000)	Placebo	MTN	ALL	ALL	Number of patients with 50% or more seizure reduction	31	39	5
	Levetiracetam 2000	MTN	ALL	ALL	Number of patients with 50% or more seizure reduction	27	42	13
	Levetiracetam 4000	MTN	ALL	ALL	Number of patients with 50% or more seizure reduction	28	38	8
	Placebo	MTN	ALL	ALL	Number of patients seizure free	39	39	1
	Levetiracetam 2000	MTN	ALL	ALL	Number of patients seizure free	42	42	4
	Levetiracetam 4000	MTN	ALL	ALL	Number of patients seizure free	38	38	2
	Placebo	MTN	ALL	ALL	Median monthly seizure frequency	31	39	6[c]
	Levetiracetam 2000	MTN	ALL	ALL	Median monthly seizure frequency	27	42	2.7[c]
	Levetiracetam 4000	MTN	ALL	ALL	Median monthly seizure frequency	28	38	2.5[c]
	Placebo	MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	15	16	5.6
	Levetiracetam 2000	MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	15	17	66.7
	Levetiracetam 4000	MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	17	17	46.8
	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	19	19	19.8
	Levetiracetam 2000	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	17	20	41.2
	Levetiracetam 4000	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	17	19	43.4

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Cereghino (2000)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	95	95	7[c]
	Placebo	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	93	95	10
	Levetiracetam 1000	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	98	98	26[c]
	Levetiracetam 1000	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	94	98	31
	Levetiracetam 3000	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	98	101	39
	Levetiracetam 3000	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	101	101	40[c]
	Placebo	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	93	95	1
	Levetiracetam 1000	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	94	98	12
	Levetiracetam 3000	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	98	101	20
	Placebo	MTN	PAR	PAR	Number of patients seizure free	93	95	0
	Levetiracetam 1000	MTN	PAR	PAR	Number of patients seizure free	94	98	3
	Levetiracetam 3000	MTN	PAR	PAR	Number of patients seizure free	98	101	8
	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	93	95	6.8
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	93	95	6.9

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to - Treat	Outcome[b] And Dispersion
Cereghino (2000) continued	Levetiracetam 1000	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	94	98	32.5
	Levetiracetam 1000	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	98	98	36.9
	Levetiracetam 3000	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	98	101	37.1
	Levetiracetam 3000	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	101	101	38.1
Glauser (2000)	Placebo	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	93	NR	10
	Oxcarbazepine 1800	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	108	NR	42
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	128	129	28[c]
	Oxcarbazepine 1800	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	135	138	55[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	128	129	1
	Oxcarbazepine 1800	TTR & MTN	PAR	PAR	Number of patients seizure free	135	138	5
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	128	129	9
	Oxcarbazepine 1800	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	136	138	35

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to -Treat	Outcome[b] And Dispersion
Glauser (2000) continued	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	57	57	33
	Oxcarbazepine 1800	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	48	50	78
	Placebo	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	44	NR	16
	Oxcarbazepine 1800	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	41	NR	45
Appleton (1999)	Placebo	TTR & MTN	ALL	ALL	Number of patients seizure free	120	128	1
	Gabapentin 1800	TTR & MTN	ALL	ALL	Number of patients seizure free	113	119	3
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	120	128	43[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	113	119	47[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure increase	120	128	30[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure increase	113	119	14[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	120	128	21[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	113	119	24[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	120	128	16[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	113	119	7[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Appleton (1999) continued	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	120	128	11
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	113	119	11
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75 or more seizure increase	120	128	13[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 75 or more seizure increase	113	119	5[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	120	128	49[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	113	119	26[c]
	Placebo	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	128	128	-0.079
	Placebo	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	120	128	-0.072
	Gabapentin 1800	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	113	119	-0.161
	Gabapentin 1800	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	119	119	-0.146
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	120	128	6.5
	Gabapentin 1800	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	113	119	17

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Biton (1999)	Placebo	TTR & MTN	GEN	GEN	Number of patients with 50% or more seizure reduction	41	41	7
	Topiramate 400	TTR & MTN	GEN	GEN	Number of patients with 50% or more seizure reduction	39	39	18
	Placebo	TTR & MTN	GEN	GEN	Number of patients with 75% or more seizure reduction	41	41	3
	Topiramate 400	TTR & MTN	GEN	GEN	Number of patients with 75% or more seizure reduction	39	39	10
	Placebo	TTR & MTN	GEN	GEN	Number of patients seizure free	41	41	0
	Topiramate 400	TTR & MTN	GEN	GEN	Number of patients seizure free	39	39	2
	Placebo	TTR & MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	41	41	1
	Topiramate 400	TTR & MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	39	39	42
	Placebo	TTR & MTN	GEN	GTC	Number of patients with 50% or more seizure reduction	40	40	8
	Topiramate 400	TTR & MTN	GEN	GTC	Number of patients with 50% or more seizure reduction	39	39	22
	Placebo	TTR & MTN	GEN	GTC	Number of patients with 75% or more seizure reduction	40	40	5
	Topiramate 400	TTR & MTN	GEN	GTC	Number of patients with 75% or more seizure reduction	39	39	13

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Biton (1999) continued	Placebo	TTR & MTN	GEN	GTC	Number of patients seizure free	40	40	2
	Topiramate 400	TTR & MTN	GEN	GTC	Number of patients seizure free	39	39	5
	Placebo	TTR & MTN	GEN	GTC	Median % reduction from baseline in seizure frequency	40	40	9
	Topiramate 400	TTR & MTN	GEN	GTC	Median % reduction from baseline in seizure frequency	30	30	57
Duchowny (1999)	Placebo	MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	101	101	39[c]
	Lamotrigine 750	MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	98	98	54[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	101	101	25[c]
	Placebo	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	101	101	16[c]
	Lamotrigine 750	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	98	98	40[c]
	Lamotrigine 750	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	98	98	42[c]
	Placebo	TTR & MTN	PAR	PAR	Median monthly seizure frequency	101	101	8
	Placebo	MTN	PAR	PAR	Median monthly seizure frequency	101	101	8.5
	Lamotrigine 750	TTR & MTN	PAR	PAR	Median monthly seizure frequency	98	98	3
	Lamotrigine 750	MTN	PAR	PAR	Median monthly seizure frequency	98	98	5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Duchowny (1999) continued	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	101	101	6.7
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	101	101	12.8
	Lamotrigine 750	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	98	98	36.1
	Lamotrigine 750	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	98	98	44
	Placebo	MTN	PAR	SG	Number of patients with 25% or more seizure reduction	46	46	17[c]
	Lamotrigine 750	MTN	PAR	SG	Number of patients with 25% or more seizure reduction	40	40	25[c]
	Placebo	MTN	PAR	SG	Number of patients with 50% or more seizure reduction	46	46	12[c]
	Placebo	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	46	46	14[c]
	Lamotrigine 750	MTN	PAR	SG	Number of patients with 50% or more seizure reduction	40	40	21[c]
	Lamotrigine 750	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	40	40	23[c]
	Placebo	TTR & MTN	PAR	SG	Median monthly seizure frequency	46	46	1.5
	Placebo	TTR & MTN	PAR	SG	Median monthly seizure frequency	46	46	1.5
	Lamotrigine 750	TTR & MTN	PAR	SG	Median monthly seizure frequency	40	40	0.8
	Lamotrigine 750	TTR & MTN	PAR	SG	Median monthly seizure frequency	40	40	1.2

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Duchowny (1999) continued	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	46	46	8.6
	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	46	46	11.2
	Lamotrigine 750	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	40	40	53
	Lamotrigine 750	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	40	40	66.7
Elterman (1999)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	45	45	9
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	41	41	16
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	45	45	1
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	41	41	7
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	45	45	0
	Placebo	MTN	PAR	PAR	Number of patients seizure free	43	45	2
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients seizure free	41	41	2
	Topiramate 400	MTN	PAR	PAR	Number of patients seizure free	41	41	4
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	45	45	10.5
	Topiramate 400	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	41	41	33.1

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Elterman (1999) contineud	Placebo	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	20	20	6
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	20	20	9
	Placebo	TTR & MTN	PAR	SG	Number of patients with 75% or more seizure reduction	20	20	3
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients with 75% or more seizure reduction	20	20	6
	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	20	20	-10.6
	Topiramate 400	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	20	20	31.6
KTSG (1999)	Placebo	TTR & MTN	PAR	CPS	Mean % reduction from baseline in seizure frequency	72	72	-14.2 SD 662.5
	Topiramate 600	TTR & MTN	PAR	CPS	Mean % reduction from baseline in seizure frequency	70	70	28.4 SD 96.7
	Placebo	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	72	72	-14.3
	Topiramate 600	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	70	70	49.4
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	85	86	11
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	89	91	45
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	85	86	1
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	80	86	2

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
KTSG (1999)	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients seizure free	89	91	7
continued	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients seizure free	78	91	13
	Placebo	TTR & MTN	PAR	PAR	Median monthly seizure frequency	85	86	5.1
	Topiramate 600	TTR & MTN	PAR	PAR	Median monthly seizure frequency	89	91	2.4
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	85	86	9.1
	Topiramate 600	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	89	91	51.3
	Placebo	TTR & MTN	PAR	SG	Mean % reduction from baseline in seizure frequency	35	39	-15.2 SD 173.1
	Topiramate 600	TTR & MTN	PAR	SG	Mean % reduction from baseline in seizure frequency	28	31	26.3 SD 128.7
	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	35	39	40.3
	Topiramate 600	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	28	31	100
	Placebo	TTR & MTN	PAR	SPS	Mean % reduction from baseline in seizure frequency	4	5	52.5 SD 64.2
	Topiramate 600	TTR & MTN	PAR	SPS	Mean % reduction from baseline in seizure frequency	9	11	60.6 SD 59.3
	Placebo	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	4	5	72.9
	Topiramate 600	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	9	11	87.5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Sachdeo (1999)	Placebo	TTR & MTN	ALL	ALL	Number of patients with 75% or more seizure reduction	50	50	0
	Topiramate 600	TTR & MTN	ALL	ALL	Number of patients with 75% or more seizure reduction	48	48	4
	Placebo	TTR & MTN	ALL	ALL	Median % reduction from baseline in seizure frequency	50	50	8.8
	Topiramate 600	TTR & MTN	ALL	ALL	Median % reduction from baseline in seizure frequency	48	48	20.6
	Placebo	TTR & MTN	ALL	ALL except ABS	Median % reduction from baseline in seizure frequency	50	50	2
	Topiramate 600	TTR & MTN	ALL	ALL except ABS	Median % reduction from baseline in seizure frequency	48	48	23.9
	Placebo	TTR & MTN	GEN	GTC, TON, ATO	Number of patients with 50% or more seizure reduction	50	50	4
	Topiramate 600	TTR & MTN	GEN	GTC, TON, ATO	Number of patients with 50% or more seizure reduction	46	48	15
	Placebo	TTR & MTN	GEN	GTC, TON, ATO	Number of patients with 75% or more seizure reduction	50	50	2
	Topiramate 600	TTR & MTN	GEN	GTC, TON, ATO	Number of patients with 75% or more seizure reduction	46	48	8
	Placebo	TTR & MTN	GEN	GTC, TON, ATO	Number of patients seizure free	50	50	0
	Topiramate 600	TTR & MTN	GEN	GTC, TON, ATO	Number of patients seizure free	46	48	1
	Placebo	TTR & MTN	GEN	GTC, TON, ATO	Median % reduction from baseline in seizure frequency	50	50	-5.2
	Topiramate 600	TTR & MTN	GEN	GTC, TON, ATO	Median % reduction from baseline in seizure frequency	46	48	25.8

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent- to - Treat	Outcome[b] And Dispersion
Sachdeo (1999) continued	Placebo	TTR & MTN	GEN	TON, ATO	Number of patients with 50% or more seizure reduction	49	50	7
	Topiramate 600	TTR & MTN	GEN	TON, ATO	Number of patients with 50% or more seizure reduction	46	48	13
	Placebo	TTR & MTN	GEN	TON, ATO	Number of patients with 75% or more seizure reduction	49	50	3
	Topiramate 600	TTR & MTN	GEN	TON, ATO	Number of patients with 75% or more seizure reduction	46	48	8
	Placebo	TTR & MTN	GEN	TON, ATO	Number of patients seizure free	49	50	0
	Placebo	MTN	GEN	TON, ATO	Number of patients seizure free	49	50	0
	Topiramate 600	TTR & MTN	GEN	TON, ATO	Number of patients seizure free	46	48	1
	Topiramate 600	MTN	GEN	TON, ATO	Number of patients seizure free	46	48	5
	Placebo	TTR & MTN	GEN	TON, ATO	Median % reduction from baseline in seizure frequency	49	50	-5.1
	Topiramate 600	TTR & MTN	GEN	TON, ATO	Median % reduction from baseline in seizure frequency	46	48	14.8

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Uthman (1998)	Placebo	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	90	90	4
	Tiagabine 16	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	61	61	5
	Tiagabine 32	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	86	86	17
	Tiagabine 56	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	55	55	16
	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	90	90	7.4
	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	90	90	7.4
	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	90	90	7.4
	Tiagabine 16	TTR & MTN	PAR	CPS	Median monthly seizure frequency	61	61	8.5
	Tiagabine 32	TTR & MTN	PAR	CPS	Median monthly seizure frequency	86	86	9.6
	Tiagabine 56	TTR & MTN	PAR	CPS	Median monthly seizure frequency	55	55	9.1
	Placebo	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	90	90	11
	Placebo	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	90	90	11
	Tiagabine 16	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	61	61	13
	Tiagabine 32	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	86	86	25
	Tiagabine 56	TTR & MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	55	55	33

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Uthman (1998) continued	Placebo	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	90	90	0.7
	Tiagabine 16	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	61	61	0.8
	Tiagabine 32	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	86	86	2.2
	Tiagabine 56	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	55	55	2.8
	Placebo	TTR & MTN	PAR	SG	Number of patients with a change in seizure type	90	90	3
	Tiagabine 16	TTR & MTN	PAR	SG	Number of patients with a change in seizure type	61	61	4
	Tiagabine 32	TTR & MTN	PAR	SG	Number of patients with a change in seizure type	88	88	5
	Tiagabine 56	TTR & MTN	PAR	SG	Number of patients with a change in seizure type	57	57	3
	Placebo	TTR & MTN	PAR	SG	Number of patients with any seizure increase	35	35	16
	Tiagabine 16	TTR & MTN	PAR	SG	Number of patients with any seizure increase	28	28	9
	Tiagabine 32	TTR & MTN	PAR	SG	Number of patients with any seizure increase	32	32	11
	Tiagabine 56	TTR & MTN	PAR	SG	Number of patients with any seizure increase	26	26	10
	Placebo	TTR & MTN	PAR	SG	Median monthly seizure frequency	38	38	1.8
	Tiagabine 16	TTR & MTN	PAR	SG	Median monthly seizure frequency	32	32	0.9
	Tiagabine 32	TTR & MTN	PAR	SG	Median monthly seizure frequency	37	37	1
	Tiagabine 56	TTR & MTN	PAR	SG	Median monthly seizure frequency	29	29	0.8
	Placebo	TTR & MTN	PAR	SPS	Number of patients with 50% or more seizure reduction	51	51	5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Uthman (1998) continued	Tiagabine 16	TTR & MTN	PAR	SPS	Number of patients with 50% or more seizure reduction	39	39	11
	Tiagabine 32	TTR & MTN	PAR	SPS	Number of patients with 50% or more seizure reduction	49	49	17
	Tiagabine 56	TTR & MTN	PAR	SPS	Number of patients with 50% or more seizure reduction	33	33	12
	Placebo	TTR & MTN	PAR	SPS	Number of patients with any seizure increase	51	51	31
	Tiagabine 16	TTR & MTN	PAR	SPS	Number of patients with any seizure increase	39	39	9
	Tiagabine 32	TTR & MTN	PAR	SPS	Number of patients with any seizure increase	49	49	19
	Tiagabine 56	TTR & MTN	PAR	SPS	Number of patients with any seizure increase	33	33	9
	Placebo	TTR & MTN	PAR	SPS	Median monthly seizure frequency	51	51	8.6
	Placebo	TTR & MTN	PAR	SPS	Median monthly seizure frequency	51	51	8.6
	Placebo	TTR & MTN	PAR	SPS	Median monthly seizure frequency	51	51	8.6
	Tiagabine 16	TTR & MTN	PAR	SPS	Median monthly seizure frequency	39	39	9.7
	Tiagabine 32	TTR & MTN	PAR	SPS	Median monthly seizure frequency	49	49	13.7
	Tiagabine 56	TTR & MTN	PAR	SPS	Median monthly seizure frequency	33	33	9.1
	Placebo	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	51	51	-10.5
	Tiagabine 16	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	39	39	23.7
	Tiagabine 32	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	49	49	12.4

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Uthman (1998) continued	Tiagabine 56	TTR & MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	33	33	36.3
	Placebo	TTR & MTN	PAR	SPS	Median difference from baseline in seizure frequency	51	51	0.9
	Tiagabine 16	TTR & MTN	PAR	SPS	Median difference from baseline in seizure frequency	39	39	2.3
	Tiagabine 32	TTR & MTN	PAR	SPS	Median difference from baseline in seizure frequency	49	49	1.7
	Tiagabine 56	TTR & MTN	PAR	SPS	Median difference from baseline in seizure frequency	33	33	3.3
Sachdeo (1997b)	Placebo	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	107	107	10
	Tiagabine 32	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	105	105	28
	Tiagabine 32	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	106	106	33
	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	107	107	8.1
	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	107	107	8.1
	Tiagabine 32	TTR & MTN	PAR	CPS	Median monthly seizure frequency	105	105	5.8
	Tiagabine 32	TTR & MTN	PAR	CPS	Median monthly seizure frequency	106	106	6.2
	Placebo	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	107	107	0.2
	Tiagabine 32	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	105	105	1.2
	Tiagabine 32	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	106	106	1.6

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Sachdeo (1997b)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	107	107	8
	Tiagabine 32	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	105	105	24
	Tiagabine 32	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	106	106	30
Ben-Menachem (1996)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	28	28	0
	Topiramate 800	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	28	28	12
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	28	28	0
	Topiramate 800	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	28	28	10
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	28	28	-17.8 Range -152.1 to 42.3
	Topiramate 800	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	28	28	35.8 Range -554.6 to 100
	Placebo	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	13	13	3
	Topiramate 800	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	11	11	9
	Placebo	TTR & MTN	PAR	SG	Number of patients seizure free	13	13	2
	Topiramate 800	TTR & MTN	PAR	SG	Number of patients seizure free	11	11	6

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Ben-Menachem (1996) continued	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	13	13	18.8
	Topiramate 800	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	11	11	19
Chadwick (1996)	Placebo	TTR & MTN	GEN	ABS	Number of patients with 50% or more seizure reduction	14	NR	1
	Gabapentin 1200	TTR & MTN	GEN	ABS	Number of patients with 50% or more seizure reduction	15	NR	1
	Placebo	TTR & MTN	GEN	ABS	Mean risk ratio	14	NR	0.174 SEM .112
	Gabapentin 1200	TTR & MTN	GEN	ABS	Mean risk ratio	15	NR	0.14 SEM .134
	Placebo	TTR & MTN	GEN	ABS	Median % reduction from baseline in seizure frequency	14	NR	-2.3
	Gabapentin 1200	TTR & MTN	GEN	ABS	Median % reduction from baseline in seizure frequency	15	NR	-5.5
	Placebo	TTR & MTN	GEN	GTC	Number of patients with 50% or more seizure reduction	57	NR	10
	Gabapentin 1200	TTR & MTN	GEN	GTC	Number of patients with 50% or more seizure reduction	40	NR	11
	Placebo	TTR & MTN	GEN	GTC	Mean adjusted risk ratio	57	NR	-0.034
	Gabapentin 1200	TTR & MTN	GEN	GTC	Mean adjusted risk ratio	40	NR	-0.181
	Placebo	TTR & MTN	GEN	GTC	Mean risk ratio	57	NR	-0.057 SEM .061
	Gabapentin 1200	TTR & MTN	GEN	GTC	Mean risk ratio	40	NR	-0.155 SEM .066
	Placebo	TTR & MTN	GEN	GTC	Median % reduction from baseline in seizure frequency	53	NR	15.2

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Chadwick (1996) continued	Gabapentin 1200	TTR & MTN	GEN	GTC	Median % reduction from baseline in seizure frequency	39	NR	29.3
	Placebo	TTR & MTN	GEN	MYO	Number of patients with 50% or more seizure reduction	56	NR	13
	Gabapentin 1200	TTR & MTN	GEN	MYO	Number of patients with 50% or more seizure reduction	39	NR	11
	Placebo	TTR & MTN	GEN	MYO	Mean risk ratio	56	NR	-0.078
	Gabapentin 1200	TTR & MTN	GEN	MYO	Mean risk ratio	39	NR	-0.117
	Placebo	TTR & MTN	GEN	MYO	Median % reduction from baseline in seizure frequency	56	NR	16.5
	Gabapentin 1200	TTR & MTN	GEN	MYO	Median % reduction from baseline in seizure frequency	39	NR	16.4
	Placebo	TTR & MTN	GEN	OTH	Number of patients with 50% or more seizure reduction	28	NR	4
	Gabapentin 1200	TTR & MTN	GEN	OTH	Number of patients with 50% or more seizure reduction	17	NR	7
	Placebo	TTR & MTN	GEN	OTH	Mean adjusted risk ratio	28	NR	0.002
	Gabapentin 1200	TTR & MTN	GEN	OTH	Mean adjusted risk ratio	17	NR	-0.182
	Placebo	TTR & MTN	GEN	OTH	Mean risk ratio	28	NR	0.002 SEM .096
	Gabapentin 1200	TTR & MTN	GEN	OTH	Mean risk ratio	17	NR	-0.182 SEM .126
	Placebo	TTR & MTN	GEN	OTH	Median % reduction from baseline in seizure frequency	25	NR	15.2
	Gabapentin 1200	TTR & MTN	GEN	OTH	Median % reduction from baseline in seizure frequency	16	NR	41.9

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Faught (1996)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	45	45	8
	Topiramate 200	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	45	45	12
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	45	45	21
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	46	46	21
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	45	45	4[c]
	Topiramate 200	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	45	45	4[c]
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	45	45	10[c]
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	46	46	10[c]
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	45	45	13.1
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	45	45	13.1
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	45	45	13.1
	Topiramate 200	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	45	45	29.6
	Topiramate 400	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	45	45	47.8
	Topiramate 600	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	46	46	44.7

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Faught (1996) continued	Placebo	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	14	14	3
	Topiramate 200	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	14	14	10
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	15	15	13
	Topiramate 600	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	13	13	10
	Placebo	TTR & MTN	PAR	SG	Number of patients seizure free	14	14	0
	Topiramate 200	TTR & MTN	PAR	SG	Number of patients seizure free	14	14	3
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients seizure free	15	15	8
	Topiramate 600	TTR & MTN	PAR	SG	Number of patients seizure free	13	13	4
	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	14	14	1
	Topiramate 200	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	14	14	62
	Topiramate 400	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	15	15	100
	Topiramate 600	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	13	13	89
Privitera (1996)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	47	47	4
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	48	48	21
	Topiramate 800	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	48	48	19
	Topiramate 1000	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	47	47	18

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Privitera (1996) continued	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	47	47	0
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	48	48	11[c]
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	47	47	1.2
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	47	47	1.2
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	47	47	1.2
	Topiramate 600	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	48	48	40.7
	Topiramate 800	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	48	48	41
	Topiramate 1000	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	47	47	37.5
	Placebo	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	17	17	6[c]
	Topiramate 600	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	12	12	8[c]
	Topiramate 800	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	17	17	8[c]
	Topiramate 1000	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	11	11	6[c]
	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	17	17	40.3
	Topiramate 600	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	12	12	65.5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Privitera (1996) continued	Topiramate 800	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	17	17	44.4
	Topiramate 1000	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	11	11	78
Sharief (1996)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	24	24	2[c]
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	23	23	8[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	24	24	1[c]
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	23	23	5[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	24	24	0
	Topiramate 400	TTR & MTN	PAR	PAR	Number of patients seizure free	23	23	2
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	24	24	1.1
	Topiramate 400	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	23	23	40.7
	Placebo	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	8	8	3
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients with 50% or more seizure reduction	14	14	10
	Placebo	TTR & MTN	PAR	SG	Number of patients with a change in seizure type	8	8	5[c]
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients with a change in seizure type	14	14	0

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Sharief (1996) continued	Placebo	TTR & MTN	PAR	SG	Number of patients seizure free	8	8	2
	Topiramate 400	TTR & MTN	PAR	SG	Number of patients seizure free	14	14	6
	Placebo	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	8	8	8.7
	Topiramate 400	TTR & MTN	PAR	SG	Median % reduction from baseline in seizure frequency	14	14	83.9
Tassinari (1996)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	30	30	3
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	30	30	14
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	30	30	1
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	30	30	7
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	30	30	0
	Topiramate 600	TTR & MTN	PAR	PAR	Number of patients seizure free	30	30	0
	Placebo	TTR & MTN	PAR	PAR	Median monthly seizure frequency	30	30	24.5 Range 1.9 to 1205.7
	Topiramate 600	TTR & MTN	PAR	PAR	Median monthly seizure frequency	30	30	8.8 Range 1 to 178.2
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	30	30	-12.2
	Topiramate 600	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	30	30	46.6

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Willmore (1996)	Placebo	TTR & MTN	PAR	CPS	Number of patients with 25% or more seizure reduction	63	70	26
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Number of patients with 25% or more seizure reduction	74	77	53
	Placebo	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	63	70	15
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	74	77	34
	Placebo	TTR & MTN	PAR	CPS	Number of patients with 75% or more seizure reduction	63	70	8
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Number of patients with 75% or more seizure reduction	74	77	19
	Placebo	TTR & MTN	PAR	CPS	Number of patients seizure free	63	70	1
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Number of patients seizure free	74	77	6
	Placebo	TTR & MTN	PAR	CPS	Mean monthly seizure frequency	63	70	26.9 SD 39.1
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Mean monthly seizure frequency	74	77	18.6 SD 39.0
	Placebo	TTR & MTN	PAR	CPS	Mean difference from baseline in seizure frequency	63	70	2.5
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Mean difference from baseline in seizure frequency	74	77	8.5
	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	63	70	11.7

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Willmore (1996) continued	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Median monthly seizure frequency	74	77	8.7
	Placebo	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	63	70	2.5
	Valproate 90 mg/kg	TTR & MTN	PAR	CPS	Median difference from baseline in seizure frequency	74	77	7.9
Anhut (1994)	Placebo	TTR & MTN	PAR	CPS	Median monthly seizure frequency	98	98	7.4
	Gabapentin 900	TTR & MTN	PAR	CPS	Median monthly seizure frequency	99	99	5.7
	Gabapentin 1200	TTR & MTN	PAR	CPS	Median monthly seizure frequency	48	48	4.4
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	99	109	10[c]
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	96	111	22[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	50	52	14[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	99	109	14[c]
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	96	111	5[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	50	52	4[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	99	109	51[c]
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	96	111	77[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	50	52	38[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Anhut (1994) continued	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	99	109	48[c]
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	96	111	19[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	50	52	12[c]
	Placebo	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	99	109	-0.025 SEM .022
	Gabapentin 900	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	96	111	-0.136 SEM .026
	Gabapentin 1200	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	50	52	-0.157 SEM .047
	Placebo	TTR & MTN	PAR	PAR	Median monthly seizure frequency	109	109	8.1
	Gabapentin 900	TTR & MTN	PAR	PAR	Median monthly seizure frequency	111	111	7.7
	Gabapentin 1200	TTR & MTN	PAR	PAR	Median monthly seizure frequency	52	52	6.8
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	99	109	0.3 SD 53.8
	Gabapentin 900	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	96	111	21.8 SD 53.7
	Gabapentin 1200	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	50	52	17.8 SD 62.1
	Placebo	TTR & MTN	PAR	SG	Median monthly seizure frequency	58	58	1
	Gabapentin 900	TTR & MTN	PAR	SG	Median monthly seizure frequency	61	61	1
	Gabapentin 1200	TTR & MTN	PAR	SG	Median monthly seizure frequency	31	31	0.6
	Placebo	TTR & MTN	PAR	SPS	Median monthly seizure frequency	40	40	3.8
	Gabapentin 900	TTR & MTN	PAR	SPS	Median monthly seizure frequency	42	42	6.5
	Gabapentin 1200	TTR & MTN	PAR	SPS	Median monthly seizure frequency	23	23	5.5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Messenheimer (1994)	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	44	44	4
	Lamotrigine 400	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	44	44	29
Bourgeois (1993)	Placebo	TTR & MTN	PAR	PAR	Mean rank of seizure frequency	34	34	35.4
	Felbamate 3600	TTR & MTN	PAR	PAR	Mean rank of seizure frequency	30	30	25.8
FSG (1993)	Placebo	TTR & MTN	GEN	ATO	Number of patients seizure free	22	22	0
	Placebo	MTN	GEN	ATO	Number of patients seizure free	22	22	0
	Felbamate 3600	TTR & MTN	GEN	ATO	Number of patients seizure free	28	28	3
	Felbamate 3600	MTN	GEN	ATO	Number of patients seizure free	28	28	5
	Placebo	MTN	GEN	ATO	Mean % reduction from baseline in seizure frequency	22	22	7 Range -57 to 88
	Placebo	TTR & MTN	GEN	ATO	Mean % reduction from baseline in seizure frequency	22	22	9 Range -64 to 85
	Felbamate 3600	TTR & MTN	GEN	ATO	Mean % reduction from baseline in seizure frequency	28	28	34 Range -156 to 100
	Felbamate 3600	MTN	GEN	ATO	Mean % reduction from baseline in seizure frequency	28	28	44 Range -145 to 100
	Placebo	TTR & MTN	GEN	GTC	Number of patients seizure free	13	13	1
	Placebo	MTN	GEN	GTC	Number of patients seizure free	13	13	1
	Felbamate 3600	TTR & MTN	GEN	GTC	Number of patients seizure free	16	16	2
	Felbamate 3600	MTN	GEN	GTC	Number of patients seizure free	16	16	7

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
FSG (1993) continued	Placebo	MTN	GEN	GTC	Mean % reduction from baseline in seizure frequency	13	13	-12 Range -293 to 100
	Placebo	TTR & MTN	GEN	GTC	Mean % reduction from baseline in seizure frequency	13	13	-11 Range -203 to 100
	Felbamate 3600	TTR & MTN	GEN	GTC	Mean % reduction from baseline in seizure frequency	16	16	28 Range -172 to 100
	Felbamate 3600	MTN	GEN	GTC	Mean % reduction from baseline in seizure frequency	16	16	40 Range -206 to 100
	Placebo	TTR & MTN	ALL	GTC, TON, ATO, MYO, CPS	Number of patients seizure free	36	36	0
	Placebo	MTN	ALL	GTC, TON, ATO, MYO, CPS	Number of patients seizure free	36	36	1
	Felbamate 3600	TTR & MTN	ALL	GTC, TON, ATO, MYO, CPS	Number of patients seizure free	37	37	0
	Felbamate 3600	MTN	ALL	GTC, TON, ATO, MYO, CPS	Number of patients seizure free	37	37	4
	Placebo	MTN	ALL	GTC, TON, ATO, MYO, CPS	Mean % reduction from baseline in seizure frequency	36	36	-5 Range -231 to 100
	Placebo	TTR & MTN	ALL	GTC, TON, ATO, MYO, CPS	Mean % reduction from baseline in seizure frequency	36	36	4 Range -176 to 74
	Felbamate 3600	TTR & MTN	ALL	GTC, TON, ATO, MYO, CPS	Mean % reduction from baseline in seizure frequency	37	37	19 Range -437 to 99
	Felbamate 3600	MTN	ALL	GTC, TON, ATO, MYO, CPS	Mean % reduction from baseline in seizure frequency	37	37	26 Range -521 to 100
	Placebo	TTR & MTN	GEN	ABS	Number of patients with 25% or more seizure reduction	30	30	12a,[c]
	Felbamate 3600	TTR & MTN	GEN	ABS	Number of patients with 25% or more seizure reduction	32	32	22a,[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
FSG (1993) continued	Placebo	TTR & MTN	GEN	ABS	Number of patients with 50% or more seizure reduction	30	30	9a,[c]
	Felbamate 3600	TTR & MTN	GEN	ABS	Number of patients with 50% or more seizure reduction	32	32	17a,[c]
	Placebo	TTR & MTN	GEN	ABS	Number of patients with 75% or more seizure reduction	30	30	4a,[c]
	Felbamate 3600	TTR & MTN	GEN	ABS	Number of patients with 75% or more seizure reduction	32	32	12a,[c]
	Placebo	TTR & MTN	GEN	ABS	Number of patients seizure free	30	30	2a,[c]
	Felbamate 3600	TTR & MTN	GEN	ABS	Number of patients seizure free	32	32	2a,[c]
	Placebo	TTR & MTN	GEN	ATO	Number of patients with 25% or more seizure reduction	22	22	6a,[c]
	Felbamate 3600	TTR & MTN	GEN	ATO	Number of patients with 25% or more seizure reduction	27	27	19a,[c]
	Placebo	TTR & MTN	GEN	ATO	Number of patients with 50% or more seizure reduction	22	22	2a,[c]
	Felbamate 3600	TTR & MTN	GEN	ATO	Number of patients with 50% or more seizure reduction	27	27	16a,[c]
	Placebo	TTR & MTN	GEN	ATO	Number of patients with 75% or more seizure reduction	22	22	1a,[c]
	Felbamate 3600	TTR & MTN	GEN	ATO	Number of patients with 75% or more seizure reduction	27	27	9a,[c]
	Placebo	TTR & MTN	GEN	ATO	Number of patients seizure free	22	22	0a
	Felbamate 3600	TTR & MTN	GEN	ATO	Number of patients seizure free	27	27	4a,[c]
	Placebo	TTR & MTN	GEN	ATO	Mean % reduction from baseline in seizure frequency	22	22	9a

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
FSG (1993) continued	Felbamate 3600	TTR & MTN	GEN	ATO	Mean % reduction from baseline in seizure frequency	27	27	34a
	Placebo	TTR & MTN	GEN	ATO, ABS	Number of patients with 25% or more seizure reduction	35	35	7a,[c]
	Felbamate 3600	TTR & MTN	GEN	ATO, ABS	Number of patients with 25% or more seizure reduction	36	36	23a,[c]
	Placebo	TTR & MTN	GEN	ATO, ABS	Number of patients with 50% or more seizure reduction	35	35	4a,[c]
	Felbamate 3600	TTR & MTN	GEN	ATO, ABS	Number of patients with 50% or more seizure reduction	36	36	18a,[c]
	Placebo	TTR & MTN	GEN	ATO, ABS	Number of patients with 75% or more seizure reduction	35	35	0a
	Felbamate 3600	TTR & MTN	GEN	ATO, ABS	Number of patients with 75% or more seizure reduction	36	36	9a,[c]
	Placebo	TTR & MTN	GEN	ATO, ABS	Number of patients seizure free	35	35	0a
	Felbamate 3600	TTR & MTN	GEN	ATO, ABS	Number of patients seizure free	36	36	3a,[c]
Matsuo (1993)	Placebo	TTR & some MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	70	73	21[c]
	Placebo	Last 12 weeks of MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	67	73	25[c]
	Lamotrigine 300	TTR & some MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	67	71	30[c]
	Lamotrigine 300	Last 12 weeks of MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	65	71	30[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Matsuo (1993) continued	Lamotrigine 500	Last 12 weeks of MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	59	72	34[c]
	Lamotrigine 500	TTR & some MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	63	72	39[c]
	Placebo	Last 12 weeks of MTN	PAR	PAR	Number of patients with 25% or more seizure increase	67	73	12[c]
	Placebo	TTR & some MTN	PAR	PAR	Number of patients with 25% or more seizure increase	70	73	13[c]
	Lamotrigine 300	Last 12 weeks of MTN	PAR	PAR	Number of patients with 25% or more seizure increase	65	71	15[c]
	Lamotrigine 300	TTR & some MTN	PAR	PAR	Number of patients with 25% or more seizure increase	67	71	18[c]
	Lamotrigine 500	Last 12 weeks of MTN	PAR	PAR	Number of patients with 25% or more seizure increase	59	72	6[c]
	Lamotrigine 500	TTR & some MTN	PAR	PAR	Number of patients with 25% or more seizure increase	63	72	7[c]
	Placebo	TTR & some MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	70	73	10[c]
	Placebo	Last 12 weeks of MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	67	73	12[c]
	Lamotrigine 300	TTR & some MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	67	71	12[c]
	Lamotrigine 300	Last 12 weeks of MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	65	71	13[c]
	Lamotrigine 500	Last 12 weeks of MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	59	72	20[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Matsuo (1993) continued	Lamotrigine 500	TTR & some MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	63	72	21[c]
	Placebo	Last 12 weeks of MTN	PAR	PAR	Number of patients with 50% or more seizure increase	67	73	4[c]
	Placebo	TTR & some MTN	PAR	PAR	Number of patients with 50% or more seizure increase	70	73	9[c]
	Lamotrigine 300	Last 12 weeks of MTN	PAR	PAR	Number of patients with 50% or more seizure increase	65	71	10[c]
	Lamotrigine 300	TTR & some MTN	PAR	PAR	Number of patients with 50% or more seizure increase	67	71	12[c]
	Lamotrigine 500	TTR & some MTN	PAR	PAR	Number of patients with 50% or more seizure increase	63	72	4[c]
	Lamotrigine 500	Last 12 weeks of MTN	PAR	PAR	Number of patients with 50% or more seizure increase	59	72	4[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients seizure free	67	73	1
	Lamotrigine 300	TTR & MTN	PAR	PAR	Number of patients seizure free	65	71	7
	Lamotrigine 500	TTR & MTN	PAR	PAR	Number of patients seizure free	59	72	5
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	67	73	8
	Placebo	TTR & some MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	70	73	10[c]
	Placebo	Last 12 weeks of MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	67	73	14[c]
	Lamotrigine 300	TTR & some MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	67	71	19[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Matsuo (1993) continued	Lamotrigine 300	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	65	71	20
	Lamotrigine 300	Last 12 weeks of MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	65	71	23[c]
	Lamotrigine 500	TTR & some MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	63	72	31[c]
	Lamotrigine 500	Last 12 weeks of MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	59	72	32[c]
	Lamotrigine 500	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	59	72	36
McLean (1993)	Placebo	TTR & MTN	PAR	CPS	Mean risk ratio	85	NR	-.01[c]
	Gabapentin 600	TTR & MTN	PAR	CPS	Mean risk ratio	47	NR	-.14[c]
	Gabapentin 1200	TTR & MTN	PAR	CPS	Mean risk ratio	80	NR	-.15[c]
	Gabapentin 1800	TTR & MTN	PAR	CPS	Mean risk ratio	51	NR	-.28[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	95	98	24[c]
	Gabapentin 600	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	49	53	23[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	91	101	37[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	53	54	32[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	95	98	8[c]
	Gabapentin 600	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	49	53	9[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
McLean (1993) continued	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	91	101	16[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	53	54	14[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	95	98	1[c]
	Gabapentin 600	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	49	53	1[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	91	101	6[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	53	54	3[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	95	98	57[c]
	Gabapentin 600	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	49	53	36[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	91	101	61[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	53	54	43[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	95	98	38[c]
	Gabapentin 600	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	49	53	13[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	91	101	30[c]
	Gabapentin 1800	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	53	54	10[c]
	Placebo	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	95	98	-.025 SEM .022
	Gabapentin 600	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	49	53	-.151 SEM .037
	Gabapentin 1200	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	91	101	-.118 SEM .027

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
McLean (1993) continued	Gabapentin 1800	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	53	54	-.233 SEM .034
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	95	98	5.9
	Gabapentin 600	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	49	53	24.3
	Gabapentin 1200	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	91	101	20
	Gabapentin 1800	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	53	54	31.9
	Placebo	TTR & MTN	PAR	PAR	Median risk ratio	95	98	-.03
	Gabapentin 600	TTR & MTN	PAR	PAR	Median risk ratio	49	53	-.138
	Gabapentin 1200	TTR & MTN	PAR	PAR	Median risk ratio	91	101	-.111
	Gabapentin 1800	TTR & MTN	PAR	PAR	Median risk ratio	53	54	-.19
	Placebo	TTR & MTN	PAR	SG	Mean risk ratio	35	NR	.12[c]
	Gabapentin 600	TTR & MTN	PAR	SG	Mean risk ratio	20	NR	-.07[c]
	Gabapentin 1200	TTR & MTN	PAR	SG	Mean risk ratio	31	NR	-.15[c]
	Gabapentin 1800	TTR & MTN	PAR	SG	Mean risk ratio	26	NR	-.37[c]
	Placebo	TTR & MTN	PAR	SPS	Mean risk ratio	47	NR	.025[c]
	Gabapentin 600	TTR & MTN	PAR	SPS	Mean risk ratio	23	NR	.025[c]
	Gabapentin 1200	TTR & MTN	PAR	SPS	Mean risk ratio	44	NR	-.05[c]
	Gabapentin 1800	TTR & MTN	PAR	SPS	Mean risk ratio	23	NR	-.11[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Schmidt (1993)	Placebo	MTN	ALL	ALL	Number of patients with 50% or more seizure reduction	64	68	6
	Zonisamide 20 mg/kg	MTN	ALL	ALL	Number of patients with 50% or more seizure reduction	67	71	20
	Placebo	MTN	ALL	ALL	Median % reduction from baseline in seizure frequency	64	68	-3
	Zonisamide 20 mg/kg	MTN	ALL	ALL	Median % reduction from baseline in seizure frequency	67	71	22.5
	Placebo	MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	63	68	8
	Zonisamide 20 mg/kg	MTN	PAR	CPS	Number of patients with 50% or more seizure reduction	66	71	20
	Placebo	MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	63	68	-3.9
	Placebo	TTR	PAR	CPS	Median % reduction from baseline in seizure frequency	63	68	-3.2
	Placebo	First month of MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	63	68	8.2
	Zonisamide 20 mg/kg	First month of MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	66	71	26.7
	Zonisamide 20 mg/kg	MTN	PAR	CPS	Median % reduction from baseline in seizure frequency	66	71	27.7
	Zonisamide 20 mg/kg	TTR	PAR	CPS	Median % reduction from baseline in seizure frequency	66	71	31
	Placebo	MTN	GEN	GEN	Number of patients with 50% or more seizure reduction	7	NR	4
	Zonisamide 20 mg/kg	MTN	GEN	GEN	Number of patients with 50% or more seizure reduction	8	NR	2

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Schmidt (1993) continued	Placebo	MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	7	NR	61.5
	Zonisamide 20 mg/kg	MTN	GEN	GEN	Median % reduction from baseline in seizure frequency	8	NR	23.2
	Placebo	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	63	68	8
	Zonisamide 20 mg/kg	MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	66	71	20
	Placebo	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	63	68	4
	Zonisamide 20 mg/kg	MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	66	71	10
	Placebo	MTN	PAR	PAR	Number of patients with any seizure reduction	63	68	28
	Zonisamide 20 mg/kg	MTN	PAR	PAR	Number of patients with any seizure reduction	66	71	43
	Placebo	MTN	PAR	PAR	Number of patients seizure free	63	68	1
	Zonisamide 20 mg/kg	MTN	PAR	PAR	Number of patients seizure free	66	71	4
	Placebo	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	63	68	-3.9
	Zonisamide 20 mg/kg	MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	66	71	26.9
	Placebo	MTN	PAR	SPS	Number of patients with 50% or more seizure reduction	3	NR	1
	Zonisamide 20 mg/kg	MTN	PAR	SPS	Number of patients with 50% or more seizure reduction	6	NR	4

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
Schmidt (1993) continued	Placebo	MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	3	NR	48.1
	Zonisamide 20 mg/kg	MTN	PAR	SPS	Median % reduction from baseline in seizure frequency	6	NR	72.6
Sivenius (1991)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	18	18	6
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	16	16	6
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	18	18	3
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	16	16	2
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	18	18	0
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	16	16	0
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	18	18	13
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	16	16	10
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	18	18	5
	Gabapentin 900	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	16	16	6
	Placebo	TTR & MTN	PAR	PAR	Median monthly seizure frequency	18	18	30
	Gabapentin 900	TTR & MTN	PAR	PAR	Median monthly seizure frequency	16	16	19.5

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
UKGSG (1990)	Placebo	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	61	66	15[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure reduction	52	61	32[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure increase	61	66	11[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 25% or more seizure increase	52	61	5[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	61	66	6[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure reduction	52	61	13[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	61	66	5[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 50% or more seizure increase	52	61	3[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	61	66	1[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 75% or more seizure reduction	52	61	5[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with 75 or more seizure increase	61	66	3[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with 75 or more seizure increase	52	61	3[c]
	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	61	66	38[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with any seizure reduction	52	61	42[c]

Evidence Table 59. Seizure frequency outcomes in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Phase of Study	Overall Seizure Type[a]	Specific Seizure Type(s)[a]	Description of Outcome	N	N Using Intent-to-Treat	Outcome[b] And Dispersion
UKGSG (1990) continued	Placebo	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	61	66	23[c]
	Gabapentin 1200	TTR & MTN	PAR	PAR	Number of patients with any seizure increase	52	61	10[c]
	Placebo	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	61	66	-0.06
	Gabapentin 1200	TTR & MTN	PAR	PAR	Mean adjusted risk ratio	52	61	-0.192
	Placebo	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	61	66	12.5
	Gabapentin 1200	TTR & MTN	PAR	PAR	Median % reduction from baseline in seizure frequency	52	61	29.2
Jawad (1989)	Placebo	TTR & MTN	PAR	PAR	Mean monthly seizure frequency	11	11	12.2
	Lamotrigine 400	TTR & MTN	PAR	PAR	Mean monthly seizure frequency	10	10	7.2
	Placebo	TTR & MTN	PAR	PAR	Median monthly seizure frequency	11	11	9
	Lamotrigine 400	TTR & MTN	PAR	PAR	Median monthly seizure frequency	10	10	6.8

[a] The following abbreviations for seizure types have been used in Evidence Table 59

ABS absence seizures
ALL all seizures
ATO atonic seizures
CPS complex partial seizures
GEN generalized seizures
GTC generalized tonic-clonic seizures
MYO myoclonic seizures
OTH other generalized seizures
PAR partial seizures
SG secondarily generalized seizures
SPS simple partial seizures
TON tonic seizures
mg/kg Milligrams per kilogram
MTN Maintenance phase of study
TTR Titration phase of study
SEM Standard error of the mean

[b] In the outcome column, a positive value for either median, % reduction from baseline, or median difference from baseline represents a beneficial reduction in seizures. This conforms to the convention in the epilepsy literature.

[c] Calculated by ECRI based on published information

Evidence Table 60. Adverse effects in studies of polytherapy

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect/ Patients in Group	Percentage
Faught (2001)	Zonisamide 400	Abdominal pain	Withdrawal	1/118	1%
	Zonisamide 400	Agitation	Withdrawal	2/118	2%
	Placebo	Anorexia		8/85	9%
	Zonisamide 400	Anorexia	Withdrawal	1/118	1%
	Zonisamide 400	Anorexia		17/118	14%
	Placebo	Ataxia		6/85	7%
	Zonisamide 400	Ataxia	Severe	1/118	1%
	Zonisamide 400	Ataxia		12/118	10%
	Zonisamide 400	Behavioral changes	Severe	1/118	1%
	Zonisamide 400	Blurred vision	Severe	1/118	1%
	Placebo	Confusion	Withdrawal	1/85	1%
	Zonisamide 400	Confusion	Withdrawal	3/118	3%
	Placebo	Depression	Withdrawal	2/85	2%
	Zonisamide 400	Depression	Withdrawal	1/118	1%
	Placebo	Dizziness	Withdrawal	1/85	1%
	Placebo	Dizziness		12/85	14%
	Zonisamide 400	Dizziness	Severe	1/118	1%
	Zonisamide 400	Dizziness		16/118	14%
	Zonisamide 400	Dry mouth	Severe	1/118	1%
	Placebo	Fatigue		12/85	14%
	Zonisamide 400	Fatigue	Withdrawal	1/118	1%
	Zonisamide 400	Fatigue		11/118	9%
	Placebo	Gall bladder disorder	Severe	1/85	1%
	Zonisamide 400	Glossitis	Severe	1/118	1%
	Placebo	Headache		11/85	13%
	Zonisamide 400	Headache	Withdrawal	2/118	2%
	Zonisamide 400	Headache		11/118	9%
	Placebo	Increase in seizures	Severe	1/85	1%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Faught (2001) continued	Zonisamide 400	Memory	Withdrawal	1/118	1%
	Zonisamide 400	Mental slowing	Withdrawal	1/118	1%
	Placebo	Migraine	Withdrawal	1/85	1%
	Zonisamide 400	Muscle spasm	Severe	1/118	1%
	Placebo	Nausea	Withdrawal	1/85	1%
	Placebo	Nausea and/or vomiting		15/85	18%
	Zonisamide 400	Nausea and/or vomiting	Severe	1/118	1%
	Zonisamide 400	Nausea and/or vomiting		14/118	12%
	Zonisamide 400	Paranoia	Severe	2/118	2%
	Zonisamide 400	Paranoid behavior	Withdrawal	1/118	1%
	Placebo	Phenytoin toxicity	Severe	1/85	1%
	Zonisamide 400	Pneumonia	Severe	1/118	1%
	Placebo	Psychomotor slowing	Withdrawal	1/85	1%
	Zonisamide 400	Psychosis	Withdrawal	1/118	1%
	Placebo	Rash	Withdrawal	1/85	1%
	Placebo	Rash	Severe	1/85	1%
	Placebo	Rhinitis		13/85	15%
	Zonisamide 400	Rhinitis		17/118	14%
	Zonisamide 400	Schizophreniform behavior	Withdrawal	1/118	1%
	Placebo	Somnolence		13/85	15%
	Zonisamide 400	Somnolence		18/118	15%
	Zonisamide 400	Status epilepticus	Severe	1/118	1%
	Zonisamide 400	Thyroid disorder	Severe	1/118	1%
	Placebo	Tremor	Withdrawal	1/85	1%
	Placebo	Uterine disorders	Severe	1/85	1%
	Zonisamide 400	Uterine disorders	Severe	1/118	1%
	Zonisamide 400	Weight loss	Withdrawal	1/118	1%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Ben-Menachem (2000)	Placebo	Accidental injury		10/105	9.5%
	Levetiracetam 3000	Accidental injury		4/181	2.2%
	Placebo	Any	Severe	1/105	1%
	Placebo	Any	Any	56/105	53%
	Levetiracetam 3000	Any	Severe	4/181	2%
	Levetiracetam 3000	Any	Any	100/181	55%
	Placebo	Asthenia		7/105	6.7%
	Levetiracetam 3000	Asthenia		25/181	13.8%
	Placebo	Confusion	Severe	1/105	1%
	Levetiracetam 3000	Convulsions	Severe	2/181	1%
	Placebo	Headache		11/105	10.5%
	Levetiracetam 3000	Headache		6/181	3.3%
	Placebo	Infection		4/105	3.8%
	Levetiracetam 3000	Infection		13/181	7.2%
	Levetiracetam 3000	Rash	Severe	1/181	1%
	Placebo	Somnolence		4/105	3.8%
	Levetiracetam 3000	Somnolence		11/181	6.1%
	Levetiracetam 3000	Spontaneous abortion	Severe	1/181	1%
Betts (2000)	Placebo	Accidental injury		6/39	15%
	Levetiracetam 2000	Accidental injury		1/42	2%
	Levetiracetam 4000	Accidental injury		5/38	13%
	Placebo	Any	Any	33/39	85%
	Levetiracetam 2000	Any	Any	35/42	83%
	Levetiracetam 4000	Any	Any	32/38	84%
	Placebo	Asthenia		6/39	15%
	Levetiracetam 2000	Asthenia		13/42	31%
	Levetiracetam 4000	Asthenia		5/38	13%
	Placebo	Dizziness		0/39	0%
	Levetiracetam 2000	Dizziness		2/42	5%
	Levetiracetam 4000	Dizziness		4/38	11%
	Placebo	Infection		3/39	8%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Betts (2000) continued	Levetiracetam 2000	Infection		1/42	2%
	Levetiracetam 4000	Infection		6/38	16%
	Placebo	Nausea		1/39	3%
	Levetiracetam 2000	Nausea		0/42	0%
	Levetiracetam 4000	Nausea		5/38	13%
	Placebo	Somnolence		10/39	26%
	Levetiracetam 2000	Somnolence		11/42	26%
	Levetiracetam 4000	Somnolence		17/38	45%
	Placebo	Urinary tract infection		1/39	3%
	Levetiracetam 2000	Urinary tract infection		0/42	0%
	Levetiracetam 4000	Urinary tract infection		4/38	11%
Cereghino (2000)	Placebo	Abdominal pain		10/95	11%
	Levetiracetam 1000	Abdominal pain		5/98	5%
	Levetiracetam 3000	Abdominal pain		3/101	3%
	Placebo	Accidental injury		23/95	24%
	Levetiracetam 1000	Accidental injury		16/98	16%
	Levetiracetam 3000	Accidental injury		13/101	13%
	Placebo	Any	Severe	10/95	11%
	Placebo	Any	Any	84/95	88%
	Levetiracetam 1000	Any	Severe	7/98	7%
	Levetiracetam 1000	Any	Any	87/98	89%
	Levetiracetam 3000	Any	Severe	2/101	2%
	Levetiracetam 3000	Any	Any	90/101	89%
	Placebo	Asthenia		11/95	12%
	Levetiracetam 1000	Asthenia		16/98	16%
	Levetiracetam 3000	Asthenia		13/101	13%
	Placebo	Death	Severe	1/95	1%
	Placebo	Diarrhea		10/95	11%
	Levetiracetam 1000	Diarrhea		7/98	7%
	Levetiracetam 3000	Diarrhea		7/101	7%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Cereghino (2000) continued	Placebo	Dizziness		7/95	7%
	Levetiracetam 1000	Dizziness		17/98	17%
	Levetiracetam 3000	Dizziness		20/101	20%
	Placebo	Flu syndrome		8/95	8%
	Levetiracetam 1000	Flu syndrome		6/98	6%
	Levetiracetam 3000	Flu syndrome		11/101	11%
	Placebo	Headache		19/95	20%
	Levetiracetam 1000	Headache		21/98	21%
	Levetiracetam 3000	Headache		21/101	21%
	Placebo	Infection		12/95	13%
	Levetiracetam 1000	Infection		27/98	28%
	Levetiracetam 3000	Infection		27/101	27%
	Placebo	Pain		13/95	14%
	Levetiracetam 1000	Pain		11/98	11%
	Levetiracetam 3000	Pain		13/101	13%
	Placebo	Rhinitis		8/95	8%
	Levetiracetam 1000	Rhinitis		13/98	13%
	Levetiracetam 3000	Rhinitis		7/101	7%
	Placebo	Somnolence		13/95	14%
	Levetiracetam 1000	Somnolence		20/98	20%
	Levetiracetam 3000	Somnolence		19/101	19%
Glauser (2000)	Placebo	Abdominal pain		13/129	10%
	Oxcarbazepine 1800	Abdominal pain		12/138	9%
	Placebo	Abnormal gait		4/129	3%
	Oxcarbazepine 1800	Abnormal gait	Withdrawal	1/138	1%
	Oxcarbazepine 1800	Abnormal gait		14/138	10%
	Placebo	Abnormal vision		2/129	2%
	Oxcarbazepine 1800	Abnormal vision		19/138	14%
	Placebo	Anorexia		13/129	10%
	Oxcarbazepine 1800	Anorexia		9/138	7%
	Placebo	Any	Severe	8/129	6%
	Placebo	Any	Any	106/129	82%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Glauser (2000) continued	Oxcarbazepine 1800	Any	Severe	7/138	5%
	Oxcarbazepine 1800	Any	Any	125/138	91%
	Placebo	Ataxia		6/129	5%
	Oxcarbazepine 1800	Ataxia	Withdrawal	1/138	1%
	Oxcarbazepine 1800	Ataxia		19/138	14%
	Oxcarbazepine 1800	Death	Severe	1/138	1%
	Oxcarbazepine 1800	Digestive problems	Withdrawal	5/138	4%
	Placebo	Diplopia		1/129	1%
	Oxcarbazepine 1800	Diplopia	Withdrawal	1/138	1%
	Oxcarbazepine 1800	Diplopia		23/138	17%
	Placebo	Dizziness		10/129	8%
	Oxcarbazepine 1800	Dizziness	Withdrawal	1/138	1%
	Oxcarbazepine 1800	Dizziness		40/138	29%
	Placebo	Fatigue		11/129	9%
	Oxcarbazepine 1800	Fatigue		18/138	13%
	Placebo	Fever		20/129	16%
	Oxcarbazepine 1800	Fever		21/138	15%
	Placebo	Headache		23/129	18%
	Oxcarbazepine 1800	Headache		44/138	32%
	Placebo	Leukopenia	Withdrawal	1/129	1%
	Placebo	Nausea		7/129	5%
	Oxcarbazepine 1800	Nausea		30/138	22%
	Placebo	Nystagmus		2/129	2%
	Oxcarbazepine 1800	Nystagmus	Withdrawal	1/138	1%
	Oxcarbazepine 1800	Nystagmus		14/138	10%
	Placebo	Pharyngitis		15/129	12%
	Oxcarbazepine 1800	Pharyngitis		12/138	9%
	Placebo	Rash		6/129	5%
	Oxcarbazepine 1800	Rash	Withdrawal	4/138	3%
	Oxcarbazepine 1800	Rash		6/138	4%
	Placebo	Rhinitis		11/129	9%
	Oxcarbazepine 1800	Rhinitis		16/138	12%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Glauser (2000) continued	Placebo	Somnolence		18/129	14%
	Oxcarbazepine 1800	Somnolence		48/138	35%
	Placebo	Upper respiratory tract infection		15/129	12%
	Oxcarbazepine 1800	Upper respiratory tract infection		10/138	7%
	Placebo	Viral infection		21/129	16%
	Oxcarbazepine 1800	Viral infection		19/138	14%
	Placebo	Vomiting		19/129	15%
	Oxcarbazepine 1800	Vomiting		50/138	36%
Appleton (1999)	Placebo	Anorexia		3/128	2%
	Gabapentin 1800	Anorexia		2/119	2%
	Placebo	Any	Severe	3/128	2%
	Gabapentin 1800	Any	Severe	14/119	12%
	Placebo	Bronchitis		1/128	1%
	Gabapentin 1800	Bronchitis		4/119	3%
	Placebo	Convulsions		4/128	3%
	Gabapentin 1800	Convulsions		3/119	3%
	Placebo	Coughing		4/128	3%
	Gabapentin 1800	Coughing		2/119	2%
	Placebo	Death	Severe	0/128	0%
	Gabapentin 1800	Death	Severe	0/119	0%
	Placebo	Diarrhea		4/128	3%
	Gabapentin 1800	Diarrhea		3/119	3%
	Placebo	Dizziness		2/128	2%
	Gabapentin 1800	Dizziness		3/119	3%
	Placebo	Emotional lability		2/128	2%
	Gabapentin 1800	Emotional lability		5/119	4%
	Placebo	Fatigue		2/128	2%
	Gabapentin 1800	Fatigue		4/119	3%
	Placebo	Fever		4/128	3%
	Gabapentin 1800	Fever		12/119	10%
	Placebo	Headache		8/128	6%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Appleton (1999) continued	Gabapentin 1800	Headache		6/119	5%
	Placebo	Hostility		3/128	2%
	Gabapentin 1800	Hostility	Withdrawal	2/119	2%
	Gabapentin 1800	Hostility		9/119	8%
	Placebo	Hyperkinesia		1/128	1%
	Gabapentin 1800	Hyperkinesia		3/119	3%
	Gabapentin 1800	Insomnia	Withdrawal	2/119	2%
	Placebo	Nausea and/or vomiting		9/128	7%
	Gabapentin 1800	Nausea and/or vomiting		10/119	8%
	Placebo	Otitis media		4/128	3%
	Gabapentin 1800	Otitis media		1/119	1%
	Placebo	Pharyngitis		11/128	9%
	Gabapentin 1800	Pharyngitis		10/119	8%
	Placebo	Respiratory infection		1/128	1%
	Gabapentin 1800	Respiratory infection		3/119	3%
	Placebo	Rhinitis		6/128	5%
	Gabapentin 1800	Rhinitis		6/119	5%
	Placebo	Somnolence		6/128	5%
	Gabapentin 1800	Somnolence	Withdrawal	2/119	2%
	Gabapentin 1800	Somnolence		10/119	8%
	Placebo	Upper respiratory tract infection		8/128	6%
	Gabapentin 1800	Upper respiratory tract infection		7/119	6%
	Placebo	Viral infection		4/128	3%
	Gabapentin 1800	Viral infection		13/119	11%
	Placebo	Weight gain		1/128	1%
	Gabapentin 1800	Weight gain		4/119	3%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Biton (1999)	Placebo	Abdominal pain		2/41	5%
	Topiramate 400	Abdominal pain		4/39	10%
	Topiramate 400	Abnormal gait	Severe	1/39	3%
	Placebo	Anorexia		3/41	7%
	Topiramate 400	Anorexia	Withdrawal	1/39	3%
	Topiramate 400	Anorexia		6/39	15%
	Placebo	Chest pain	Severe	1/41	2%
	Placebo	Dizziness		6/41	15%
	Topiramate 400	Dizziness		4/39	10%
	Placebo	Dyspepsia	Severe	1/41	2%
	Placebo	Fatigue		3/41	7%
	Topiramate 400	Fatigue		7/39	18%
	Placebo	Granulocytopenia	Withdrawal	1/41	2%
	Placebo	Headache	Severe	2/41	5%
	Placebo	Headache		8/41	20%
	Topiramate 400	Headache		5/39	13%
	Placebo	Impotence	Severe	1/41	2%
	Topiramate 400	Injury	Severe	1/39	3%
	Placebo	Memory difficulty		0/41	0%
	Topiramate 400	Memory difficulty		5/39	13%
	Placebo	Nervousness		0/41	0%
	Topiramate 400	Nervousness		4/39	10%
	Topiramate 400	Pain	Severe	1/39	3%
	Placebo	Pharyngitis		2/41	5%
	Topiramate 400	Pharyngitis		4/39	10%
	Placebo	Psychomotor slowing		1/41	2%
	Topiramate 400	Psychomotor slowing		4/39	10%
	Placebo	Saliva	Severe	1/41	2%
	Placebo	Somnolence		6/41	15%
	Topiramate 400	Somnolence		10/39	26%
	Placebo	Speech problems		1/41	2%
	Topiramate 400	Speech problems	Severe	1/39	3%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Biton (1999) continued	Topiramate 400	Speech problems		4/39	10%
	Placebo	Upper respiratory tract infection		13/41	32%
	Topiramate 400	Upper respiratory tract infection		16/39	41%
	Topiramate 400	Viral infection	Severe	1/39	3%
	Placebo	Weight loss		1/41	2%
	Topiramate 400	Weight loss		6/39	15%
Duchowny (1999)	Placebo	Abdominal pain		7/101	7%
	Lamotrigine 750	Abdominal pain		13/98	13%
	Placebo	Accidental injury		15/101	15%
	Lamotrigine 750	Accidental injury		14/98	14%
	Placebo	Any	Severe	9/101	9%
	Placebo	Any	Any	96/101	95%
	Lamotrigine 750	Any	Severe	7/98	7%
	Lamotrigine 750	Any	Any	92/98	94%
	Placebo	Asthenia		6/101	6%
	Lamotrigine 750	Asthenia		11/98	11%
	Placebo	Ataxia		2/101	2%
	Lamotrigine 750	Ataxia		10/98	10%
	Placebo	Brain tumor	Withdrawal	1/101	1%
	Placebo	Diarrhea		13/101	13%
	Lamotrigine 750	Diarrhea		13/98	13%
	Placebo	Dizziness		5/101	5%
	Lamotrigine 750	Dizziness		21/98	21%
	Placebo	Fever		12/101	12%
	Lamotrigine 750	Fever		14/98	14%
	Placebo	Headache		15/101	15%
	Lamotrigine 750	Headache		18/98	18%
	Placebo	Increase in seizures	Withdrawal	1/101	1%
	Placebo	Infection		22/101	22%
	Lamotrigine 750	Infection		21/98	21%
	Placebo	Nausea		2/101	2%
	Lamotrigine 750	Nausea		11/98	11%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Duchowny (1999) continued	Placebo	Otitis media		11/101	11%
	Lamotrigine 750	Otitis media		9/98	9%
	Placebo	Pharyngitis		10/101	10%
	Lamotrigine 750	Pharyngitis		11/98	11%
	Placebo	Rash	Withdrawal	3/101	3%
	Placebo	Rash		18/101	18%
	Lamotrigine 750	Rash	Withdrawal	4/98	4%
	Lamotrigine 750	Rash		1/98	1%
	Placebo	Rhinitis		17/101	17%
	Lamotrigine 750	Rhinitis		14/98	14%
	Placebo	Somnolence		18/101	18%
	Lamotrigine 750	Somnolence		24/98	24%
	Placebo	Threatened suicide	Withdrawal	1/101	1%
	Placebo	Tremor		2/101	2%
	Lamotrigine 750	Tremor	Withdrawal	1/98	1%
	Lamotrigine 750	Tremor		12/98	12%
	Placebo	Vomiting		19/101	19%
	Lamotrigine 750	Vomiting		22/98	22%
Elterman (1999)	Placebo	Aggression		3/45	7%
	Topiramate 400	Aggression		4/41	10%
	Placebo	Anorexia		5/45	11%
	Topiramate 400	Anorexia		5/41	12%
	Placebo	Bleeding		2/45	4%
	Topiramate 400	Bleeding		6/41	15%
	Placebo	Bodily injury		4/45	9%
	Topiramate 400	Bodily injury		8/41	20%
	Topiramate 400	Constipation	Severe	1/41	2%
	Placebo	Coughing		5/45	11%
	Topiramate 400	Coughing		6/41	15%
	Placebo	Death	Severe	0/45	0%
	Topiramate 400	Death	Severe	0/41	0%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Elterman (1999) continued	Placebo	Diarrhea		10/45	22%
	Topiramate 400	Diarrhea		4/41	10%
	Placebo	Emotional lability		2/45	4%
	Topiramate 400	Emotional lability		5/41	12%
	Placebo	Fatigue		3/45	7%
	Topiramate 400	Fatigue		6/41	15%
	Placebo	Fever		11/45	24%
	Topiramate 400	Fever		12/41	29%
	Placebo	Hospitalization for increase in seizures	Severe	2/45	4%
	Placebo	Impaired concentration		1/45	2%
	Topiramate 400	Impaired concentration		5/41	12%
	Placebo	Memory difficulty		0/45	0%
	Topiramate 400	Memory difficulty		3/41	7%
	Placebo	Mood problems		5/45	11%
	Topiramate 400	Mood problems		4/41	10%
	Placebo	Nervousness		3/45	7%
	Topiramate 400	Nervousness		4/41	10%
	Placebo	Otitis media		5/45	11%
	Topiramate 400	Otitis media		4/41	10%
	Placebo	Rash	Withdrawal	1/45	2%
	Placebo	Rash		4/45	9%
	Topiramate 400	Rash		5/41	12%
	Placebo	Sinusitis		12/45	27%
	Topiramate 400	Sinusitis		7/41	17%
	Placebo	Somnolence		6/45	13%
	Topiramate 400	Somnolence		5/41	12%
	Placebo	Upper respiratory tract infection		16/45	36%
	Topiramate 400	Upper respiratory tract infection		17/41	41%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Elterman (1999) continued	Placebo	Viral infection	Severe	1/45	2%
	Placebo	Viral infection		2/45	4%
	Topiramate 400	Viral infection		6/41	15%
KTSG (1999)	Placebo	Abdominal pain		2/86	2%
	Topiramate 600	Abdominal pain		19/91	21%
	Placebo	Ambylopia	Withdrawal	2/86	2%
	Placebo	Ambylopia		4/86	5%
	Topiramate 600	Ambylopia		10/91	11%
	Placebo	Anorexia		5/86	6%
	Topiramate 600	Anorexia		19/91	21%
	Placebo	Any	Any	42/86	49%
	Topiramate 600	Any	Any	74/91	81%
	Placebo	Ataxia	Withdrawal	1/86	1%
	Placebo	Ataxia		2/86	2%
	Topiramate 600	Ataxia		7/91	8%
	Placebo	Dizziness		18/86	21%
	Topiramate 600	Dizziness		18/91	20%
	Placebo	General weakness		2/86	2%
	Topiramate 600	General weakness		5/91	5%
	Placebo	Headache		6/86	7%
	Topiramate 600	Headache		10/91	11%
	Placebo	Memory difficulty		1/86	1%
	Topiramate 600	Memory difficulty		6/91	7%
	Placebo	Nausea and/or vomiting		7/86	8%
	Topiramate 600	Nausea and/or vomiting	Withdrawal	4/91	4%
	Topiramate 600	Nausea and/or vomiting		15/91	16%
	Placebo	Psychomotor slowing		1/86	1%
	Topiramate 600	Psychomotor slowing	Withdrawal	1/91	1%
	Topiramate 600	Psychomotor slowing		8/91	9%
	Placebo	Somnolence		8/86	9%
	Topiramate 600	Somnolence		18/91	20%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
KTSG (1999) continued	Placebo	Speech problems		1/86	1%
	Topiramate 600	Speech problems		9/91	10%
	Topiramate 600	Tremor	Withdrawal	2/91	2%
	Placebo	Weight loss		0/86	0%
	Topiramate 600	Weight loss		8/91	9%
Sachdeo (1999)	Placebo	Anorexia		10/50	20%
	Topiramate 600	Anorexia		19/48	40%
	Placebo	Any	Severe	5/50	10%
	Topiramate 600	Any	Severe	11/48	23%
	Placebo	Behavioral problems		5/50	10%
	Topiramate 600	Behavioral problems		10/48	21%
	Placebo	Dizziness		0/50	0%
	Topiramate 600	Dizziness		5/48	10%
	Placebo	Fatigue		2/50	4%
	Topiramate 600	Fatigue		9/48	19%
	Placebo	Nervousness		5/50	10%
	Topiramate 600	Nervousness		10/48	21%
	Placebo	Somnolence		11/50	22%
	Topiramate 600	Somnolence		20/48	42%
	Placebo	Weight loss		0/50	0%
	Topiramate 600	Weight loss		5/48	10%
Uthman (1998)	Placebo	Abnormal thinking		3/91	3%
	Tiagabine 16	Abnormal thinking		2/61	3%
	Tiagabine 32	Abnormal thinking		7/88	8%
	Tiagabine 56	Abnormal thinking		8/57	14%
	Placebo	Depression		0/91	0%
	Tiagabine 16	Depression		4/61	7%
	Tiagabine 32	Depression		2/88	2%
	Tiagabine 56	Depression		4/57	7%
	Placebo	Dizziness		15/91	16%
	Tiagabine 16	Dizziness		18/61	30%
	Tiagabine 32	Dizziness		29/88	33%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Uthman (1998) continued	Tiagabine 56	Dizziness		17/57	30%
	Placebo	Nervous system	Withdrawal	1/91	1%
	Placebo	Nervous system		57/91	63%
	Tiagabine 16	Nervous system	Withdrawal	2/61	3%
	Tiagabine 16	Nervous system		42/61	69%
	Tiagabine 32	Nervous system	Withdrawal	10/88	11%
	Tiagabine 32	Nervous system		62/88	70%
	Tiagabine 56	Nervous system	Withdrawal	8/57	14%
	Tiagabine 56	Nervous system		44/57	77%
	Placebo	Tremor		3/91	3%
	Tiagabine 16	Tremor		6/61	10%
	Tiagabine 32	Tremor		13/88	15%
	Tiagabine 56	Tremor		12/57	21%
Sachdeo (1997b)	Placebo	Abdominal pain		1/107	0.9%
	Tiagabine 32	Abdominal pain		10/105	9.5%
	Tiagabine 32	Abdominal pain		8/106	7.5%
	Placebo	Amnesia		1/107	0.9%
	Tiagabine 32	Amnesia		5/105	4.8%
	Tiagabine 32	Amnesia		7/106	6.6%
	Placebo	Any	Severe	2/107	2%
	Tiagabine 32	Any	Severe	2/105	2%
	Tiagabine 32	Any	Severe	2/106	2%
	Placebo	Emotional lability		1/107	0.9%
	Tiagabine 32	Emotional lability		8/105	7.6%
	Tiagabine 32	Emotional lability		1/106	0.9%
	Placebo	Nervousness		1/107	0.9%
	Tiagabine 32	Nervousness		11/105	10.5%
	Tiagabine 32	Nervousness		10/106	9.4%
	Placebo	Vomiting		3/107	2.8%
	Tiagabine 32	Vomiting		4/105	3.8%
	Tiagabine 32	Vomiting		10/106	9.4%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Ben-Menachem (1996)	Placebo	Any	Severe	0/28	0%
	Topiramate 800	Any	Severe	0/28	0%
	Placebo	Death	Severe	0/28	0%
	Topiramate 800	Death	Severe	0/28	0%
	Placebo	Dizziness		1/28	4%
	Topiramate 800	Dizziness		6/28	21%
	Placebo	Fatigue		10/28	36%
	Topiramate 800	Fatigue		22/28	79%
	Placebo	Headache		10/28	36%
	Topiramate 800	Headache		6/28	21%
	Placebo	Impaired concentration		0/28	0%
	Topiramate 800	Impaired concentration		7/28	25%
	Placebo	Paresthesia		1/28	4%
	Topiramate 800	Paresthesia		5/28	18%
	Placebo	Weight loss		0/28	0%
	Topiramate 800	Weight loss		7/28	25%
Chadwick (1996)	Placebo	Amblyopia		2/71	3%
	Gabapentin 1200	Amblyopia		3/58	5%
	Placebo	Any	Severe	10/71	14%
	Placebo	Any	Moderate	22/71	31%
	Placebo	Any	Mild	8/71	11%
	Placebo	Any	Any	40/71	56%
	Gabapentin 1200	Any	Severe	9/58	16%
	Gabapentin 1200	Any	Moderate	16/58	28%
	Gabapentin 1200	Any	Mild	14/58	24%
	Gabapentin 1200	Any	Any	39/58	67%
	Placebo	Ataxia		5/71	7%
	Gabapentin 1200	Ataxia		4/58	7%
	Placebo	Convulsions		8/71	11%
	Gabapentin 1200	Convulsions		5/58	9%
	Placebo	Death	Severe	0/71	0%
	Gabapentin 1200	Death	Severe	1/58	2%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Chadwick (1996) continued	Placebo	Dizziness		3/71	4%
	Gabapentin 1200	Dizziness		6/58	10%
	Placebo	Emotional lability		3/71	4%
	Gabapentin 1200	Emotional lability		4/58	7%
	Placebo	Fatigue		4/71	6%
	Gabapentin 1200	Fatigue		6/58	10%
	Placebo	Headache		6/71	8%
	Gabapentin 1200	Headache		2/58	3%
	Placebo	Nausea and/or vomiting		4/71	6%
	Gabapentin 1200	Nausea and/or vomiting		4/58	7%
	Placebo	Rash		2/71	3%
	Gabapentin 1200	Rash		3/58	5%
	Placebo	Somnolence		3/71	4%
	Gabapentin 1200	Somnolence		7/58	12%
	Placebo	Thrombocytopenia		0/71	0%
	Gabapentin 1200	Thrombocytopenia		3/58	5%
	Placebo	Weight gain		5/71	7%
	Gabapentin 1200	Weight gain		4/58	7%
Faught (1996)	Placebo	Abnormal thinking		1/45	2%
	Topiramate 200	Abnormal thinking		9/45	20%
	Topiramate 400	Abnormal thinking		6/45	13%
	Topiramate 600	Abnormal thinking		14/46	30%
	Placebo	Any	Severe	0/45	0%
	Topiramate 200	Any	Severe	0/45	0%
	Topiramate 400	Any	Severe	0/45	0%
	Topiramate 600	Any	Severe	0/46	0%
	Placebo	Ataxia		4/45	9%
	Topiramate 200	Ataxia		9/45	20%
	Topiramate 400	Ataxia		13/45	29%
	Topiramate 600	Ataxia		12/46	26%
	Placebo	Death	Severe	0/45	0%
	Topiramate 200	Death	Severe	0/45	0%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Faught (1996) continued	Topiramate 400	Death	Severe	0/45	0%
	Topiramate 600	Death	Severe	0/46	0%
	Placebo	Diplopia		2/45	4%
	Topiramate 200	Diplopia		3/45	7%
	Topiramate 400	Diplopia		11/45	24%
	Topiramate 600	Diplopia		3/46	7%
	Placebo	Dizziness		13/45	29%
	Topiramate 200	Dizziness		16/45	36%
	Topiramate 400	Dizziness		15/45	33%
	Topiramate 600	Dizziness		16/46	35%
	Placebo	Fatigue		5/45	11%
	Topiramate 200	Fatigue		5/45	11%
	Topiramate 400	Fatigue		3/45	7%
	Topiramate 600	Fatigue		9/46	20%
	Placebo	Headache		13/45	29%
	Topiramate 200	Headache		13/45	29%
	Topiramate 400	Headache		14/45	31%
	Topiramate 600	Headache		13/46	28%
	Placebo	Nystagmus		8/45	18%
	Topiramate 200	Nystagmus		8/45	18%
	Topiramate 400	Nystagmus		9/45	20%
	Topiramate 600	Nystagmus		7/46	15%
	Placebo	Paresthesia		1/45	2%
	Topiramate 200	Paresthesia		8/45	18%
	Topiramate 400	Paresthesia		9/45	20%
	Topiramate 600	Paresthesia		4/46	9%
	Placebo	Somnolence		4/45	9%
	Topiramate 200	Somnolence		13/45	29%
	Topiramate 400	Somnolence		12/45	27%
	Topiramate 600	Somnolence		14/46	30%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Privitera (1996)	Topiramate 1000	Abdominal pain	Severe	1/47	2%
	Placebo	Abnormal thinking		3/47	6%
	Topiramate 600	Abnormal thinking		16/48	33%
	Topiramate 800	Abnormal thinking		21/48	44%
	Topiramate 1000	Abnormal thinking		12/47	26%
	Placebo	Anorexia		2/47	4%
	Topirama te 600	Anorexia		5/48	10%
	Topiramate 800	Anorexia		3/48	6%
	Topiramate 1000	Anorexia		10/47	21%
	Placebo	Ataxia		4/47	9%
	Topiramate 600	Ataxia		7/48	15%
	Topiramate 800	Ataxia		9/48	19%
	Topiramate 1000	Ataxia		9/47	19%
	Placebo	Confusion		4/47	9%
	Topiramate 600	Confusion		10/48	21%
	Topiramate 800	Confusion		11/48	23%
	Topiramate 1000	Confusion		13/47	28%
	Placebo	Death	Severe	0/47	0%
	Topiramate 600	Death	Severe	0/48	0%
	Topiramate 800	Death	Severe	0/48	0%
	Topiramate 1000	Death	Severe	0/47	0%
	Placebo	Diplopia		6/47	13%
	Topiramate 600	Diplopia		7/48	15%
	Topiramate 800	Diplopia		10/48	21%
	Topiramate 1000	Diplopia		13/47	28%
	Placebo	Dizziness		7/47	15%
	Topiramate 600	Dizziness		16/48	33%
	Topiramate 800	Dizziness		17/48	35%
	Topiramate 1000	Dizziness		18/47	38%
	Placebo	Fatigue		4/47	9%
	Topiramate 600	Fatigue		18/48	38%
	Topiramate 800	Fatigue		11/48	23%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Privitera (1996) continued	Topiramate 1000	Fatigue		11/47	23%
	Placebo	Headache		15/47	32%
	Topiramate 600	Headache		16/48	33%
	Topiramate 800	Headache		13/48	27%
	Topiramate 1000	Headache		9/47	19%
	Placebo	Impaired concentration		0/47	0%
	Topiramate 600	Impaired concentration		8/48	17%
	Topiramate 800	Impaired concentration		4/48	8%
	Topiramate 1000	Impaired concentration		10/47	21%
	Placebo	Nystagmus		8/47	17%
	Topiramate 600	Nystagmus		4/48	8%
	Topiramate 800	Nystagmus		11/48	23%
	Topiramate 1000	Nystagmus		13/47	28%
	Placebo	Paresthesia		3/47	6%
	Topiramate 600	Paresthesia		11/48	23%
	Topiramate 800	Paresthesia		9/48	19%
	Topiramate 1000	Paresthesia		6/47	13%
	Topiramate 1000	Shortness of breath	Severe	1/47	2%
	Placebo	Somnolence		6/47	13%
	Topiramate 600	Somnolence		6/48	13%
	Topiramate 800	Somnolence		15/48	31%
	Topiramate 1000	Somnolence		16/47	34%
Sharief (1996)	Placebo	Abnormal vision		0/24	0%
	Topiramate 400	Abnormal vision		6/23	26%
	Placebo	Amnesia		0/24	0%
	Topiramate 400	Amnesia		3/23	13%
	Placebo	Anxiety		1/24	4%
	Topiramate 400	Anxiety		5/23	22%
	Placebo	Any	Severe	0/24	0%
	Topiramate 400	Any	Severe	0/23	0%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Sharief (1996) continued	Placebo	Aphasia		0/24	0%
	Topiramate 400	Aphasia		3/23	13%
	Placebo	Asthenia		1/24	4%
	Topiramate 400	Asthenia		4/23	17%
	Placebo	Central nervous system	Withdrawal	1/24	4%
	Topiramate 400	Central nervous system	Withdrawal	5/23	22%
	Placebo	Confusion		4/24	17%
	Topiramate 400	Confusion		3/23	13%
	Placebo	Depression		3/24	13%
	Topiramate 400	Depression		2/23	9%
	Topiramate 400	Dyspepsia	Withdrawal	1/23	4%
	Placebo	Emotional lability		0/24	0%
	Topiramate 400	Emotional lability		3/23	13%
	Placebo	Fatigue		4/24	17%
	Topiramate 400	Fatigue		6/23	26%
	Placebo	Headache		5/24	21%
	Topiramate 400	Headache		3/23	13%
	Placebo	Impaired concentration		1/24	4%
	Topiramate 400	Impaired concentration		4/23	17%
	Placebo	Injury		3/24	13%
	Topiramate 400	Injury		1/23	4%
	Placebo	Nervousness		3/24	13%
	Topiramate 400	Nervousness		2/23	9%
	Placebo	Pharyngitis		0/24	0%
	Topiramate 400	Pharyngitis		3/23	13%
	Placebo	Somnolence		4/24	17%
	Topiramate 400	Somnolence		8/23	35%
	Placebo	Speech problems		2/24	8%
	Topiramate 400	Speech problems		3/23	13%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Sharief (1996) continued	Placebo	Upper respiratory tract infection		2/24	8%
	Topiramate 400	Upper respiratory tract infection		4/23	17%
	Placebo	Weight loss		2/24	8%
	Topiramate 400	Weight loss		6/23	26%
Tassinari (1996)	Placebo	Abnormal thinking		0/30	0%
	Topiramate 600	Abnormal thinking		5/30	17%
	Placebo	Amnesia	Withdrawal	1/30	3%
	Placebo	Amnesia		2/30	7%
	Topiramate 600	Amnesia		2/30	7%
	Placebo	Anxiety		3/30	10%
	Topiramate 600	Anxiety		2/30	7%
	Placebo	Confusion		0/30	0%
	Topiramate 600	Confusion		3/30	10%
	Placebo	Convulsions aggravated		2/30	7%
	Topiramate 600	Convulsions aggravated		3/30	10%
	Placebo	Depression		2/30	7%
	Topiramate 600	Depression		5/30	17%
	Placebo	Diarrhea		1/30	3%
	Topiramate 600	Diarrhea		3/30	10%
	Placebo	Dizziness		3/30	10%
	Topiramate 600	Dizziness		7/30	23%
	Placebo	Emotional lability		1/30	3%
	Topiramate 600	Emotional lability		4/30	13%
	Placebo	Fatigue		3/30	10%
	Topiramate 600	Fatigue		6/30	20%
	Placebo	Headache		3/30	10%
	Topiramate 600	Headache		8/30	27%
	Placebo	Impaired concentration		0/30	0%
	Topiramate 600	Impaired concentration		2/30	7%
	Topiramate 600	Increased seizures	Withdrawal	1/30	3%
	Placebo	Nausea		2/30	7%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Tassinari (1996) continued	Topiramate 600	Nausea	Withdrawal	1/30	3%
	Topiramate 600	Nausea		3/30	10%
	Topiramate 600	Seizure-associated injuries	Withdrawal	1/30	3%
	Placebo	Somnolence		4/30	13%
	Topiramate 600	Somnolence	Withdrawal	1/30	3%
	Topiramate 600	Somnolence		6/30	20%
	Placebo	Upper respiratory tract infection		1/30	3%
	Topiramate 600	Upper respiratory tract infection		3/30	10%
	Placebo	Weight loss		2/30	7%
	Topiramate 600	Weight loss		5/30	17%
Willmore (1996)	Placebo	Abdominal pain		4/70	6%
	Valproate 90 mg/kg	Abdominal pain		18/77	23%
	Placebo	Anorexia		0/70	0%
	Valproate 90 mg/kg	Anorexia		9/77	12%
	Placebo	Asthenia		5/70	7%
	Valproate 90 mg/kg	Asthenia		21/77	27%
	Valproate 90 mg/kg	Erythema	Withdrawal	1/77	1%
	Valproate 90 mg/kg	Leukopenia	Withdrawal	1/77	1%
	Placebo	Nausea		10/70	14%
	Valproate 90 mg/kg	Nausea		37/77	48%
	Valproate 90 mg/kg	Nausea and/or vomiting	Withdrawal	3/77	4%
	Valproate 90 mg/kg	Psychosis	Withdrawal	1/77	1%
	Placebo	Somnolence		8/70	11%
	Valproate 90 mg/kg	Somnolence		21/77	27%
	Placebo	Tremor		4/70	6%
	Valproate 90 mg/kg	Tremor		19/77	25%
	Placebo	Vomiting		5/70	7%
	Valproate 90 mg/kg	Vomiting		21/77	27%
Anhut (1994)	Placebo	Any	Any	57/109	52%
	Gabapentin 900	Any	Any	76/111	68%
	Gabapentin 1200	Any	Any	33/52	63%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Anhut (1994) continued	Placebo	Ataxia		3/109	3%
	Gabapentin 900	Ataxia		12/111	11%
	Gabapentin 1200	Ataxia		1/52	2%
	Placebo	Convulsions		3/109	3%
	Gabapentin 900	Convulsions		8/111	7%
	Gabapentin 1200	Convulsions		0/52	0%
	Gabapentin 900	Death	Severe	1/111	1%
	Placebo	Diplopia		2/109	2%
	Gabapentin 900	Diplopia		5/111	5%
	Gabapentin 1200	Diplopia		2/52	4%
	Placebo	Dizziness		9/109	8%
	Gabapentin 900	Dizziness		23/111	21%
	Gabapentin 1200	Dizziness		7/52	13%
	Placebo	Fatigue		5/109	5%
	Gabapentin 900	Fatigue		10/111	9%
	Gabapentin 1200	Fatigue		6/52	12%
	Placebo	Headache		8/109	7%
	Gabapentin 900	Headache		2/111	2%
	Gabapentin 1200	Headache		3/52	6%
	Placebo	Increased appetite		2/109	2%
	Gabapentin 900	Increased appetite		3/111	3%
	Gabapentin 1200	Increased appetite		3/52	6%
	Placebo	Nausea and/or vomiting		10/109	9%
	Gabapentin 900	Nausea and/or vomiting		7/111	6%
	Gabapentin 1200	Nausea and/or vomiting		2/52	4%
	Placebo	Somnolence		13/109	12%
	Gabapentin 900	Somnolence		24/111	22%
	Gabapentin 1200	Somnolence		7/52	13%
	Placebo	Tremor		2/109	2%
	Gabapentin 900	Tremor		2/111	2%
	Gabapentin 1200	Tremor		4/52	8%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Messenheimer (1994)	Lamotrigine 400	Central nervous system	Withdrawal	2/44	5%
	Placebo	Rash	Withdrawal	1/44	2%
	Lamotrigine 400	Rash	Withdrawal	3/44	7%
Bourgeois (1993)	Felbamate 3600	Agitation	Withdrawal	1/30	3%
	Placebo	Anorexia		0/34	0%
	Felbamate 3600	Anorexia		6/30	20%
	Placebo	Anxiety		2/34	6%
	Felbamate 3600	Anxiety		4/30	13%
	Placebo	Constipation		1/34	3%
	Felbamate 3600	Constipation		6/30	20%
	Placebo	Dizziness		5/34	15%
	Felbamate 3600	Dizziness	Withdrawal	1/30	3%
	Felbamate 3600	Dizziness		7/30	23%
	Placebo	Dyspepsia		3/34	9%
	Felbamate 3600	Dyspepsia		5/30	17%
	Placebo	Fatigue		2/34	6%
	Felbamate 3600	Fatigue		6/30	20%
	Placebo	Headache		4/34	12%
	Felbamate 3600	Headache		12/30	40%
	Placebo	Insomnia		2/34	6%
	Felbamate 3600	Insomnia		11/30	37%
	Placebo	Nausea		1/34	3%
	Felbamate 3600	Nausea		11/30	37%
	Placebo	Psychosis	Withdrawal	1/34	3%
	Placebo	Somnolence		3/34	9%
	Felbamate 3600	Somnolence		3/30	10%
	Felbamate 3600	Stupor	Severe	1/30	3%
	Placebo	Vomiting		1/34	3%
	Felbamate 3600	Vomiting		4/30	13%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
FSG (1993)	Placebo	Abnormal gait		0/36	0%
	Felbamate 3600	Abnormal gait		5/37	14%
	Placebo	Anorexia		5/36	14%
	Felbamate 3600	Anorexia		18/37	49%
	Placebo	Any	Severe	3/36	8%
	Felbamate 3600	Any	Severe	8/37	22%
	Placebo	Ataxia		1/36	3%
	Felbamate 3600	Ataxia		4/37	11%
	Placebo	Diarrhea		8/36	22%
	Felbamate 3600	Diarrhea		1/37	3%
	Placebo	Fatigue		2/36	6%
	Felbamate 3600	Fatigue		6/37	16%
	Placebo	Fever		5/36	14%
	Felbamate 3600	Fever		8/37	22%
	Placebo	Headache		5/36	14%
	Felbamate 3600	Headache		4/37	11%
	Placebo	Injury		10/36	28%
	Felbamate 3600	Injury		6/37	16%
	Placebo	Insomnia		5/36	14%
	Felbamate 3600	Insomnia		6/37	16%
	Placebo	Nervousness		5/36	14%
	Felbamate 3600	Nervousness		5/37	14%
	Placebo	Pancreatitis	Withdrawal	1/36	3%
	Placebo	Purpura		3/36	8%
	Felbamate 3600	Purpura		4/37	11%
	Placebo	Rhinitis		4/36	11%
	Felbamate 3600	Rhinitis		1/37	3%
	Placebo	Somnolence		3/36	8%
	Felbamate 3600	Somnolence	Withdrawal	1/37	3%
	Felbamate 3600	Somnolence		16/37	43%
	Placebo	Upper respiratory tract infection		10/36	28%
	Felbamate 3600	Upper respiratory tract infection		14/37	38%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
FSG (1993) continued	Placebo	Vomiting		5/36	14%
	Felbamate 3600	Vomiting		15/37	41%
Matsuo (1993)	Lamotrigine 500	Allergic reaction	Severe	1/72	1%
	Lamotrigine 500	Ataxia	Withdrawal	1/72	1%
	Placebo	Ataxia	Any	7/73	10%
	Lamotrigine 300	Ataxia	Any	7/71	10%
	Lamotrigine 500	Ataxia	Any	20/72	28%
	Lamotrigine 500	Blurred vision	Withdrawal	3/72	4%
	Placebo	Blurred vision	Any	7/73	10%
	Lamotrigine 300	Blurred vision	Any	8/71	11%
	Lamotrigine 500	Blurred vision	Any	18/72	25%
	Lamotrigine 500	Delerium	Severe	1/72	1%
	Lamotrigine 500	Delusions	Severe	1/72	1%
	Lamotrigine 500	Diplopia	Withdrawal	2/72	3%
	Placebo	Diplopia	Any	6/73	8%
	Lamotrigine 300	Diplopia	Any	17/71	24%
	Lamotrigine 500	Diplopia	Any	35/72	49%
	Lamotrigine 500	Dizziness	Withdrawal	4/72	6%
	Placebo	Dizziness	Withdrawal	1/73	1%
	Placebo	Dizziness	Any	20/73	27%
	Lamotrigine 300	Dizziness	Any	22/71	31%
	Lamotrigine 500	Dizziness	Any	39/72	54%
	Lamotrigine 500	Headache	Withdrawal	3/72	4%
	Placebo	Headache	Withdrawal	1/73	1%
	Placebo	Headache	Any	19/73	26%
	Lamotrigine 300	Headache	Any	23/71	32%
	Lamotrigine 500	Headache	Any	23/72	32%
	Lamotrigine 500	Nausea	Withdrawal	3/72	4%
	Placebo	Nausea	Withdrawal	1/73	1%
	Placebo	Nausea	Any	8/73	11%
	Lamotrigine 300	Nausea	Withdrawal	1/71	1%
	Lamotrigine 300	Nausea	Any	13/71	18%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Matsuo (1993) continued	Lamotrigine 500	Nausea	Any	18/72	25%
	Placebo	Pain	Any	2/73	3%
	Lamotrigine 300	Pain	Any	9/71	13%
	Lamotrigine 500	Pain	Any	5/72	7%
	Lamotrigine 500	Panic	Severe	1/72	1%
	Lamotrigine 300	Psychosis	Severe	1/71	1%
	Placebo	Rash	Any	7/73	10%
	Lamotrigine 300	Rash	Withdrawal	1/71	1%
	Lamotrigine 300	Rash	Any	12/71	17%
	Lamotrigine 500	Rash	Any	7/72	10%
	Placebo	Somnolence	Any	5/73	7%
	Lamotrigine 300	Somnolence	Any	15/71	21%
	Lamotrigine 500	Somnolence	Any	7/72	10%
	Lamotrigine 500	Vomiting	Withdrawal	1/72	1%
	Placebo	Vomiting	Any	3/73	4%
	Lamotrigine 300	Vomiting	Any	8/71	11%
	Lamotrigine 500	Vomiting	Any	13/72	18%
McLean (1993)	Gabapentin 1200	Agitation	Withdrawal	1/101	1%
	Placebo	Any	Any	71/98	72%
	Gabapentin 600	Any	Any	46/53	87%
	Gabapentin 1200	Any	Any	89/101	88%
	Gabapentin 1800	Any	Any	49/54	91%
	Placebo	Ataxia		11/98	11%
	Gabapenti n 600	Ataxia		6/53	11%
	Gabapentin 1200	Ataxia		26/101	26%
	Gabapentin 1800	Ataxia		10/54	19%
	Placebo	Diplopia		4/98	4%
	Gabapentin 600	Diplopia		5/53	9%
	Gabapentin 1200	Diplopia		11/101	11%
	Gabapentin 1800	Diplopia		2/54	4%
	Placebo	Dizziness		9/98	9%
	Gabapentin 600	Dizziness		13/53	25%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
McLean (1993) continued	Gabapentin 1200	Dizziness		25/101	25%
	Gabapentin 1800	Dizziness		10/54	19%
	Placebo	Dyspnea	Withdrawal	1/98	1%
	Placebo	Fatigue		7/98	7%
	Gabapentin 600	Fatigue	Withdrawal	1/53	2%
	Gabapentin 600	Fatigue		6/53	11%
	Gabapentin 1200	Fatigue	Withdrawal	1/101	1%
	Gabapentin 1200	Fatigue		11/101	11%
	Gabapentin 1800	Fatigue		7/54	13%
	Placebo	Headache		12/98	12%
	Gabapentin 600	Headache		10/53	19%
	Gabapentin 1200	Headache		9/101	9%
	Gabapentin 1800	Headache		11/54	20%
	Gabapentin 1800	Hemiparesis	Withdrawal	1/54	2%
	Gabapentin 1800	Low hemoglobin	Withdrawal	1/54	2%
	Gabapentin 600	Myoclonic jerks	Withdrawal	1/53	2%
	Placebo	Nausea and/or vomiting		9/98	9%
	Gabapentin 600	Nausea and/or vomiting		7/53	13%
	Gabapentin 1200	Nausea and/or vomiting		6/101	6%
	Gabapentin 1800	Nausea and/or vomiting		5/54	9%
	Placebo	Nystagmus		13/98	13%
	Gabapentin 600	Nystagmus		5/53	9%
	Gabapentin 1200	Nystagmus		17/101	17%
	Gabapentin 1800	Nystagmus		9/54	17%
	Placebo	Rhinitis		10/98	10%
	Gabapentin 600	Rhinitis		4/53	8%
	Gabapentin 1200	Rhinitis		11/101	11%
	Gabapentin 1800	Rhinitis		7/54	13%
	Placebo	Somnolence		12/98	12%
	Gabapentin 600	Somnolence		4/53	8%
	Gabapentin 1200	Somnolence		36/101	36%
	Gabapentin 1800	Somnolence		11/54	20%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
McLean (1993) continued	Placebo	Tremor		9/98	9%
	Gabapentin 600	Tremor		4/53	8%
	Gabapentin 1200	Tremor		15/101	15%
	Gabapentin 1800	Tremor		7/54	13%
	Gabapentin 600	Urinary frequency	Withdrawal	1/53	2%
Schmidt (1993)	Placebo	Abdominal pain		3/68	4%
	Zonisamide 20 mg/kg	Abdominal pain		5/71	7%
	Placebo	Abnormal thinking		1/68	1%
	Zonisamide 20 mg/kg	Abnormal thinking		8/71	11%
	Placebo	Anorexia		1/68	1%
	Zonisamide 20 mg/kg	Anorexia		9/71	13%
	Placebo	Any	Any	19/68	28%
	Zonisamide 20 mg/kg	Any	Any	42/71	59%
	Placebo	Ataxia		0/68	0%
	Zonisamide 20 mg/kg	Ataxia		8/71	11%
	Placebo	Confusion		0/68	0%
	Zonisamide 20 mg/kg	Confusion	Withdrawal	1/71	1%
	Zonisamide 20 mg/kg	Confusion		4/71	6%
	Placebo	Dizziness		3/68	4%
	Zonisamide 20 mg/kg	Dizziness		12/71	17%
	Placebo	Fatigue		8/68	12%
	Zonisamide 20 mg/kg	Fatigue		16/71	23%
	Zonisamide 20 mg/kg	Increase in seizures	Withdrawal	1/71	1%
	Placebo	Nausea and/or vomiting		3/68	4%
	Zonisamide 20 mg/kg	Nausea and/or vomiting		3/71	4%
	Placebo	Nervousness		2/68	3%
	Zonisamide 20 mg/kg	Nervousness		7/71	10%
	Placebo	Somnolence		3/68	4%
	Zonisamide 20 mg/kg	Somnolence		10/71	14%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
Sivenius (1991)	Placebo	Blurred vision		2/18	11%
	Gabapentin 900	Blurred vision		1/16	6%
	Placebo	Depression		0/18	0%
	Gabapentin 900	Depression		0/16	0%
	Placebo	Dizziness		0/18	0%
	Gabapentin 900	Dizziness		2/16	13%
	Placebo	Drowsiness		2/18	11%
	Gabapentin 900	Drowsiness		4/16	25%
Sivenius (1991)	Placebo	Eczema		1/18	6%
	Gabapentin 900	Eczema		1/16	6%
	Placebo	Gastric irritability		1/18	6%
	Gabapentin 900	Gastric irritability		1/16	6%
	Placebo	Headache		1/18	6%
	Gabapentin 900	Headache		0/16	0%
	Placebo	Mania		1/18	6%
	Gabapentin 900	Mania		0/16	0%
	Placebo	Nystagmus		1/18	6%
	Gabapentin 900	Nystagmus		1/16	6%
	Placebo	Tremor	Mild	1/18	6%
	Gabapentin 900	Tremor	Mild	1/16	6%
UKGSG (1990)	Placebo	Altered mental state	Withdrawal	1/66	2%
	Placebo	Any	Any	27/66	41%
	Gabapentin 1200	Any	Any	38/61	62%
	Placebo	Confusion	Withdrawal	1/66	2%
	Placebo	Dizziness		3/66	4.5%
	Gabapentin 1200	Dizziness		4/61	6.6%
	Gabapentin 1200	Fatigue	Withdrawal	1/61	2%
	Gabapentin 1200	Fatigue		8/61	13.1%
	Placebo	General feeling of ill health	Withdrawal	1/66	2%
	Placebo	Generalized seizures	Withdrawal	1/66	2%
	Placebo	Headache		6/66	9.1%

Evidence Table 60. Adverse effects in studies of polytherapy (continued)

Reference	Drug And Dose (mg/day)	Adverse Effect	Severity of Adverse Effect	Patients With Effect / Patients in Group	Percentage
UKGSG (1990) continued	Gabapentin 1200	Increase in seizures	Withdrawal	1/61	2%
	Gabapentin 1200	Jitteriness	Withdrawal	1/61	2%
	Gabapentin 1200	Loss of speech	Withdrawal	1/61	2%
	Gabapentin 1200	Low white blood cell count	Withdrawal	1/61	2%
	Gabapentin 1200	Rash	Withdrawal	1/61	2%
	Placebo	Somnolence		3/66	4.5%
	Gabapentin 1200	Somnolence		9/61	14.8%
	Gabapentin 1200	Vomiting	Withdrawal	1/61	2%
	Gabapentin 1200	Weight gain		3/61	4.9%

Evidence Table 61. Quality of life outcomes and mood outcomes in studies of polytherapy

Primary Efficacy Study	Study Reporting Quality of Life	Drug And Dose (mg/day)	Quality of Life Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Cereghino (2000)	Cramer (2000)	Levetiracetam 1000 or 3000	QOLIE-31	Seizure worry	Better	Yes
		Levetiracetam 1000 or 3000	QOLIE-31	Overal quality of life	Better	Yes
		Levetiracetam 1000 or 3000	QOLIE-31	Emotional well-being	Better	No
		Levetiracetam 1000 or 3000	QOLIE-31	Energy-fatigue	Better	No
		Levetiracetam 1000 or 3000	QOLIE-31	Cognitive functioning	Better	Yes
		Levetiracetam 1000 or 3000	QOLIE-31	Medication effects	Better	No
		Levetiracetam 1000 or 3000	QOLIE-31	Social function	Better	No
		Levetiracetam 1000 or 3000	QOLIE-31	Health status	Better	No
		Levetiracetam 1000 or 3000	QOLIE-31	Total score	Better	Yes
Uthman (1998)	Dodrill (1997)	Tiagabine 32 or 56	Profile of Mood States	Tension-anxiety	Worse	No
		Tiagabine 32 or 56	Profile of Mood States	Depression-dejection	Better	No
		Tiagabine 32 or 56	Profile of Mood States	Anger-hostility	Worse	No
		Tiagabine 32 or 56	Profile of Mood States	Vigor-activity	Better	No
		Tiagabine 32 or 56	Profile of Mood States	Fatigue-inertia	Worse	No
		Tiagabine 32 or 56	Profile of Mood States	Confusion-bewilderment	Worse	No
		Tiagabine 32 or 56	Profile of Mood States	Total mood disturbance	Worse	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Family background	Better	No

Evidence Table 61. Quality of life outcomes and mood outcomes in studies of polytherapy (continued)

Primary Efficacy Study	Study Reporting Quality of Life	Drug And Dose (mg/day)	Quality of Life Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Uthman (1998) continued	Dodrill (1997)	Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Emotional adjustment	Worse	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Interpersonal adjustment	Worse	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Vocational adjustment	Better	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Financial status	Worse	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Adjustment to seizures	Better	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Medicine and medical management	Worse	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Overall functioning	Better	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Lie Scale	Better	No
		Tiagabine 32 or 56	Washington Psychosocial Seizure Inventory	Rare Items	Better	No
		Tiagabine 32 or 56	Mood Rating Scale	Mood Rating Scale	Better	No

QOLIE-31 Quality of life in epilepsy, 31 item scale to measure quality of life

Evidence Table 62. Cognitive function outcomes in studies of polytherapy

Primary Efficacy Study	Study Reporting Quality of Life	Drug And Dose (mg/day)	Functional Status/Ability Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Uthman (1998)	Dodrill (1997)	Tiagabine 32 or 56	Lafayette Grooved Pegboard	Preferred hand	Better	No
		Tiagabine 32 or 56	Lafayette Grooved Pegboard	Nonpreferred hand	Worse	No
		Tiagabine 32 or 56	Stroop Test	Reading speed	Better	No
		Tiagabine 32 or 56	Stroop Test	Reading speed, errors	Better	No
		Tiagabine 32 or 56	Stroop Test	Interference	Better	No
		Tiagabine 32 or 56	Stroop Test	Interference, errors	Worse	No
		Tiagabine 32 or 56	Benton Visual Retention Test	Form F	Worse	Yes
		Tiagabine 32 or 56	Benton Visual Retention Test	Form G	Worse	No
		Tiagabine 32 or 56	Controlled Oral Word Association Test	Controlled Oral Word Association Test	Worse	No
		Tiagabine 32 or 56	Symbol Digit Modalities Test	Symbol Digit Modalities Test	Worse	No
		Tiagabine 32 or 56	Rey Auditory Verbal Learning Test	Trial 1-5, first list recall	Better	No
		Tiagabine 32 or 56	Rey Auditory Verbal Learning Test	Trial 6, second list recall	Better	No
		Tiagabine 32 or 56	Rey Auditory Verbal Learning Test	Trial 7, first list recall	Better	No
		Tiagabine 32 or 56	Rey Auditory Verbal Learning Test	Trial 8, first delay recall	Better	No
		Tiagabine 32 or 56	Rey Auditory Verbal Learning Test	Trial 9, first delay recognition	Worse	No
		Tiagabine 32 or 56	Wonderlic Personnel Test	Items correct	Better	No

Evidence Table 62. Cognitive function outcomes in studies of polytherapy (continued)

Primary Efficacy Study	Study Reporting Quality of Life	Drug And Dose (mg/day)	Functional Status/Ability Scale	Subscale	Was Drug Better or Worse Than Baseline	Was The Difference Statistically Significant
Uthman (1998) continued	Dodrill (1997)	Tiagabine 32 or 56	Wonderlic Personnel Test	Items wrong	Better	No
		Tiagabine 32 or 56	Digit Cancellation	Number right	Worse	No
		Tiagabine 32 or 56	Digit Cancellation	Number omitted	Better	No

Evidence Table 63. Meta-analysis of seizure freedom in trials of polytherapy, high dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Faught (2001)	203	0.15 (-0.13 to 0.43)	0.3	-1.02	No	NA
Ben-Menachem (2000)	286	0.37 (0.13 to 0.61)	0	0.72	No	NA
Betts (2000)	77	0.14 (-0.31 to 0.59)	0.54	-0.64	No	NA
Cereghino (2000)	196	0.57 (0.29 to 0.85)	0	2.09	Yes	NA
Glauser (2000)	267	0.21 (-0.03 to 0.45)	0.09	-0.68	No	NA
Appleton (1999)	247	0.14 (-0.11 to 0.39)	0.27	-1.19	No	NA
Biton (1999)	80	0.46 (0.02 to 0.9)	0.04	0.78	No	NA
Elterman (1999)	86	0.45 (0.02 to 0.87)	0.04	0.76	No	NA
KTSG (1999)	177	0.35 (0.05 to 0.64)	0.02	0.42	No	NA
Sachdeo (1999)	98	0.29 (-0.11 to 0.69)	0.15	0.02	No	NA
Sharief (1996)	47	0.6 (0.03 to 1.17)	0.04	1.09	No	NA
Tassinari (1996)	60	0 (-0.51 to 0.51)	1	-1.12	No	NA
Willmore (1996)	147	0.33 (0 to 0.65)	0.05	0.26	No	NA
FSG (1993)	73	0 (-0.46 to 0.46)	1	-1.24	No	NA
Matsuo (1993)	145	0.3 (-0.03 to 0.62)	0.07	0.08	No	NA
Schmidt (1993)	139	0.24 (-0.1 to 0.57)	0.16	-0.3	No	NA
Random Effects Summary Effect Size (Cohen's h)		**0.29 (0.20 to 0.37)**	**0.000000**			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were more likely to become seizure free than patients who received a placebo.

NA Not applicable

Evidence Table 64. Meta-analysis of seizure freedom in trials of polytherapy, low dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Faught (2001)	203	0.15 (-0.13 to 0.43)	0.3	-0.97	No	NA
Ben-Menachem (2000)	286	0.37 (0.13 to 0.61)	0	0.78	No	NA
Betts (2000)	81	0.31 (-0.13 to 0.74)	0.17	0.12	No	NA
Cereghino (2000)	193	0.35 (0.07 to 0.63)	0.01	0.53	No	NA
Glauser (2000)	267	0.21 (-0.03 to 0.45)	0.09	-0.62	No	NA
Appleton (1999)	247	0.14 (-0.11 to 0.39)	0.27	-1.14	No	NA
Biton (1999)	80	0.46 (0.02 to 0.9)	0.04	0.81	No	NA
Elterman (1999)	86	0.45 (0.02 to 0.87)	0.04	0.79	No	NA
KTSG (1999)	177	0.35 (0.05 to 0.64)	0.02	0.47	No	NA
Sachdeo (1999)	98	0.29 (-0.11 to 0.69)	0.15	0.06	No	NA
Sharief (1996)	47	0.6 (0.03 to 1.17)	0.04	1.11	No	NA
Tassinari (1996)	60	0 (-0.51 to 0.51)	1	-1.09	No	NA
Willmore (1996)	147	0.33 (0 to 0.65)	0.05	0.3	No	NA
FSG (1993)	73	0 (-0.46 to 0.46)	1	-1.21	No	NA
Matsuo (1993)	144	0.4 (0.08 to 0.73)	0.02	0.78	No	NA
Schmidt (1993)	139	0.24 (-0.1 to 0.57)	0.16	-0.26	No	NA
Random Effects Summary Effect Size (Cohen's h)		**0.28 (0.20 to 0.36)**	**0.000000**			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were more likely to become seizure free than patients who received a placebo.

NA Not applicable

Evidence Table 65. Sensitivity analyses of seizure freedom in trials of polytherapy, high dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.29 (0.20 to 0.37)	0.000000
Largest effect size	Sharief (1996)	0.28 (0.20 to 0.36)	0.000000
Smallest effect size	Felbamate Study Group (1993)	0.29 (0.21 to 0.38)	0.000000
Largest sample size	Ben-Menachem (2000)	0.27 (0.19 to 0.36)	0.000000
Smallest sample size	Tassinari (1996)	0.28 (0.20 to 0.36)	0.000000

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were more likely to become seizure free than patients who received add-on placebo.

Evidence Table 66. Sensitivity analyses of seizure freedom in trials of polytherapy, low dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.28 (0.20 to 0.36)	0.000000
Largest effect size	Sharief (1996)	0.27 (0.19 to 0.35)	0.000000
Smallest effect size	Felbamate Study Group (1993)	0.29 (0.20 to 0.37)	0.000000
Largest sample size	Ben-Menachem (2000)	0.27 (0.18 to 0.35)	0.000000
Smallest sample size	Tassinari (1996)	0.27 (0.19 to 0.35)	0.000000

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were more likely to become seizure free than patients who received add-on placebo.

Evidence Table 67. Meta-analysis of 50% reduction in trials of polytherapy, high dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Faught (2001)	203	0.36 (0.08 to 0.64)	0.01	-1.03	No	No
Ben-Menachem (2000)	286	0.54 (0.3 to 0.78)	0	0.26	No	No
Betts (2000)	77	0.22 (-0.23 to 0.67)	0.33	-1.27	No	No
Cereghino (2000)	196	0.81 (0.53 to 1.09)	0	2.2	Yes	No
Glauser (2000)	267	0.4 (0.16 to 0.64)	0	-0.93	No	No
Appleton (1999)	247	0.1 (-0.15 to 0.35)	0.44	-3.33	Yes	No
Biton (1999)	80	0.64 (0.2 to 1.08)	0	0.61	No	No
Duchowny (1999)	199	0.34 (0.07 to 0.62)	0.02	-1.17	No	No
Elterman (1999)	86	0.42 (0 to 0.85)	0.05	-0.39	No	No
KTSG (1999)	177	0.83 (0.53 to 1.12)	0	2.2	Yes	No
Sachdeo (1999)	98	0.61 (0.22 to 1.01)	0	0.53	No	No
Uthman (1998)	145	0.71 (0.38 to 1.05)	0	1.24	No	No
Sachdeo (1997b)	213	0.57 (0.3 to 0.84)	0	0.46	No	No
Ben-Menachem (1996)	56	1.43 (0.9 to 1.95)	0	3.47	Yes	Yes
Chadwick (1996)	97	0.24 (-0.16 to 0.64)	0.25	-1.31	No	No
Faught (1996)	91	0.61 (0.2 to 1.02)	0	0.52	No	No
Privitera (1996)	94	0.74 (0.34 to 1.15)	0	1.16	No	No
Sharief (1996)	47	0.68 (0.1 to 1.25)	0.02	0.59	No	No
Tassinari (1996)	60	0.86 (0.35 to 1.37)	0	1.38	No	No
Willmore (1996)	147	0.49 (0.17 to 0.81)	0	-0.09	No	No
Anhut (1994)	161	0.48 (0.15 to 0.81)	0	-0.19	No	No
FSG (1993)	71	0.88 (0.42 to 1.35)	0	1.59	No	No
Matsuo (1993)	145	0.28 (-0.05 to 0.6)	0.1	-1.42	No	No
McLean (1993)	152	0.49 (0.16 to 0.82)	0	-0.1	No	No
Schmidt (1993)	139	0.52 (0.18 to 0.85)	0	0.06	No	No
Sivenius (1991)	34	-0.12 (-0.79 to 0.56)	0.73	-1.83	No	No
UKGSG (1990)	127	0.35 (0 to 0.7)	0.05	-0.91	No	No
Random Effects Summary Effect Size (Cohen's h)		**0.52 (0.43 to 0.62)**	**0.000000**			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were more likely to experience 50% reduction than patients who received a placebo.

NA Not applicable

Evidence Table 68. Meta-analysis of 50% reduction in trials of polytherapy, low dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Faught (2001)	203	0.36 (0.08 to 0.64)	0.01	-0.51	No	No
Ben-Menachem (2000)	286	0.54 (0.3 to 0.78)	0	0.87	No	No
Betts (2000)	81	0.45 (0.01 to 0.88)	0.04	0.06	No	No
Cereghino (2000)	193	0.53 (0.25 to 0.81)	0	0.71	No	No
Glauser (2000)	267	0.4 (0.16 to 0.64)	0	-0.31	No	No
Appleton (1999)	247	0.1 (-0.15 to 0.35)	0.44	-2.73	Yes	No
Biton (1999)	80	0.64 (0.2 to 1.08)	0	0.94	No	No
Duchowny (1999)	199	0.34 (0.07 to 0.62)	0.02	-0.64	No	No
Elterman (1999)	86	0.42 (0 to 0.85)	0.05	-0.05	No	No
KTSG (1999)	177	0.83 (0.53 to 1.12)	0	2.69	Yes	No
Sachdeo (1999)	98	0.61 (0.22 to 1.01)	0	0.9	No	No
Uthman (1998)	151	0.16 (-0.17 to 0.48)	0.35	-1.71	No	No
Sachdeo (1997b)	212	0.44 (0.17 to 0.71)	0	0.07	No	No
Ben-Menachem (1996)	56	1.43 (0.9 to 1.95)	0	3.75	Yes	Yes
Chadwick (1996)	97	0.24 (-0.16 to 0.64)	0.25	-0.95	No	No
Faught (1996)	90	0.21 (-0.2 to 0.63)	0.31	-1.05	No	No
Privitera (1996)	95	0.85 (0.45 to 1.26)	0	2.07	Yes	No
Sharief (1996)	47	0.68 (0.1 to 1.25)	0.02	0.84	No	No
Tassinari (1996)	60	0.86 (0.35 to 1.37)	0	1.67	No	No
Willmore (1996)	147	0.49 (0.17 to 0.81)	0	0.36	No	No
Anhut (1994)	220	0.31 (0.04 to 0.57)	0.02	-0.96	No	No
FSG (1993)	71	0.88 (0.42 to 1.35)	0	1.9	No	No
Matsuo (1993)	144	0.05 (-0.28 to 0.38)	0.77	-2.35	Yes	No
McLean (1993)	151	0.27 (-0.06 to 0.6)	0.11	-0.98	No	No
Schmidt (1993)	139	0.52 (0.18 to 0.85)	0	0.5	No	No
Sivenius (1991)	34	-0.12 (-0.79 to 0.56)	0.73	-1.61	No	No
UKGSG (1990)	127	0.35 (0 to 0.7)	0.05	-0.49	No	No
Random Effects Summary Effect Size (Cohens'h)		**0.45 (0.35 to 0.55)**	**0.000000**			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were more likely to experience 50% reduction than patients who received a placebo.

NA Not applicable

Evidence Table 69. Sensitivity analyses of 50% reduction in trials of polytherapy, high dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.52 (0.43 to 0.62)	0.000000
Largest effect size	Ben-Menachem (1996)	0.50 (0.41 to 0.58)	0.000000
Smallest effect size	Sivenius (1991)	0.53 (0.44 to 0.63)	0.000000
Largest sample size	Ben-Menachem (2000)	0.52 (0.42 to 0.62)	0.000000
Smallest sample size	Sivenius (1991)	0.53 (0.44 to 0.63)	0.000000

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were more likely to experience 50% or more seizure reduction than patients who received add-on placebo.

Evidence Table 70. Sensitivity analyses of 50% reduction in trials of polytherapy, low dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.45 (0.35 to 0.55)	0.000000
Largest effect size	Ben-Menachem (1996)	0.43 (0.34 to 0.52)	0.000000
Smallest effect size	Sivenius (1991)	0.46 (0.36 to 0.56)	0.000000
Largest sample size	Ben-Menachem (2000)	0.45 (0.35 to 0.55)	0.000000
Smallest sample size	Sivenius (1991)	0.46 (0.36 to 0.56)	0.000000

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were more likely to experience 50% or more seizure reduction than patients who received add-on placebo.

Evidence Table 71. Meta-analysis of any reduction in trials of polytherapy, high dose groups

Reference	N	Cohen's h (CI)[a]	P-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Anhut (1994)	161	0.54 (0.21 to 0.87)	0	1.13	No	NA
McLean (1993)	152	0.47 (0.14 to 0.8)	0.01	0.63	No	NA
Schmidt (1993)	139	0.39 (0.06 to 0.72)	0.02	0.08	No	NA
Sivenius (1991)	34	-0.21 (-0.88 to 0.47)	0.55	-1.76	No	NA
UKGSG (1990)	127	0.23 (-0.11 to 0.58)	0.19	-0.91	No	NA
Random Effects Summary Effect Size (Cohens'h)		0.37 (0.19 to 0.55)	0.000061			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were more likely to experienced seizure reductions than patients who received add-on placebo.
NA Not applicable

Evidence Table 72. Meta-analysis of any reduction in trials of polytherapy, low dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Anhut (1994)	220	0.46 (0.2 to 0.73)	0	1.35	No	NA
McLean (1993)	151	0.2 (-0.13 to 0.54)	0.23	-0.74	No	NA
Schmidt (1993)	139	0.39 (0.06 to 0.72)	0.02	0.51	No	NA
Sivenius (1991)	34	-0.21 (-0.88 to 0.47)	0.55	-1.56	No	NA
UKGSG (1990)	127	0.23 (-0.11 to 0.58)	0.19	-0.5	No	NA
Random Effects Summary Effect Size (Cohens'h)		**0.31 (0.15 to 0.47)**	**0.000162**			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were more likely to experienced seizure reductions than patients who received add-on placebo.
NA Not applicable

Evidence Table 73. Sensitivity analyses of any reduction in trials of polytherapy, high dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.37 (0.19 to 0.55)	0.000061
Largest effect size	Anhut (1994)	0.32 (0.11 to 0.52)	0.002667
Smallest effect size	Sivenius (1991)	0.41 (0.25 to 0.58)	0.000001
Largest sample size	Anhut (1994)	0.32 (0.11 to 0.52)	0.002667
Smallest sample size	Sivenius (1991)	0.41 (0.25 to 0.58)	0.000001

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were more likely to experience any seizure reduction than patients who received add-on placebo.

Evidence Table 74. Sensitivity analyses of any reduction in trials of polytherapy, low dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.31 (0.15 to 0.47)	0.000162
Largest effect size	Anhut (1994)	0.24 (0.05 to 0.43)	0.012211
Smallest effect size	Sivenius (1991)	0.34 (0.19 to 0.5)	0.000019
Largest sample size	Anhut (1994)	0.24 (0.05 to 0.43)	0.012211
Smallest sample size	Sivenius (1991)	0.34 (0.19 to 0.5)	0.000019

[a]The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were more likely to experience any seizure reduction than patients who received add-on placebo.

Evidence Table 75. Meta-analysis of any increase in trials of polytherapy, high dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Appleton (1999)	247	0.36 (0.11 to 0.61)	0	-0.21	No	NA
Anhut (1994)	161	0.45 (0.12 to 0.78)	0.01	0.44	No	NA
McLean (1993)	152	0.45 (0.12 to 0.79)	0.01	0.48	No	NA
Sivenius (1991)	34	-0.21 (-0.88 to 0.47)	0.55	-1.76	No	NA
UKGSG (1990)	127	0.43 (0.08 to 0.78)	0.02	0.29	No	NA
Random Effects Summary Effect Size (Cohen's h)		**0.38 (0.23 to 0.53)**	**0.000001**			

[a]A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were less likely to experience seizure increases than patients who received add-on placebo.
NA Not applicable

Evidence Table 76. Meta-analysis of any increase in trials of polytherapy, low dose groups

Reference	N	Cohen's h (CI)[a]	p-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Appleton (1999)	247	0.36 (0.11 to 0.61)	0	-0.42	No	NA
Anhut (1994)	220	0.6 (0.33 to 0.86)	0	1.69	No	NA
McLean (1993)	151	0.31 (-0.03 to 0.64)	0.07	-0.63	No	NA
Sivenius (1991)	34	-0.21 (-0.88 to 0.47)	0.55	-1.83	No	NA
UKGSG (1990)	127	0.43 (0.08 to 0.78)	0.02	0.14	No	NA
Random Effects Summary Effect Size (Cohen's h)		**0.39 (0.22 to 0.57)**	**0.000012**			

[a] A positive effect size indicates that the drug treatment was beneficial: patients who received an add-on drug were less likely to experience seizure increases than patients who received add-on placebo.
NA Not applicable

Evidence Table 77. Sensitivity analyses of any increase in trials of polytherapy, high dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.38 (0.23 to 0.53)	0.000001
Largest effect size	Anhut (1994)	0.36 (0.19 to 0.54)	0.000042
Smallest effect size	Sivenius (1991)	0.41 (0.26 to 0.57)	0.000000
Largest sample size	Anhut (1994)	0.39 (0.19 to 0.59)	0.000127
Smallest sample size	Sivenius (1991)	0.41 (0.26 to 0.57)	0.000000

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were less likely to experience any seizure increase than patients who received add-on placebo.

Evidence Table 78. Sensitivity analyses of any increase in trials of polytherapy, low dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		0.39 (0.22 to 0.57)	0.000012
Largest effect size	Anhut (1994)	0.33 (0.16 to 0.5)	0.000127
Smallest effect size	Sivenius (1991)	0.43 (0.29 to 0.58)	0.000000
Largest sample size	Anhut (1994)	0.38 (0.14 to 0.63)	0.002404
Smallest sample size	Sivenius (1991)	0.43 (0.29 to 0.58)	0.000000

[a] The effect size was Cohen's h. A positive effect size indicates that patients who received add-on drug were less likely to experience any seizure increase than patients who received add-on placebo.

Evidence Table 79. Meta-analysis of trial exits due to adverse effects in trials of polytherapy, high dose groups

Reference	N	Cohen's h (CI)[a]	P-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Faught (2001)	203	-0.12 (-0.4 to 0.16)	0.39	0.4	No	No
Ben-Menachem (2000)	286	-0.03 (-0.27 to 0.21)	0.81	1.25	No	No
Betts (2000)	77	0.06 (-0.38 to 0.51)	0.78	1.06	No	No
Cereghino (2000)	196	-0.07 (-0.35 to 0.21)	0.63	0.77	No	No
Glauser (2000)	267	-0.29 (-0.53 to -0.05)	0.02	-1	No	No
Appleton (1999)	247	-0.15 (-0.4 to 0.1)	0.25	0.25	No	No
Biton (1999)	80	-0.01 (-0.45 to 0.43)	0.97	0.76	No	No
Duchowny (1999)	199	0.04 (-0.24 to 0.31)	0.8	1.54	No	No
Elterman (1999)	86	0.3 (-0.12 to 0.72)	0.17	2.23	Yes	No
KTSG (1999)	177	-0.19 (-0.48 to 0.11)	0.22	-0.07	No	No
Sachdeo (1999)	98	0 (-0.4 to 0.4)	1	0.89	No	No
Uthman (1998)	148	-0.26 (-0.59 to 0.08)	0.13	-0.47	No	No
Sachdeo (1997b)	213	-0.2 (-0.47 to 0.07)	0.15	-0.16	No	No
Ben-Menachem (1996)	56	-0.96 (-1.49 to -0.44)	0	-2.96	Yes	Yes
Chadwick (1996)	129	0.06 (-0.29 to 0.41)	0.74	1.35	No	No
Faught (1996)	91	-0.31 (-0.72 to 0.1)	0.14	-0.64	No	No
Privitera (1996)	94	-0.56 (-0.96 to -0.15)	0.01	-1.87	No	No
Sharief (1996)	47	-0.66 (-1.23 to -0.09)	0.02	-1.67	No	No
Tassinari (1996)	60	-0.28 (-0.78 to 0.23)	0.28	-0.39	No	No
Willmore (1996)	147	-0.28 (-0.6 to 0.05)	0.1	-0.61	No	No

Evidence Table 79. Meta-analysis of trial exits due to adverse effects in trials of polytherapy, high dose groups (continued)

Reference	N	Cohen's h (CI)[a]	P-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Anhut (1994)	161	-0.01 (-0.34 to 0.32)	0.96	1.01	No	No
Messenheimer (1994)	98	-0.35 (-0.75 to 0.04)	0.08	-0.89	No	No
Bourgeois (1993)	64	-0.52 (-1.01 to -0.03)	0.04	-1.39	No	No
FSG (1993)	73	0 (-0.45 to 0.46)	0.98	0.78	No	No
Matsuo (1993)	145	-0.53 (-0.85 to -0.2)	0	-2.16	Yes	No
McLean (1993)	152	-0.18 (-0.52 to 0.15)	0.28	-0.05	No	No
Schmidt (1993)	139	-0.24 (-0.57 to 0.09)	0.16	-0.37	No	No
Sivenius (1991)	34	0 (-0.67 to 0.67)	1	0.52	No	No
UKGSG (1990)	127	-0.21 (-0.56 to 0.14)	0.24	-0.18	No	No
Jawad (1989)	24	0 (-0.8 to 0.8)	1	0.43	No	No
Random Effects Summary Effect Size (Cohens'h)		**-0.18 (-0.26 to -0.11)**	**0.000003**			

[a] A negative effect size indicates that the drug treatment was harmful: patients who received an add-on drug were more likely to exit studies due to adverse effects than patients who received a placebo.

NA Not applicable

Evidence Table 80. Meta-analysis of trial exits due to adverse effects in trials of polytherapy, low dose groups

Reference	N	Cohen's h (CI)[a]	P-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
Faught (2001)	203	-0.12 (-0.4 to 0.16)	0.39	0.21	No	No
Ben-Menachem (2000)	286	-0.03 (-0.27 to 0.21)	0.81	1.02	No	No
Betts (2000)	81	-0.27 (-0.7 to 0.17)	0.23	-0.54	No	No
Cereghino (2000)	193	-0.04 (-0.32 to 0.25)	0.8	0.8	No	No
Glauser (2000)	267	-0.29 (-0.53 to -0.05)	0.02	-1.22	No	No
Appleton (1999)	247	-0.15 (-0.4 to 0.1)	0.25	0.04	No	No
Biton (1999)	80	-0.01 (-0.45 to 0.43)	0.97	0.64	No	No
Duchowny (1999)	199	0.04 (-0.24 to 0.31)	0.8	1.35	No	No
Elterman (1999)	86	0.3 (-0.12 to 0.72)	0.17	2.1	Yes	No
KTSG (1999)	177	-0.19 (-0.48 to 0.11)	0.22	-0.25	No	No
Sachdeo (1999)	98	0 (-0.4 to 0.4)	1	0.75	No	No
Uthman (1998)	152	0.04 (-0.28 to 0.37)	0.79	1.2	No	No
Sachdeo (1997b)	212	-0.04 (-0.31 to 0.23)	0.76	0.81	No	No
Ben-Menachem (1996)	56	-0.96 (-1.49 to -0.44)	0	-3.06	Yes	Yes
Chadwick (1996)	129	0.06 (-0.29 to 0.41)	0.74	1.2	No	No
Faught (1996)	90	0.21 (-0.21 to 0.62)	0.33	1.71	No	No
Privitera (1996)	95	-0.66 (-1.06 to -0.25)	0	-2.49	Yes	No
Sharief (1996)	47	-0.66 (-1.23 to -0.09)	0.02	-1.76	No	No
Tassinari (1996)	60	-0.28 (-0.78 to 0.23)	0.28	-0.49	No	No
Willmore (1996)	147	-0.28 (-0.6 to 0.05)	0.1	-0.78	No	No
Anhut (1994)	220	-0.19 (-0.46 to 0.07)	0.15	-0.32	No	No
Messenheimer (1994)	98	-0.35 (-0.75 to 0.04)	0.08	-1.02	No	No
Bourgeois (1993)	64	-0.52 (-1.01 to -0.03)	0.04	-1.5	No	No
FSG (1993)	73	0 (-0.45 to 0.46)	0.98	0.67	No	No
Matsuo (1993)	144	-0.18 (-0.51 to 0.15)	0.28	-0.18	No	No
McLean (1993)	151	-0.28 (-0.61 to 0.06)	0.1	-0.76	No	No
Schmidt (1993)	139	-0.24 (-0.57 to 0.09)	0.16	-0.53	No	No
Sivenius (1991)	34	0 (-0.67 to 0.67)	1	0.44	No	No

Evidence Table 80. Meta-analysis of trial exits due to adverse effects in trials of polytherapy, low dose groups (continued)

Reference	N	Cohen's h (CI)[a]	P-value	Standardized Residual	Outlier by Standardized Residual	Greatest Outlier by Q
UKGSG (1990)	127	-0.21 (-0.56 to 0.14)	0.24	-0.33	No	No
Jawad (1989)	24	0 (-0.8 to 0.8)	1	0.37	No	No
Random Effects Summary Effect Size (Cohens'h)		**-0.16 (-0.23 to -0.08)**	**0.000066**			

[a] A negative effect size indicates that the drug treatment was harmful: patients who received an add-on drug were more likely to exit studies due to adverse effects than patients who received a placebo.
NA Not applicable

Evidence Table 81. Sensitivity analyses of trial exits due to adverse effects in trials of polytherapy, high dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		-0.18 (-0.26 to -0.11)	0.000003
Largest effect size	Ben-Menachem (1996)	-0.17 (-0.23 to -0.10)	0.000002
Smallest effect size	Elterman (1999)	-0.19 (-0.27 to -0.12)	0.000000
Largest sample size	Ben-Menachem (2000)	-0.19 (-0.27 to -0.11)	0.000002
Smallest sample size	Jawad (1989)	-0.18 (-0.26 to -0.11)	0.000003

[a] The effect size was Cohen's h. A negative effect size indicates that patients who received add-on drug were more likely to exit trials due to adverse effects than patients who received add-on placebo.

Evidence Table 82. Sensitivity analyses of trial exits due to adverse effects in trials of polytherapy, low dose groups

Trials Included in Sensitivity Analysis	Trials Removed	Random Effects Summary Effect Size[a] (CI)	P value
All trials included		-0.16 (-0.23 to -0.08)	0.000066
Largest effect size	Ben-Menachem (1996)	-0.14 (-0.21 to -0.07)	0.000056
Smallest effect size	Elterman (1999)	-0.17 (-0.24 to -0.09)	0.000011
Largest sample size	Ben-Menachem (2000)	-0.16 (-0.24 to -0.08)	0.000057
Smallest sample size	Jawad (1989)	-0.16 (-0.24 to -0.08)	0.000073

[a] The effect size was Cohen's h. A negative effect size indicates that patients who received add-on drug were more likely to exit trials due to adverse effects than patients who received add-on placebo.

Evidence Table 83. Scales used to measure quality of life in trials of polytherapy

Reference	Corresponding Primary Efficacy Trial	Drug	Scales Used to Measure Quality of Life	Total Number of Subscales
Cramer (2000)]	Cereghino (2000)	Levetiracetam	Quality of Life in Epilepsy-31 Seizure worry Overall quality of life Emotional well-being Energy-fatigue Cognitive functioning Medication effects Social function Health status Total score	9
Dodrill (1997)	Uthman (1998)	Tiagabine	Washington Psychosocial Seizure Inventory Family background Emotional adjustment Interpersonal adjustment Vocational adjustment Financial status Adjustment to seizures Medicine and medical management Overall functioning Lie scale Rare items	10

Evidence Table 84. Scales used to measure mood in trials of polytherapy

Reference	Corresponding Primary Efficacy Trial	Drug	Scales Used to Measure Mood	Total Number of Subscales
Dodrill (1997)	Uthman (1998)	Tiagabine	Profile of Mood States Tension-anxiety Depression-dejection Anger-hostility Vigor-activity Fatigue-inertia Confusion-bewilderment Total mood disturbance Mood Rating Scale	8

Evidebce Table 85. Scales used to measure cognitive function in trials of polytherapy

Reference	Corresponding Primary Efficacy Trial	Drug	Scales Used to Measure Cognitive Function	Total Number of Subscales
Dodrill (1997)	Uthman (1998)	Tiagabine	Lafayette Grooved Pegboard Preferred hand Nonpreferred hand Stroop Test Reading speed Reading speed, errors Interference Interference, errors Benton Visual Retention Test Form F Form G Controlled Oral Word Association Test Symbol Digit Modalities Test Rey Auditory Verbal Learning Test Trial 1-5, first list recall Trial 6, second list recall Trial 7, first list recall Trial 8, first delay recall Trial 9, first delay recognition Wonderlic Personnel Test Items correct items wrong Digit Cancellation Number right Number omitted	19

Evidence Table 86. Mortality results in trials of polytherapy

Reference	Drug	Dose(s) (mg/day)	Mortality Prior to Randomization	Mortality in Placebo Group	Mortality in Group With Lowest Dose	Mortality in Group With Next Higher Dose	Mortality in Group With Highest Dose
Cereghino (2000)	Levetiracetam	1000, 3000	1/295 (0.3%)	1/95 (1%)	NR	NR	NA
Glauser (2000)	Oxcarbazepine	1800	0/267 (0%)	NR	1/138 (1%)	NA	NA
Appleton (1999)	Gabapentin	1800	0/247 (0%)	0/128 (0%)	0/119 (0%)	NA	NA
Elterman (1999)	Topiramate	400	0/86 (0%)	0/45 (0%)	0/41 (0%)	NA	NA
Ben-Menachem (1996)	Topiramate	800	0/56 (0%)	0/28 (0%)	0/28 (0%)	NA	NA
Chadwick (1996)	Gabapentin	1200	0/129 (0%)	0/71 (0%)	1/58 (2%)	NA	NA
Faught (1996)	Topiramate	200, 400, 600	0/90 (0%)	0/45 (0%)	0/45 (0%)	0/45 (0%)	0/46 (0%)
Privitera (1996)	Topiramate	600, 800, 1000	0/95 (0%)	0/47 (0%)	0/48 (0%)	0/48 (0%)	0/47 (0%)
Anhut (1994)	Gabapentin	900	0/272 (0%)	NR	1/111 (1%)	NR	NA

mg/day milligrams per day
NA Not applicable

Evidence Table 87. Studies of optimized current therapy that met the inclusion criteria

Reference	Country	Optimization Strategy		
		Maximum Tolerable Dose	Drug Reduction	Changing Dosing Frequency
Semah (1994)	France	✓		
Mirza (1993)	United States		✓	
May (1992)	Germany		✓	
Duncan (1990)	United Kingdom		✓	
Ryan (1990)	United Kingdom			✓
Specht (1989)	Germany		✓	
Callaghan (1984)	United Kingdom		✓	
Armour (1988)	United Kingdom		✓	
Schmidt (1983a)	Germany	✓		
Schmidt (1983b)	Germany		✓	
Thompson (1982)	United Kingdom		✓	
Total number of studies		**2**	**8**	**1**

Evidence Table 88. Excluded articles examining drug optimization strategies

Reference	Reason for exclusion
Armour (1988)	Baseline seizure rates for five patients indicated that they were so well controlled that "no improvement would be detected in the followup period." As a result, investigators abandoned 3 month baseline period and instead obtained baseline seizure frequency data from historical seizure records. Each subjects baseline seizure frequency was changed to consist of the period of time from the last recorded dose change until the initiation of drug withdrawal. This period of time "varied considerably between subjects so the strict statistical basis of the study was weakened." This approach resulted in the seizure frequency for the five pateints with low seizure rates to appear to be higher than they actually were during the original 3 month baseline period, thus biasing the study.

Evidence Table 89. General information of studies of optimized current therapy

Reference	Author Affiliation	Country	Multicenter	For-Profit Funding	Phrase Used to Describe Patients	Minimum Number of AEDs	Minimum Monthly Seizure Frequency	Minimum Duration of Condition	Side Effects in The Definition of Treatment-Resistant Epilepsy
Studies of drug reduction									
Mirza (1993)	Bowman Gray School of Medicine	United States	No	Yes	Uncontrolled seizures, active generalized convulsive seizures, the use of 4 or more AEDs	4	NR	NR	No
May (1992)	Gesellschaft fur Epilepsieforschung	Germany	No	No	Therapy resistant, different types of epilepsy, the effectiveness of phenytoin was questionable	2	NR	NR	No
Duncan (1990)	Institute of Neurology	United Kingdom	No	Yes	Patients with severe active epilepsy	2	NR	NR	No
Specht (1989)	Epilepsie-Zentrum Bethel	Germany	No	No	Children with difficult-to-treat epilepsies	2	NR	NR	Yes
Callaghan (1984)	Cork Regional Hospital	United Kingdom	No	Yes	Patients with frequent seizures while on polypharmacy	2	2	NR	No
Schmidt (1983)	Abteilung fur Neurologie	Germany	No	No	Uncontrolled complex partial seizures despite adequate two-drug treatment	2	NR	NR	Yes
Thompson (1982)	National Hospital for Nervous Diseases	United Kingdom	No	No	Patients on polypharmacy who underwent a reduction in the number of different anticonvulsants prescribed	2	NR	NR	No

Evidence Table 89. General information of studies of optimized current therapy (continued)

Reference	Author Affiliation	Country	Multicenter	For-Profit Funding	Phrase Used to Describe Patients	Minimum Number of AEDs	Minimum Monthly Seizure Frequency	Minimum Duration of Condition	Side Effects in The Definition of Treatment-Resistant Epilepsy
Other studies of optimized current therapy									
Semah (1994)	Clinique Neurologique Paul Castaigne, Hopital de la Salpetriere, Paris, France.	France	No	Yes	Uncontrolled partial seizures with or without secondary generalization	1	3	NR	No
Schmidt (1983)	Abteilung fur Neurologie, Klinikum Charlottenburg, Freie Universitat Berlin, Spandauer Damm 130, D-1000 Berlin 19	Germany	No	No	Uncontrolled chronic epilepsy with complex partial seizures despite single drug treatment	1	NR	NR	No

Evidence Table 90. Design characteristics of studies of optimized current therapy

Reference	Study Reported Maximum Tolerable Dose of Prior Drugs	Required Good Compliance to Prior Drugs	All Patients Seen During Presurgical Evaluation	Patients Continued to Take Their Prestudy Drugs	Prospective	Randomized	Type of Control
Studies of drug reduction							
Mirza (1993)	No	No	No	No	Yes	No	None
May (1992)	No	No	No	No	Yes	No	No change in treatment
Duncan (1990)	No	No	No	No	Yes	No	No change in treatment
Specht (1989)	No	No	No	No	Yes	No	None
Callaghan (1984)	No	No	No	No	Yes	No	None
Schmidt (1983)	Yes	Yes	No	No	Yes	No	None
Thompson (1982)	No	No	No	No	Yes	No	No change in treatment
Other studies of optimized current therapy							
Semah (1994)	No	No	No	Yes	Yes	No	None
Schmidt (1983)	No	No	No	Yes	Yes	No	None

Evidence Table 90. Design characteristics of studies of optimized current therapy (continued)

Reference	Patients Received a Placebo During The Baseline	Patients Blinded	Observers Blinded	Length of Baseline (Weeks)	Length of Titration Period (Weeks)	Length of Maintenance Period (Weeks)	Plasma Levels Monitored
Studies of drug reduction							
Mirza (1993)	No	No	No	90 days	12 to 17 months	4 to 9 months	Yes
May (1992)	No	No	Yes	52	NR	NR	Yes
Duncan (1990)	No	Yes	Yes	2	1 to 7	4	Yes
Specht (1989)	No	No	No	2	2 to 7	2 to 4	No
Callaghan (1984)	No	No	No	6 months	2 weeks to 3 months	2 years	Yes
Schmidt (1983)	No	No	No	5 to 197	2 to 20	4 to 260	Yes
Thompson (1982)	No	No	Yes	3 months	3 months	3 months	Yes
Other studies of optimized current therapy							
Semah (1994)	No	No	No	2 months	NR	6 months	Yes
Schmidt (1983)	No	No	No	NR	NR	4 to 115	Yes

Evidence Table 91. Reporting characteristics of trials of optimized current therapy

Reference	Reporting								Seizure Types	Seizure Diaries Used
	Individual Patient Data	Baseline Seizure Frequency	Seizure Frequency	Adverse Effects	Quality of Life	Functional Status / Ability	Return to Work	Return to School		
Studies of drug reduction										
Mirza (1993)	No	Yes	Yes	Yes	No	No	No	No	Generalized and partial	No
May (1992)	No	Yes	No	No	No	Yes	No	No	Generalized and partial	NR
Duncan (1990)	No	Yes	Yes	Yes	Yes	Yes	No	No	Generalized and partial	Yes
Specht (1989)	Yes	Yes	Yes	Yes	No	No	No	No	Generalized and partial	No
Callaghan (1984)	No	Yes	Yes	Yes	No	Yes	No	No	Generalized and partial	NR
Schmidt (1983)	Yes	Yes	Yes	Yes	No	No	No	No	Generalized and partial	Yes
Thompson (1982)	No	Yes	Yes	No	Yes	Yes	No	No	Generalized and partial	NR
Other studies of optimized current therapy										
Semah (1994)	No	No	Yes	Yes	No	No	No	No	Partial	Yes
Schmidt (1983)	No	No	Yes	No	No	No	No	No	Generalized and partial	Yes

Evidence Table 92. Treatment descriptions, numbers of patients and attrition in studies of optimized current therapy

Reference	Description of Treatment	Number of Patients						Patient Characteristics Reported For Those Who Started or Completed The Study
		Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics	
Studies of drug reduction								
Mirza (1993)	Withdrawal of 3 or 4 AEDs	44	0	0	0	44	44	Started
May (1992)	No change in treatment	12	0	0	0	12	12	Started
	Withdrawal of phenytoin	17	0	0	0	17	17	Started
Duncan (1990)	No change in treatment	25	0	0	0	25	25	Started
	Withdrawal of phenytoin	23	0	0	1	22	23	Started
	Withdrawal of carbamazepine	24	0	0	1	23	24	Started
	Withdrawal of valproate	25	0	0	0	25	25	Started
Specht (1989)	Withdrawal of clonazepam	40	0	0	0	40	40	Started
Callaghan (1984)	Withdrawal of up to 3 AEDs	35	6	0	0	29	35	Started
Schmidt (1983)	Withdrawal of at exactly one AED	36	0	0	0	36	36	Started
Thompson (1982)	No change in treatment	10	0	0	0	10	10	Started
	Withdrawal of at least 1 AED	20	0	0	0	20	20	Started

Evidence Table 92. Treatment descriptions, numbers of patients and attrition in studies of optimized current therapy (continued)

Reference	Description of Treatment	Number of Patients						Patient Characteristics Reported For Those Who Started or Completed The Study
		Started The Study	Exited Due to an Increase in Seizures	Exited Due to Adverse Effects	Exited For Other Reasons	Completed The Study	With Reported Patient Characteristics	
Studies of drug reduction (continued)								
Semah (1994)	Increase dose of carbamazepine until either seizure control or side effects	18	NR	NR	NR	7	18	Started
Schmidt (1983)	Increase dose of phenytoin, carbamazepine, or phenobarbital until side effects occur	35	0	0	0	35	35	Started

[a] Calculated by ECRI based on reported information

Evidence Table 93. Age, gender, and duration of condition of patients in studies of optimized current therapy

Reference	Treatment Description	Age				Males	Females	Duration of Epilepsy		
		Mean	SD	Minimum	Maximum			Mean	SD	Median
Studies of drug reduction										
Mirza (1993)	Reduction	30.2	NR	8	68	25	19	NR	NR	29.1[a]
May (1992)	No change	46.3	13.3	NR	NR	8	4	40.5	14.2	NR
	Reduction	55.2	8.7	NR	NR	7	10	49.4	8.4	NR
Duncan (1990)	No change	42	NR	25	65	19	6	NR	NR	37
	Reduction (phenytoin)	35	NR	19	65	16	7	NR	NR	25
	Reduction (carbamazepine)	31	NR	19	59	17	7	NR	NR	23
	Reduction (valproate)	25	NR	17	48	13	12	NR	NR	17
Specht (1989)	Reduction	9.9	NR	2.4	22.7	25	15	5.75	NR	NR
Callaghan (1984)	Reduction	26	NR	6	24	25	10	18	NR	NR
Schmidt (1983)	Reduction	38	12	16	74	NR	NR	21	10	NR
Thompson (1982)	No change	33.5	15.1	NR	NR	2	8	19.2	8.7	NR
	Reduction	28	13.5	NR	NR	10	10	19.5	11.3	NR
Other studies of optimized current therapy										
Semah (1994)	Other	28.9	10.2	18	65	9	9	17.8	13.1	NR
Schmidt (1983)	Other	36	10	20	59	NR	NR	19	9	NR

[a] Calculated by ECRI based on reported information.

Evidence Table 94. Baseline seizure frequencies and specific types of partial seizures in studies of optimized current therapy

Reference	Treatment Description	Seizure Type For Baseline Seizure Frequency	Mean Baseline Seizure Frequency	SD of Baseline Seizure Frequency	Median Baseline Seizure Frequency
Studies of drug reduction					
Mirza (1993)	Reduction	Generalized and partial	2 day	NR	NR
May (1992)	No change	Generalized and partial	22.8 year	25.6 year	NR
	Reduction	Generalized and partial	25.6 year	25.7 year	NR
Duncan (1990)	No change	Generalized and partial	1.6	NR	9.7[a]
	Reduction (phenytoin)	Generalized and partial	2.8	NR	13.7[a]
	Reduction (carbamazepine)	Generalized and partial	1.7	NR	12.0[a]
	Reduction (valproate)	Generalized and partial	2.6	NR	17.0[a]
Specht (1989)	Reduction	Generalized and partial	157.8[a]	302.0[a]	40.9[a]
Callaghan (1984)	Reduction	Generalized and partial	15	NR	NR
Schmidt (1983)	Reduction	Generalized and partial	6.1[a]	12.4[a]	3.4[a]
Thompson (1982)	No change	Partial	6.8	9.7	NR
	Reduction	Partial	21.1	34.6	NR
Other studies of optimized current therapy					
Semah (1994)	Other	NR	NR	NR	NR
Schmidt (1983)	Other	NR	NR	NR	NR

[a] Calculated by ECRI based on reported information.

Evidence Table 95. Specific types of generalized seizures in studies of optimized current therapy

Reference	Treatment Description	Any Generalized Seizures	Numbers of Patients									
			Tonic-Clonic	Tonic	Atonic	Myoclonic	Absence	Atypical Absence	Lennox-Gastaut Syndrome	Clonic	West Syndrome	Other Generalized
Studies of drug reduction												
Mirza (1993)	Reduction	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
May (1992)	No change	NR	3	0	0	0	2	0	0	0	0	0
	Reduction	NR	5	0	0	0	6	0	0	0	0	0
Duncan (1990)	No change	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Reduction (phenytoin)	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Reduction (carbamazepine)	7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Reduction (valproate)	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Specht (1989)	Reduction	33	NR	NR	NR	NR	NR	NR	19	NR	2	NR
Callaghan (1984)	Reduction	26	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schmidt (1983)	Reduction	29	29	0	0	0	0	0	0	0	0	0
Thompson (1982)	No change	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Reduction	14	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other studies of optimized current therapy												
Semah (1994)	Other	0	0	0	0	0	0	0	0	0	0	0
Schmidt (1983)	Other	32	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Evidence Table 96. Specific types of partial seizures in studies of optimized current therapy

Reference	Treatment Description	Any Partial Seizure	Numbers of Patients		
			Complex Partial	Simple Partial	Secondarily Generalized
Studies of drug reduction					
Mirza (1993)	Reduction	NR	8	NR	38
May (1992)	No change	NR	10	2	2
	Reduction	NR	11	1	3
Duncan (1990)	No change	17	NR	NR	NR
	Reduction (phenytoin)	19	NR	NR	NR
	Reduction (carbamazepine)	16	NR	NR	NR
	Reduction (valproate)	22	NR	NR	NR
Specht (1989)	Reduction	11	NR	NR	NR
Callaghan (1984)	Reduction	9	5	4	9
Schmidt (1983)	Reduction	36	36	0	0
Thompson (1982)	No change	9	NR	NR	NR
	Reduction	16	NR	NR	NR
Other studies of optimized current therapy					
Semah (1994)	Other	18	NR	NR	NR
Schmidt (1983)	Other	35	35	NR	NR

Evidence Table 97. Known etiology and prior AED use in studies of optimized current therapy

Reference	Treatment Description	Number of Patients			
		With Known Etiology	On One AED Prior to The Study	On Two AEDs Prior to The Study	On Three or More AEDs Prior to The Study
Studies of drug reduction					
Mirza (1993)	Reduction	NR	0	0	44
May (1992)	No change	NR	NR	NR	NR
	Reduction	NR	NR	NR	NR
Duncan (1990)	No change	17	0	NR	NR
	Reduction (phenytoin)	16	0	NR	NR
	Reduction (carbamazepine)	22	0	NR	NR
	Reduction (valproate)	17	0	NR	NR
Specht (1989)	Reduction	NR	0	18	22
Callaghan (1984)	Reduction	6[a]	0	19	16f
Schmidt (1983)	Reduction	22	0	36	0
Thompson (1982)	No change	NR	NR	NR	NR
	Reduction	NR	NR	NR	NR
Other studies of optimized current therapy					
Semah (1994)	Other	NR	5	12	1
Schmidt (1983)	Other	20	35	0	0

[a] Calculated by ECRI based on reported information.

Evidence Table 98. Prior AEDs used in studies of optimized current therapy

Reference	Treatment Description	Number of Patients Receiving S pecific Prior Drugs								
		Benzodiazepam	Carbamazepine	Clonzaepam	Diazepam	Ethosuximide	Phenytoin	Phenobarbital	Primidone	Valproate
Studies of drug reduction										
Mirza (1993)	Reduction	44	0	0	0	0	44	44	35	44
May (1992)	No change	0	12	0	0	0	0	11	1	2
	Reduction	0	17	0	0	2	0	0	2	2
Duncan (1990)	No change	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Reduction (phenytoin)	NR	NR	NR	NR	NR	23	NR	NR	NR
	Reduction (carbamazepine)	NR	24	NR	NR	NR	NR	NR	NR	NR
	Reduction (valproate)	NR	NR	NR	NR	NR	NR	NR	NR	25
Specht (1989)	Reduction	0	9	40	1	4	9	9	16	15
Callaghan (1984)	Reduction	0	>0	>0	0	>0	>0	>0	>0	>0
Schmidt (1983)	Reduction	0	11	6	0	0	30	4	15	4
Thompson (1982)	No change	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Reduction	NR	>0	>0	NR	NR	>0	>0	>0	>0
Other studies of optimized current therapy										
Semah (1994)	Other	NR	18	NR	NR	NR	>0	>0	NR	>0
Schmidt (1983)	Other	0	4	0	0	0	25	6	0	0

[a] Calculated by ECRI based on reported information.
>0 At least one patient had received the drug, but the study did not report the exact number of patients who received the drug.

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in seizure frequency

Reference	Treatment Description	Overall Seizure Type[a]	Specific Seizure Type[a]	Description of Outcome	Number of Patients	Outcome[b]	Dispersion
Studies of drug reduction							
Mirza (1993)	Reduction	ALL	ALL	Number of patients with 50% or more reduction	44	30	
	Reduction	ALL	ALL	Number of patients seizure free	44	14	
Duncan (1990)	No change	ALL	ALL	Mean monthly seizure frequency	22	2.6	
	Reduction (phenytoin)	ALL	ALL	Mean monthly seizure frequency	23	3.3	
	Reduction (carbamazepine)	ALL	ALL	Mean monthly seizure frequency	25	2.9	
	Reduction (valproate)	ALL	ALL	Mean monthly seizure frequency	25	2.1	
Specht (1989)	Reduction	ALL	ALL	Number of patients with 50% or more reduction	35	9[c]	
	Reduction	ALL	ALL	Number of patients with 75% or more reduction	35	4[c]	
	Reduction	ALL	ALL	Number of patients with any increase in seizures	35	14[c]	
	Reduction	ALL	ALL	Number of patients with any reduction in seizures	35	20[c]	
	Reduction	ALL	ALL	Mean % reduction from baseline	35	-2.0[c]	
	Reduction	ALL	ALL	Mean difference from baseline	35	35.3[c]	
	Reduction	ALL	ALL	Mean monthly seizure frequency	35	122.6[c]	
	Reduction	ALL	ALL	Median % reduction from baseline	35	20.3[c]	
	Reduction	ALL	ALL	Median difference from baseline	35	2.2[c]	

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in seizure frequency (continued)

Reference	Treatment Description	Overall Seizure Type[a]	Specific Seizure Type[a]	Description of Outcome	Number of Patients	Outcome[b]	Dispersion
Specht (1989) continued	Reduction	ALL	ALL	Median monthly seizure frequency	35	32.3[c]	
	Reduction	ALL	ALL	Number of patients seizure free	35	4[c]	
Callaghan (1984)	Reduction	ALL	ALL	Number of patients with 50% or more reduction	35	19[c]	
	Reduction	ALL	ALL	Number of patients with any increase in seizures	35	3	
	Reduction	ALL	ALL	Number of patients seizure free	35	6	
Schmidt (1983)	Reduction	ALL	ALL	Number of patients with 50% or more reduction	36	8[c]	
	Reduction	ALL	ALL	Number of patients with 75% or more reduction	36	3[c]	
	Reduction	ALL	ALL	Number of patients with any increase in seizures	36	15[c]	
	Reduction	ALL	ALL	Number of patients with any reduction in seizures	36	21[c]	
	Reduction	ALL	ALL	Mean % reduction from baseline	36	-107.3[c]	
	Reduction	ALL	ALL	Mean difference from baseline	36	-0.5[c]	
	Reduction	ALL	ALL	Mean monthly seizure frequency	36	6.5[c]	
	Reduction	ALL	ALL	Median % reduction from baseline	36	11.9[c]	
	Reduction	ALL	ALL	Median difference from baseline	36	0.5[c]	
	Reduction	ALL	ALL	Median monthly seizure frequency	36	3.8[c]	
	Reduction	ALL	ALL	Number of patients seizure free	36	2[c]	

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in seizure frequency (continued)

Reference	Treatment Description	Overall Seizure Type[a]	Specific Seizure Type[a]	Description of Outcome	Number of Patients	Outcome[b]	Dispersion
Thompson (1982)	No change	GEN	GTC	Mean monthly seizure frequency	9	0.4	SD 1
	No change	PAR	PAR	Mean monthly seizure frequency	9	9.9	SD 12.9
	Reduction	PAR	PAR	Mean monthly seizure frequency	16	18.1	SD 35.6
	Reduction	GEN	GTC	Mean monthly seizure frequency	14	3.6	SD 3.1
Other studies of optimized current therapy							
Semah (1994)	Other	PAR	PAR	Number of patients with 50% or more reduction at 2 months	18	7	
	Other	PAR	PAR	Number of patients with 50% or more reduction at 6 months	18	3	
	Other	PAR	PAR	Number of patients seizure free	18	1	
Schmidt (1983)	Other	ALL	ALL	Number of patients seizure free	27	6	

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in mood and cognitive function (continued)

					Pretreatment		Posttreatment		
Reference	Domain	Measure	Patients in Drug Reduction Group	Patients in Control Group	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)	Followup Time	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)
Reitz (1992)	Psychomotor function	Finger Tapping: Dominant hand	17	12	25.8 (9.5)	28.5 (9.0)	10 wks	30.3 (10.6)	30.1 (10.4)
		Finger tapping: Non-dominant hand	17	12	24.8 (8.7)	27.1 (8.4)		26.2 (8.0)	27.4 (8.0)
		Pegboard: Dominant hand	17	12	90.1 (70.1)	83.1 (53.1)		71.8 (23.7)	71.5 (19.0)
		Pegboard: Non-dominant hand	17	12	89.0 (38.7)	79.7 (29.8)		87.1 (42.8)	78.0 (26.3)
		Pursuit rotor: Failure dominant hand	17	12	26.3 (10.1)	22.1 (10.7)		23.8 (12.6)	28.4 (20.5)
		Pursuit rotor: Failure duration dominant hand	17	12	153.0 (63.0)	141.0 (74.0)		159.0 (66.0)	132.0 (67.0)
		Pursuit rotor: Failure non-dominant hand	17	12	26.7 (12.1)	23.7 (8.5)		23.1 (15.2)	20.8 (12.2)
		Pursuit rotor: Failure duration non-dominant hand	17	12	161.0 (73.0)	123.0 (61.0)		163.0 (74.0)	139.0 (93.0)
	Memory	LGT-Immediate recall	17	12	5.88 (2.76)	7.88 (3.26)	10 wks	5.92 (2.11)	6.83 (2.89)
		LGT-Delayed recall	17	12	4.53 (2.72)	5.33 (3.64)		4.66 (2.15)	4.42 (2.84)
		Digit span forward	17	12	4.88 (1.32)	4.76 (1.92)		4.25 (1.14)	4.67 (1.15)
		Digit span backwards	17	12	3.29 (1.21)	3.41 (1.93)		3.00 (1.28)	2.92 (1.09)
	Concentration/ attention	Modified FCTC	17	12	45.8 (16.2)	41.1 (17.5)	10 wks	525.7 (16.5)	50.9 (16.9)
		d2-test T-F	17	12	267.0 (102.0)	285.0 (108.0)		242.0 (50.0)	258.0 (61.0)
		d2-test Q	17	12	11.7 (10.2)	9.0 (10.5)		10.7 (7.0)	12.7 (6.3)

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in mood and cognitive function (continued)

					Pretreatment		Posttreatment		
Reference	Domain	Measure	Patients in Drug Reduction Group	Patients in Control Group	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)	Followup Time	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)
Reference (1990)	Memory and conceptual processing	Digit symbol substitution test	PHT: 19	21	PHT: 15 (rng: 4 to 37)	15 (rng: 3 to 40)	5 to 11 wks	PHT: 17 (rng: 4 to 45)	14 (rng: 2 to 38)
			CBZ: 12		CBZ: 16 (rng: 5 to 60			CBZ:16 (rng: 4 to 70)	
			VPA: 13		VPA: 23 (rng: 2 to 54)			VPA: 25 (rng: to 56)	
	Memory and concentration	Digit scan forward	PHT: 19	21	PHT: 5.1 (1.2)	5.0 (1.0)	5 to 11 wks	PHT: 3.6 (1.1)	3.1 (1.2)
			CBZ: 12		CBZ: 5.5 (1.6)			CBZ: 3.3 (1.5)	
			VPA: 13		VPA: 5.4 (1.2)			VPA: 4.0 (1.4)	
	Attention and concentration	Letter cancellation task	PHT: 19	21	PHT: 57.9 (23.7)	55.2 (24.5)	5 to 11 wks	PHT: 65.1 (30.5)	48.7 (24.9)
			CBZ: 12		CBZ: 62.6 (33.7)			CBZ: 56.4 (39.0)	
			VPA: 13		VPA: 81.5 (27.9)			VPA: 82.9 (29.7)	

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in mood and cognitive function (continued)

					Pretreatment		Posttreatment		
Reference	Domain	Measure	Patients in Drug Reduction Group	Patients in Control Group	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)	Followup Time	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)
Reference (1990) continued	Psychomotor function	Tapping Rate: Dominant hand	PHT: 19	21	PHT: 47.1 (10.7)	48.0 (13.2)	5 to 11 wks	PHT: 51.9 (12.0)	49.2 (14.0)
			CBZ: 12		CBZ: 50.8 (16.1)			CBZ: 55.5 (20.0)	
			VPA: 13		VPA: 51.9 (14.0)			VPA: 58.5 (14.5)	
	Psychomotor function	Tapping Rate: Non-dominant hand	PHT: 19	21	PHT: 43.2 (8.8)	41.5 (12.1)	5 to 11 wks	PHT: 46.8 (9.2)	42.0 (12.9)
			CBZ: 12		CBZ: 44.5 (16.5)			CBZ: 48.1 (16.6)	
			VPA: 13		VPA: 44.3 (12.8)			VPA: 49.0 (14.4)	
	Mood	MHQ-Anxiety	PHT: 19	21	PHT: 6.1 (3.7)	5.6 (4.2)	5 to 11 wks	PHT: 4.5 (3.4)	4.3 (3.4)
			CBZ: 12		CBZ: 4.0 (3.6)			CBZ: 5.5 (3.1)	
			VPA: 13		VPA: 4.8 (4.0)			VPA: 5.0 (3.1)	
		MHQ-Phobia	PHT: 19	21	PHT: 3.6 (2.5)	3.4 (2.8)	5 to 11 wks	PHT: 5.9 (2.6)	8.0 (3.5)
			CBZ: 12		CBZ: 3.0 (2.9)			CBZ: 7.1 (3.2)	
			VPA: 13		VPA: 4.2 (3.0)			VPA: 6.2 (3.4)	

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in mood and cognitive function (continued)

					Pretreatment		Posttreatment		
Reference	**Domain**	**Measure**	**Patients in Drug Reduction Group**	**Patients in Control Group**	**Drug Reduction Arm: Mean Score (SD)**	**Control Arm: Mean Score (SD)**	**Followup Time**	**Drug Reduction Arm: Mean Score (SD)**	**Control Arm: Mean Score (SD)**
Reference (1990) continued		MHQ-Obsession	PHT: 19	21	PHT: 5.9 (2.6)	8.0 (3.5)	5 to 11 wks	PHT: 6.6 (3.1)	8.1 (3.7)
			CBZ: 12		CBZ: 7.1 (3.2)			CBZ: 8.7 (3.2)	
			VPA: 13		VPA: 6.2 (3.4)			VPA: 7.3 (3.4)	
		MHQ-Somatic anxiety	PHT: 19	21	PHT: 5.1 (2.8)	4.4 (3.4)	5 to 11 wks	PHT: 3.7 (2.7)	4.0 (2.6)
			CBZ: 12		CBZ: 5.0 (2.3)			CBZ: 4.3 (2.4)	
			VPA: 13		VPA: 5.1 (2.0)			VPA: 4.3 (2.4)	
		MHQ-Depression	PHT: 19	21	PHT: 4.5 (2.1)	4.7 (3.3)	5 to 11 wks	PHT: 4.0 (2.9)	4.8 (2.6)
			CBZ: 12		CBZ: 3.9 (2.8)			CBZ: 4.6 (2.4)	
			VPA: 13		VPA: 2.9 (1.8)			VPA: 3.5 (1.6)	
		MHQ-Hysteria	PHT: 19	21	PHT: 5.2 (3.4)	5.6 (3.4)	5 to 11 wks	PHT: 4.8 (2.3)	5.3 (2.7)
			CBZ: 12		CBZ: 4.3 (2.3)			CBZ: 5.3 (3.3)	
			VPA: 13		VPA: 4.6 (3.9)			VPA: 4.7 (2.6)	

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in mood and cognitive function (continued)

					Pretreatment		Posttreatment		
Reference	**Domain**	**Measure**	**Patients in Drug Reduction Group**	**Patients in Control Group**	**Drug Reduction Arm: Mean Score (SD)**	**Control Arm: Mean Score (SD)**	**Followup Time**	**Drug Reduction Arm: Mean Score (SD)**	**Control Arm: Mean Score (SD)**
Thompson (1982)	Memory	Pictures: Immediate recall	20	10	8.4 (2.7)	8.9 (2.1)	6 mos	9.8 (3.3)	9.9 (2.7)
		Pictures: Delayed recall	20	10	6.2 (2.3)	8.5 (2.4)		8.3 (3.0)	8.8 (2.7)
		Pictures: Recognition	20	10	36.3 (3.4)	38.1 (1.9)		37.1 (3.5)	37.8 (2.2)
	Memory	Words: Immediate recall	20	10	7.4 (2.8)	8.2 (2.8)	6 mos	7.5 (2.6)	7.2 (2.3)
		Words: Delayed recall	20	10	4.1 (2.3)	4.7 (3.1)		5.0 (2.7)	5.6 (2.0)
		Words: Recognition	20	10	33.1 (4.7)	32.8 (3.5)		31.8 (4.8)	32.7 (3.3)
	Concentration	Stroop: Naming speed (s) III-II	20	10	40.7 (53.0)	23.6 (23.2)	6 mos	20.0 (21.9)	25.2 (21.0)
		Stroop: Naming speed (s) errors	20	10	3.2 (2.7)	1.0 (1.1)		2.2 (1.9)	2.2 (1.5)
		Visual scanning speeds (s)	20	10	120.5 (64.3)	78.5 (20.6)		86.1 (36.4)	86.8 (18.0)
		With auditory task	20	10	138.3 (76.7)	91.6 (21.9)		94.8 (41.2)	98.5 (24.3)
		Total number scanned	20	10	134.8 (46.4)	139.7 (51.9)		165.4 (54.5)	140.6 (54.9)
		Total number errors	20	10	9.8 (8.9)	7.4 (6.8)		6.6 (5.0)	7.1 (9.4)

Evidence Table 99. Outcomes in studies of optimized current therapy – changes in mood and cognitive function (continued)

Reference	Domain	Measure	Patients in Drug Reduction Group	Patients in Control Group	Pretreatment		Posttreatment		
					Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)	Followup Time	Drug Reduction Arm: Mean Score (SD)	Control Arm: Mean Score (SD)
Thompson (1982) continued	Mental speed	Perceptual speed for words	20	10	0.098 (0.034)	0.076 (0.015)	6 mos	0.077 (0.021)	0.076 (0.013)
		Perceptual speed for pictures	20	10	0.091 (0.029)	0.076 (0.018)		0.082 (0.024)	0.078 (0.016)
		Decision making for color	20	10	1.425 (1.296)	0.841 (0.197)		0.959 (0.424)	0.838 (0.242)
		Decision making for pictures	20	10	1.612 (1.140)	0.976 (0.293)		1.151 (0.457)	1.032 (0.257)
		Visuomotor response	20	10	0.420 (0.317)	0.405 (0.205)		0.366 (0.130)	0.371 (0.152)
	Motor speed	Dominant hand	20	10	61.3 (15.9)	64.7 (15.1)	6 mos	68.5 (11.8)	67.0 (15.2)
		Non-dominant hand	20	10	49.8 (16.7)	54.0 (15.2)		61.6 (10.5)	57.8 (13.5)
		Both hands	20	10	44.0 (15.3)	53.0 (19.6)		51.2 (12.8)	53.9 (21.2)
	Mood	MACL: Anxiety	20	10	3.9 (2.4)	2.1 (1.7)	6 mos	1.7 (1.5)	1.5 (1.5)
		MACL: Fatigue	20	10	3.6 (4.5)	1.9 (2.3)		2.1 (3.9)	2.2 (1.8)
		MACL: Activity	20	10	4.4 (4.1)	4.0 (2.5)		6.2 (3.4)	4.5 (2.4)
		MACL: Depression	20	10	3.4 (4.0)	1.5 (2.8)		2.2 (4.5)	1.1 (2.6)
		MHQ: Anxiety	20	10	6.1 (3.8)	5.2 (3.9)		5.1 (3.3)	4.4 (2.4)
		MHQ: Depression	20	10	4.8 (3.2)	3.5 (2.5)		4.2 (3.6)	3.2 (2.2)
		MHQ: Total score	20	10	32.8 (14.6)	31.2 (10.0)		29.4 (15.4)	26.9 (6.7)

[a] The abbreviations used in Evidence Table 99 appear on the following page

[b] In the outcome column, a positive value for either median % reduction from baseline or median difference from baseline represents a beneficial reduction in seizures. This conforms to the convention in the epilepsy literature.

[c] Calculated by ECRI based on published information

Abbreviations used in Evidence Table 99

ALL	all seizures
CPS	complex partial seizures
GEN	generalized seizures
GTC	generalized tonic-clonic seizures
PAR	partial seizures
SPS	simple partial seizures
mos	months
wks	weeks

Evidence Table 100. Adverse effects in studies of optimized current therapy

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Studies of drug reduction					
Mirza (1993)	Reduction	Status epilepticus	Severe	1/44	2 %
	Reduction	Transient increase in seizure frequency		15/44	34 %
Duncan (1990)	No change	Agitation, new onset		7/22[a]	32 %[a]
	Reduction (phenytoin)	Agitation, new onset		2/23[a]	9 %[a]
	Reduction (carbamazepine)	Agitation, new onset		3/25[a]	12 %[a]
	Reduction (valproate)	Agitation, new onset		3/25[a]	12 %[a]
	No change	Anorexia, new onset		2/22[a]	9 %[a]
	Reduction (phenytoin)	Anorexia, new onset		3/23[a]	13 %[a]
	Reduction (carbamazepine)	Anorexia, new onset		4/25[a]	16 %[a]
	Reduction (valproate)	Anorexia, new onset		2/25[a]	8 %[a]
	No change	Anxiety, new onset		3/22[a]	14 %[a]
	Reduction (phenytoin)	Anxiety, new onset		3/23[a]	13 %[a]
	Reduction (carbamazepine)	Anxiety, new onset		2/25[a]	8 %[a]
	Reduction (valproate)	Anxiety, new onset		3/25[a]	12 %[a]
	No change	Auditory hallucinations, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Auditory hallucinations, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Auditory hallucinations, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Auditory hallucinations, new onset		0/25[a]	0 %[a]

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Duncan (1990) continued	No change	Depersonalization, new onset		1/22[a]	5 %[a]
	Reduction (phenytoin)	Depersonalization, new onset		2/23[a]	9 %[a]
	Reduction (carbamazepine)	Depersonalization, new onset		1/25[a]	4 %[a]
	Reduction (valproate)	Depersonalization, new onset		0/25[a]	0 %[a]
	No change	Depression, new onset		6/22[a]	27 %[a]
	Reduction (phenytoin)	Depression, new onset		5/23[a]	22 %[a]
	Reduction (carbamazepine)	Depression, new onset		1/25[a]	4 %[a]
	Reduction (valproate)	Depression, new onset		5/25[a]	20 %[a]
	No change	Derealisation, new onset		1/22[a]	5 %[a]
	Reduction (phenytoin)	Derealisation, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Derealisation, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Derealisation, new onset		0/25[a]	0 %[a]
	No change	Disorientation, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Disorientation, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Disorientation, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Disorientation, new onset		0/25[a]	0 %[a]
	No change	Distorted taste/smell, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Distorted taste/smell, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Distorted taste/smell, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Distorted taste/smell, new onset		0/25[a]	0 %[a]

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Duncan (1990) continued	No change	Dizziness, new onset		5/22[a]	23 %[a]
	Reduction (phenytoin)	Dizziness, new onset		1/23[a]	4 %[a]
	Reduction (carbamazepine)	Dizziness, new onset		4/25[a]	16 %[a]
	Reduction (valproate)	Dizziness, new onset		3/25[a]	12 %[a]
	No change	Flu-like illness, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Flu-like illness, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Flu-like illness, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Flu-like illness, new onset		1/25[a]	4 %[a]
	No change	Headache, new onset		2/22[a]	9 %[a]
	Reduction (phenytoin)	Headache, new onset		4/23[a]	17 %[a]
	Reduction (carbamazepine)	Headache, new onset		2/25[a]	8 %[a]
	Reduction (valproate)	Headache, new onset		6/25[a]	24 %[a]
	No change	Hyperacusis, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Hyperacusis, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Hyperacusis, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Hyperacusis, new onset		0/25[a]	0 %[a]
	No change	Hypo/eraesthesiae, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Hypo/eraesthesiae, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Hypo/eraesthesiae, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Hypo/eraesthesiae, new onset		0/25[a]	0 %[a]

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Duncan (1990) continued	No change	Impaired memory/concentration, new onset		2/22[a]	9 %[a]
	Reduction (phenytoin)	Impaired memory/concentration, new onset		2/23[a]	9 %[a]
	Reduction (carbamazepine)	Impaired memory/concentration, new onset		5/25[a]	20 %[a]
	Reduction (valproate)	Impaired memory/concentration, new onset		1/25[a]	4 %[a]
	No change	Incoordination, new onset		2/22[a]	9 %[a]
	Reduction (phenytoin)	Incoordination, new onset		2/23[a]	9 %[a]
	Reduction (carbamazepine)	Incoordination, new onset		3/25[a]	12 %[a]
	Reduction (valproate)	Incoordination, new onset		1/25[a]	4 %[a]
	No change	Insomnia, new onset		4/22[a]	18 %[a]
	Reduction (phenytoin)	Insomnia, new onset		4/23[a]	17 %[a]
	Reduction (carbamazepine)	Insomnia, new onset		3/25[a]	12 %[a]
	Reduction (valproate)	Insomnia, new onset		5/25[a]	20 %[a]
	No change	Irritability, new onset		5/22[a]	23 %[a]
	Reduction (phenytoin)	Irritability, new onset		5/23[a]	22 %[a]
	Reduction (carbamazepine)	Irritability, new onset		2/25[a]	8 %[a]
	Reduction (valproate)	Irritability, new onset		1/25[a]	4 %[a]
	No change	Lack of energy, new onset		3/22[a]	14 %[a]
	Reduction (phenytoin)	Lack of energy, new onset		4/23[a]	17 %[a]
	Reduction (carbamazepine)	Lack of energy, new onset		5/25[a]	20 %[a]
	Reduction (valproate)	Lack of energy, new onset		8/25[a]	32 %[a]

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Duncan (1990) continued	No change	Muscle ache, new onset		3/22[a]	14 %[a]
	Reduction (phenytoin)	Muscle ache, new onset		5/23[a]	22 %[a]
	Reduction (carbamazepine)	Muscle ache, new onset		4/25[a]	16 %[a]
	Reduction (valproate)	Muscle ache, new onset		5/25[a]	20 %[a]
	No change	Nausea and/or vomiting, new onset		5/22[a]	23 %[a]
	Reduction (phenytoin)	Nausea and/or vomiting, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Nausea and/or vomiting, new onset		2/25[a]	8 %[a]
	Reduction (valproate)	Nausea and/or vomiting, new onset		3/25[a]	12 %[a]
	No change	Onset of new seizure type		0/23[a]	0 %[a]
	Reduction (phenytoin)	Onset of new seizure type		0/24[a]	0 %[a]
	Reduction (carbamazepine)	Onset of new seizure type		0/25[a]	0 %[a]
	Reduction (valproate)	Onset of new seizure type		0/25[a]	0 %[a]
	No change	Paranoia, new onset		1/22[a]	5 %[a]
	Reduction (phenytoin)	Paranoia, new onset		1/23[a]	4 %[a]
	Reduction (carbamazepine)	Paranoia, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Paranoia, new onset		0/25[a]	0 %[a]
	No change	Paresthesia, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Paresthesia, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Paresthesia, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Paresthesia, new onset		0/25[a]	0 %[a]

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Duncan (1990) continued	No change	Photophobia/sore eyes, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Photophobia/sore eyes, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Photophobia/sore eyes, new onset		1/25[a]	4 %[a]
	Reduction (valproate)	Photophobia/sore eyes, new onset		1/25[a]	4 %[a]
	No change	Sweating, new onset		4/22[a]	18 %[a]
	Reduction (phenytoin)	Sweating, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Sweating, new onset		6/25[a]	24 %[a]
	Reduction (valproate)	Sweating, new onset		1/25[a]	4 %[a]
	No change	Tremor, new onset		4/22[a]	18 %[a]
	Reduction (phenytoin)	Tremor, new onset		2/23[a]	9 %[a]
	Reduction (carbamazepine)	Tremor, new onset		2/25[a]	8 %[a]
	Reduction (valproate)	Tremor, new onset		2/25[a]	8 %[a]
	No change	Twitching, new onset		3/22[a]	14 %[a]
	Reduction (phenytoin)	Twitching, new onset		4/23[a]	17 %[a]
	Reduction (carbamazepine)	Twitching, new onset		5/25[a]	20 %[a]
	Reduction (valproate)	Twitching, new onset		2/25[a]	8 %[a]
	No change	Visual hallucinations, new onset		0/22[a]	0 %[a]
	Reduction (phenytoin)	Visual hallucinations, new onset		0/23[a]	0 %[a]
	Reduction (carbamazepine)	Visual hallucinations, new onset		0/25[a]	0 %[a]
	Reduction (valproate)	Visual hallucinations, new onset		0/25[a]	0 %[a]

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Specht (1989)	Reduction	Any		19/40	48 %
	Reduction	Nonictal withdrawal symptoms		4/40	10 %
	Reduction	Seizure exacerbation and psychic symptoms		5/40	13 %
	Reduction	Seizures during drug withdrawal		14/40	35 %
	Reduction	Seizures during drug withdrawal		14/40	35 %
	Reduction	Transitory exacerbation of seizures		10/40	25 %
Callaghan (1984)	Reduction	Increase in seizures	Withdrawal	6/35	17 %
Schmidt (1983)	Reduction	Anxiety, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Anxiety, Number of side effects occurring after drug withdrawal		1/36	3 %
	Reduction	Ataxia, Number of side effects disappearing after drug withdrawal		5/36	14 %
	Reduction	Ataxia, Number of side effects occurring after drug withdrawal		1/36	3 %
	Reduction	Diplopia, Number of side effects disappearing after drug withdrawal		1/36	3 %
	Reduction	Diplopia, Number of side effects occurring after drug withdrawal		0/36	0 %
	Reduction	Exanthemia, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Exanthemia, Number of side effects occurring after drug withdrawal		0/36	0 %
	Reduction	Fever, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Fever, Number of side effects occurring after drug withdrawal		0/36	0 %
	Reduction	Gingival hyperplasia, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Gingival hyperplasia, Number of side effects occurring after drug withdrawal		0/36	0 %

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Schmidt (1983) continued	Reduction	Myalgia, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Myalgia, Number of side effects occurring after drug withdrawal		0/36	0 %
	Reduction	Myoclonias, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Myoclonias, Number of side effects occurring after drug withdrawal		0/36	0 %
	Reduction	Nausea, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Nausea, Number of side effects occurring after drug withdrawal		1/36	3 %
	Reduction	Nystagmus, Number of side effects disappearing after drug withdrawal		7/36	19 %
	Reduction	Nystagmus, Number of side effects occurring after drug withdrawal		4/36	11 %
	Reduction	Sedation, Number of side effects disappearing after drug withdrawal		2/36	6 %
	Reduction	Sedation, Number of side effects occurring after drug withdrawal		2/36	6 %
	Reduction	Tremor, Number of side effects disappearing after drug withdrawal		0/36	0 %
	Reduction	Tremor, Number of side effects occurring after drug withdrawal		0/36	0 %
	Reduction	Vertigo, Number of side effects disappearing after drug withdrawal		2/36	6 %
	Reduction	Vertigo, Number of side effects occurring after drug withdrawal		1/36	3 %
	Reduction	Vomiting, Number of side effects disappearing after drug withdrawal		1/36	3 %
	Reduction	Vomiting, Number of side effects occurring after drug withdrawal		0/36	0 %

Evidence Table 100. Adverse effects in studies of optimized current therapy (continued)

Reference	Treatment Description	Description of Adverse Effect	Severity of Adverse Effect	Patients With This Effect / Patients in The Group	Percentage
Other studies of optimized current therapy					
Semah (1994)	Other	Any	Any	14/18	78%
	Other	Ataxia		2/18	11%
	Other	Diplopia		4/18	22%
	Other	Drowsiness		7/18	39%
	Other	Dyspnea		2/18	11%
	Other	Headache		2/18	11%
	Other	Memory difficulty		2/18	11%
	Other	Nausea		3/18	17%
	Other	Tremor		2/18	11%

[a] Information reported by a secondary publication, Duncan (1988).

Evidence Table 101. Comparison of patients in drug reduction and control arms of controlled trials

Reference	Demographic	Study Arm	N	Pretreatment	Type of Effect Size	Effect Size (CI)	P =
May (1992)	Age (yrs)	Treatment	17	55.2 (8.7) yrs	Original metric	**8.90 (0.29 to 17.51) yrs**	**0.043**
		Control	12	46.3 (13.3) yrs			
	Sex ratio (males:females)	Treatment	17	8:4	Cohen's h	0.31 (0.43 to 1.04)	0.418
		Control	12	7:17			
	Duration of epilepsy (yrs)	Treatment	17	49.4 (8.4) yrs	Original metric	**8.9 (0.10 to 17.90)**	**0.053**
		Control	12	40.5 (14.2) yrs			
	Number of seizures in previous year	Treatment	17	25.6 (25.7)	Original metric	2.8 (16.15 to 21.75)	0.772
		Control	12	22.8 (25.6)			
	Phenytoin dose (mg)	Treatment	17	182.4 (38.3) mg	Original metric	**-46.80 (-80.78 to –12.82)**	**0.007**
		Control	12	229.2 (50.6) mg			
	Phenytoin serum conc (mg/l[3])	Treatment	17	5.4 (2.0)	Original metric	**-3.40 (-5.37 to –1.43)**	**0.0007**
		Control	12	8.8 (3.4)			
Duncan (1990)	Age (years)	PHT	23	35 (rng: 19 to 65)	NC	NC	**0.01[a]**
		CBZ	22	31 (rng: 19 to 59)	NC	NC	**0.006[a]**
		VPA	25	25 (rng: 17 to 48)	NC	NC	**<0.0001[a]**
		Control	25	42 (rng: 25 to 65)			
	Duration of epilepsy (years)	PHT	23	25 (rng: 7 to 51)	NC	NC	**0.03[a]**
		CBZ	22	23 (rng: 10 to 56)	NC	NC	**0.009[a]**
		VPA	25	17 (rng: 7 to 39)	NC	NC	**0.0001[a]**
		Control	25	37 (rng: 16 to 56)			

Evidence Table 101. Comparison of patients in drug reduction and control arms of controlled trials (continued)

Reference	Demographic	Study Arm	N	Pretreatment	Type of Effect Size	Effect Size (CI)	P =
Duncan (1990) continued	Number of seizures in previous 6 months	PHT	23	82 (rng: 5 to 598)	NC	NC	NS
		CBZ	22	72 (rng: 1 to 2210)	NC	NC	NS
		VPA	25	102 (rng: 12 to 910)	NC	NC	NS
		Control	25	58 (rng: 3 to 404			
	IQ (full scale)	PHT	23	78 (10.9)	Original metric	2.0 (-48.7 to 8.82)	0.565
		CBZ	22	82 (13.9)	Original metric	6.00 (-1.69 to 13.69)	0.126
		VPA	25	81 (14.9)	Original metric	5.00 (-2.75 to 12.75)	0.206
		Control	25	76 (13.0)			
	Ratio males:females	PHT	23	16: 7	Cohen's h	-0.09 (-0.66 to 0.47)	0.745
		CBZ	22	17:7	Cohen's h	0.02 (-0.55 to 0.59)	0.946
		VPA	25	13:12	Cohen's h	-0.32 (-0.87 to 0.24)	0.263
		Control	25	19:6			

Evidence Table 101. Comparison of patients in drug reduction and control arms of controlled trials (continued)

Reference	Demographic	Study Arm	N	Pretreatment	Typr of Effect Size	Effect Size (CI)	P =
Thompson (1982)	Age (years)	Treatment	10	28 (10.9)	Original metric	-5.50 (-14.16 to 3.16)	0.213024
		Control	20	33.5 (12.4)			
	Duration of epilepsy	Treatment	10	19.5 (11.3)	Original metric	0.30 (-7.70 to 8.30)	0.941
		Control	20	19.2 (8.7)			
	Ratio males:females	Treatment	10	2:8	Cohen's h	0.32 (-0.44 to 1.08)	0.405396
		Control	20	10:10			
	Full scale IQ	Treatment	10	93.8 (13.5)	Original metric	-2.30 (-12.95 to 8.35)	0.672
		Control	20	96.1 (15.1)			

[a] P-values extracted from article because reported data did not allow us to calculate the value
NC Not calculable given available information
NS Not statistically significant
CBZ Carbamazepine
PHT Phenytoin
VPA Valproate
IQ Intelligence quotient
Rng Range

Question 5

Which methods of nondrug treatment for epilepsy after initial treatment failure lead to improved outcomes for patients with treatment-resistant epilepsy?

Evidence Table 102. All studies meeting the inclusion criteria for surgical interventions and the interventions examined

Reference	Temporal Lobe Surgery	Frontal Lobe Surgery	Parietal Lobe Surgery	Occipital Lobe Surgery	Multiple Subpial Transections	Hemispherectomy	Corpus Callosotomy	Surgical Control Patients
Bouilleret (2002)	✓							
Alsaadi (2001)	✓							
Bauer (2001)								✓
Boling (2001)	✓							
Carreno (2001)						✓		
Ferrier (2001)		✓						
Hennessy (2001)	✓							
Hennessy (2001)	✓							
Hodaie (2001)							✓	
Jan (2001)	✓							
Kanemoto (2001)	✓							
Kohler (2001)	✓							
Kral (2001)		✓						
Kumlien (2001)								✓
Kwan (2001)							✓	
Maehara (2001)							✓	
Miranda (2001)	✓							
Mulligan (2001)					✓			
Nees (2001)	✓							
Orbach (2001)					✓			
Schramm (2001)	✓							
Schramm (2001)						✓		
Siegel (2001)		✓						
Sotero de Menezes (2001)	✓							
Verma (2001)	✓							
Wiebe (2001)	✓							✓
Wilson (2001)	✓							

Evidence Table 102. All studies meeting the inclusion criteria for surgical interventions and the interventions examined (continued)

Reference	Temporal Lobe Surgery	Frontal Lobe Surgery	Parietal Lobe Surgery	Occipital Lobe Surgery	Multiple Subpial Transections	Hemispherectomy	Corpus Callosotomy	Surgical Control Patients
Anhoury (2000)	✓							
Canizares (2000)	✓							
Derry (2000)	✓							
Di Rocco (2000)						✓		
Dupont (2000)	✓							
Eberhardt (2000)	✓							
Fandino-Franky (2000)							✓	
Foldvary (2000)	✓							
Holmes (2000)	✓							
Hong (2000)		✓						
Iannelli (2000)	✓							
Markand (2000)	✓							✓
Mosewich (2000)		✓						
Rao (2000)	✓							
Robinson (2000)	✓							
Shimizu (2000)						✓		
Shimizu (2000)					✓			
Westerveld (2000)	✓							
Wurm (2000)	✓							
Altshuler (1999)	✓							
Assaf (1999)	✓							
Battaglia (1999)						✓		
Chassoux (1999)		✓						
Eriksson (1999)	✓	✓						
Ferrier (1999)		✓						
Henry (1999)	✓							
Holmes (1999)	✓							
Leung (1999)	✓							
Mathern (1999)	✓							
Matsuzaka (1999)							✓	
McInerney (1999)							✓	

Evidence Table 102. All studies meeting the inclusion criteria for surgical interventions and the interventions examined (continued)

Reference	Temporal Lobe Surgery	Frontal Lobe Surgery	Parietal Lobe Surgery	Occipital Lobe Surgery	Multiple Subpial Transections	Hemispherectomy	Corpus Callosotomy	Surgical Control Patients
Mitchell (1999)	✓							
Parrent (1999)	✓							
Pinard (1999)							✓	
Rossi (1999)	✓							
Salanova (1999)	✓							
Son (1999)	✓							
Visudhiphan (1999)	✓							
Wennberg (1999)		✓						
Blumer (1998)	✓							
Carmant (1998)							✓	
Helmstaedter (1998)		✓						
Holmes (1998)								✓
Maher (1998)	✓							
Radhakrishnan (1998)	✓							
Ring (1998)	✓							
Smith (1998)					✓			
Swartz (1998)		✓						
Szabo (1998)	✓							
Wolf (1998)								✓
Wyllie (1998)	✓					✓		
Bizzi (1997)	✓							
Blume (1997)	✓							
Cappabianca (1997)	✓	✓						
Casazza (1997)	✓							
Ho (1997)	✓							
Hufnagel (1997)					✓			
Keene (1997)	✓							
Kilpatrick (1997)	✓							
McLachlan (1997)	✓							✓
Pacia (1997)					✓			
Patil (1997)					✓			

Evidence Table 102. All studies meeting the inclusion criteria for surgical interventions and the interventions examined (continued)

Reference	Temporal Lobe Surgery	Frontal Lobe Surgery	Parietal Lobe Surgery	Occipital Lobe Surgery	Multiple Subpial Transections	Hemispherectomy	Corpus Callosotomy	Surgical Control Patients
Reeves (1997)	✓							
Schwartz (1997)	✓							
Silander (1997)	✓							
Sisodiya (1997)	✓							
Smith (1997)		✓						
Sorenson (1997)							✓	
Vining (1997)						✓		
Adam (1996)	✓							
Andersen (1996)							✓	
Goldstein (1996)	✓							
Hermanns (1996)								✓
Holmes (1996)	✓							
Peacock (1996)						✓		
Rose (1996)	✓							
Rossi (1996)							✓	
Sakas (1996)							✓	
Sirven (1996)	✓							
Acciarri (1995)	✓	✓						
Berkovic (1995)	✓							
Claverie (1995)							✓	
Davies (1995)	✓							
Jooma (1995a)	✓							
Jooma (1995b)	✓							
Liu (1995)	✓							
Morrell (1995)					✓			
Renowden (1995)	✓							
Salanova (1995)			✓					
Salanova (1995)			✓					
Sawhney (1995)					✓			
Schramm (1995)						✓		
Sperling (1995)	✓							

Evidence Table 102. All studies meeting the inclusion criteria for surgical interventions and the interventions examined (continued)

Reference	Temporal Lobe Surgery	Frontal Lobe Surgery	Parietal Lobe Surgery	Occipital Lobe Surgery	Multiple Subpial Transections	Hemispherectomy	Corpus Callosotomy	Surgical Control Patients
Thadani (1995)	✓							
Vickrey (1995)								✓
Vossler (1995)	✓							
Wyler (1995)	✓							
Blume (1994)	✓							
Guldvog (1994a)	✓							
Guldvog (1994b)	✓							
Naylor (1994)	✓							
Chelune (1993)	✓							
Reutens (1993)							✓	
Bladin (1992)	✓							
Salanova (1992)				✓				
Adler (1991)		✓						
Berkovic (1991)	✓							
Blume (1991)				✓				
Cohen (1991)							✓	
Elwes (1991)	✓							
Fuiks (1991)							✓	
Garcia Sola (1991)		✓						
Guldvog (1991)								✓
Hopkins (1991)	✓							
Nordgren (1991)							✓	
Oguni (1991)							✓	
Palmini (1991)		✓						
Rasmussen (1991)		✓						
Rasmussen (1991)	✓							
Shimizu (1991)					✓			
Wieser (1991)	✓							
Bidzinski (1990)	✓							
Huttenlocher (1990)								✓
Mackenzie (1990)	✓							

Evidence Table 102. All studies meeting the inclusion criteria for surgical interventions and the interventions examined (continued)

Reference	Temporal Lobe Surgery	Frontal Lobe Surgery	Parietal Lobe Surgery	Occipital Lobe Surgery	Multiple Subpial Transections	Hemispherectomy	Corpus Callosotomy	Surgical Control Patients
Marino (1990)							✓	
Mizrahi (1990)	✓							
Provinciali (1990)							✓	
Sass (1990)							✓	
Walczak (1990)	✓							
Yeh (1990)	✓							
So (1989)	✓							
Sperling (1989)	✓							
Estes (1988)	✓							
Ivnik (1988)	✓							
Murro (1988)							✓	
Purves (1988)							✓	
Spencer (1988)							✓	
Tinuper (1988)						✓		
Bladin (1987)	✓							
Cutfield (1987)	✓							
Drake (1987)	✓							
Garcia-Flores (1987)							✓	
Gates (1987)							✓	
Harbord (1987)								✓
Lindsay (1987)						✓		
King (1986)	✓							
Lieb (1986)	✓							
Meyer (1986)	✓							
Carey (1985)	✓							
Delgado-Escueta (1985)	✓							
Ojemann (1985)	✓							
Powell (1985)	✓							

Evidence Table 103. Studies of temporal lobe surgery – general study information

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Bouilleret (2002)	18	1993-2000	France		No	Prospective	Nested case-control with individual patient data
Alsaadi (2001)	49	1989-1994	United States	Department of Neurology, University of California San Francisco, 400 Parnassus Avenue, Room A889, San Francisco, California 94143, USA.	No	Retrospective	Nested case-control
Boling (2001)	18	1981-1999	Canada	Dr. W. Boling, Department of Neurosurgery, Montreal Neurol. Inst. and Hospital, Montreal, Que. H3A 2B4. Canada	No	Retrospective	Case series
Hennessy (2001)	116	1975-1995	England	Epilepsy Centre, Kings College Hospital, Denmark Hill, London SE5, Department of Biostatistics and Computing, Institute of Psychiatry, de Crespigny Park, London SE5.	No	Retrospective	Nested case-control
Hennessy (2001)	80	1975-1995	England	Epilepsy Centre, King's College Hospital, Denmark Hill, London SE5, UK. Michael@hennessy72.fsnet.co.uk	No	Retrospective	Nested case-control
Jan (2001)	29	1990-1996	Canada		No	Retrospective	Case series
Kanemoto (2001)	52	1987-1999	Japan		No	Retrospective	Case series
Kohler (2001)	58	1986-1999	United States	Neuropsychiatry Section, Department of Psychiatry, University of Pennsylvania, Philadelphia 19104-4283, USA. kohler@bblmail.psycha.upenn.edu	No	Retrospective	Case series
Miranda (2001)	50	1976-1998	Canada		No	Retrospective	Case series
Nees (2001)	50	1992-1994	England		No	Retrospective	Case series
Schramm (2001)	61	1993-1999	Germany	Department of Neurosurgery, University of Bonn, Germany. schrammj@mailer.meb.uni-bonn.de	No	Prospective	Case series

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Sotero de Menezes (2001)	15	1978-1993	United States	Department of Neurology, Children's Hospital and Regional Medical Center, University of Washington, Seattle 98105, USA. msoter@chmc.org	No	Retrospective	Nested case-control with individual patient data
Verma (2001)	13	1989-1996	United States	Department of Medicine (Neurology), Duke University Medical Center, 27710, Durham, NC, USA	No	Retrospective	Nested case-control with individual patient data
Wiebe (2001)	40	1996-2000	Canada	Department of Clinical Neurological Sciences, University of Western Ontario, and London Health Sciences Centre, Canada. swiebe@uwo.ca	No	Prospective	RCT
Wilson (2001)	90	1990-1993	Australia	Comprehensive Epilepsy Program, Epilepsy Research Institute, Austin & Repatriation Medical Centre (A&RMC), Melbourne, Australia. s.wilson@psych.unimelb.edu.au	No	Retrospective	Case series
Anhoury (2000)	121	1988-1997	England	Raymond Way Neuropsychiatry Research Group, University Department of Clinical Neurology, Institute of Neurology, London, England.	No	Retrospective	Case series
Canizares (2000)	33	1998-1999	Spain	Department of Psychiatry and Clinical Psychobiology of the University of Barcelona, Spain.	No	Prospective	Case series
Derry (2000)	39	1996-1998	Canada	Department of Psychology, London Health Sciences Centre, University of Western Ontario, Canada. pderry@julian.uwo.ca	No	Prospective	Case series
Dupont (2000)	30	1994-1999	France	Service Hospitalier Frederic Joliot, Commissariat a l'Energie Atomique, 91401 Orsay Cedex, France. dupont@shfj.cea.fr	No	Not reported	Nested case-control
Eberhardt (2000)	26	1995-1999	Germany	Department of Neurosurgery, University of Erlangen-Nuremberg, Germany. neoruradiologie@rzmail.uni-erlangen.de	No	Prospective	Nested case-control with individual patient data
Foldvary (2000)	79	1962-1984	United States	Department of Neurology, Duke University Medical Center, Durham, NC, USA.	No	Retrospective	Nested case-control

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Holmes (2000)	23	1993-1997	United States	Regional Epilepsy Center, University of Washington, Seattle, 98104, USA. mdholmes@u.washington.edu	No	Retrospective	Nested case-control
Iannelli (2000)	37	1981-1997	Italy	Institute of Neurosurgery, Section of Pediatric Neurosurgery, Catholic University, Rome, Italy. Iannel@tiscalinet.it	No	Retrospective	Case series
Markand (2000)	53	1994-1997	United States	Department of Neurology, Division of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA. omarkand@iupui.edu	No	Prospective	Controlled
Rao (2000)	119	1995-1998	India	R. Madhavan Nayar Center for Comprehensive Epilepsy Care, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India.	No	Retrospective	Case series
Robinson (2000)	22	1993-1998	United States	Department of Neurosurgery, Epilepsy Center, St. Louis Children's Hospital, Washington University School of Medicine, Missouri 63110, USA.	No	Prospective	Nested case-control
Westerveld (2000)	82		United States	Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut 06520-8082, USA. westerm@msn.com	Yes	Retrospective	Case series
Wurm (2000)	16	1997-1998	Austria	Department of Neurosurgery, OO Landesnervenklinik Wagner Jauregg, Linz, Austria. gabriele.wurm@lkh.ooe.gv.at	No	Not reported	Case series
Altshuler (1999)	49	1974-1990	United States	UCLA Department of Psychiatry and Biobehavioral Sciences, Mood Disorders Research Program 90095-7057, USA.	No	Retrospective	Case series
Assaf (1999)	75	1989-1995	United States	Department of Neurology, Saint Louis University, Missouri 63110, USA.	No	Retrospective	Case series
Eriksson (1999)	75	1987-1995	Sweden	Institute of Clinical Neuroscience, Dept. of Neurology, Sahlgrenska University Hospital, Goteborg, Sweden.	No	Retrospective	Case series
Henry (1999)	38	1991-1994	United States	Department of Neurology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.	No	Retrospective	Case series

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Holmes (1999)	13	1992-1996	United States	Department of Neurology, University of Washington School of Medicine, Seattle, USA.	No	Retrospective	Nested case-control with individual patient data
Leung (1999)	11	1994-1998	Hong Kong	Division of Neurosurgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong.	No	Retrospective	Case series
Mathern (1999)	31	1986-1997	United States	Division of Neurosurgery, The Mental Retardation Research Center, University of California, Los Angeles, USA. gmathern@ucla.edu	No	Prospective	Case series
Mitchell (1999)	45	1993-1995	Australia	Brain Imaging Research Institute, Austin and Repatriation Medical Centre, Heidelberg, Victoria, Australia.	No	Retrospective	Case series
Parrent (1999)	19	1994-1997	Canada	London Health Sciences Centre, Ontario, Canada. andrew.parrent@lhsc.on.ca	No	Retrospective	Case series
Rossi (1999)	28	1980-1996	Italy	Institute of Neurosurgery, Catholic University, Medical School, Rome, Italy.	No	Retrospective	Case series
Salanova (1999)	145	1984-1995	United States	Department of Neurology, Indiana University School of Medicine, Indianapolis 46202, USA. vsalanov@iumc.iupui.edu	No	Retrospective	Nested case-control
Son (1999)	71	1994-1999	South Korea	Department of Neurosurgery, Seoul National University College of Medicine, Korea.	No	Retrospective	Case series
Visudhiphan (1999)	14	1993-1998	Thailand	Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.	No	Retrospective	Case series
Blumer (1998)	44	1994-1995	United States	Department of Psychiatry, University of Tennessee, and Epi-Care Center, Memphis 38103, USA.	No	Prospective	Case series
Maher (1998)	93	1994-1996	Canada	Department of Medicine, University of Manitoba, Winnipeg, Canada.	Yes	Retrospective	Case series
Radhakrishnan (1998)	175	1988-1991	United States	Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA.	No	Retrospective	Nested case-control

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Ring (1998)	60	1995-1996	England	National Hospital for Neurology and Neurosurgery, London, UK.	No	Prospective	Case series
Szabo (1998)	14	1989-1994	United States	Department of Neurology, The Cleveland Clinic Foundation, Ohio 44195, USA.	No	Retrospective	Nested case-control with individual patient data
Wyllie (1998)	72	1990-1996	United States	Department of Neurology, The Cleveland Clinic Foundation, OH 44195, USA.	No	Retrospective	Case series
Bizzi (1997)	19	1990-1994	United States	Columbia Children's Hospital and Children's Medical Center, Dallas, Tex., USA.	No	Retrospective	Case series
Blume (1997)	14	1977-1994	Canada	University Hospital, University of Western Ontario, London, Canada.	No	Retrospective	Case series
Cappabianca (1997)	10	1985-1994	Italy	Department of Neurosurgery, University Federico II School of Medicine, Naples, Italy.	No	Retrospective	Case series
Casazza (1997)	40	1988-1994	Italy	Istituto Nazionale Neurologico C. Besta, Milano, Italy.	No	Retrospective	Case series
Ho (1997)	63	1989-1993	Australia	Department of Neurology, Austin and Repatriation Medical Centre, Melbourne, Australia.	No	Retrospective	Case series
Keene (1997)	44	1975-1996	Canada	Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada.	No	Retrospective	Case series
Kilpatrick (1997)	36	1993-1995	Australia	Department of Neurology, The Melbourne Neuroscience Centre, The Royal Melbourne Hospital, Victoria, Australia.	No	Not reported	Nested case-control with individual patient data
McLachlan (1997)	56	1992-1995	Canada	Department of Clinical Neurological Sciences, University of Western Ontario, London, Canada.	No	Prospective	Controlled
Reeves (1997)	190	1988-1991	United States	Department of Neurology, Mayo Clinic, Rochester, Minnesota 55905, USA.	No	Retrospective	Case series
Schwartz (1997)	29	1992-1994	United States	Department of Neurological Surgery, Columbia-Presbyterian Medical Center, New York, New York, USA.	No	Prospective	Nested case-control with individual patient data

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Silander (1997)	94	1980-1990	Sweden	Dr. H.C. Silander, Department of Neurosurgery, University Hospital, S-751 85 Uppsala. Sweden	Yes	Retrospective	Case series
Sisodiya (1997)	27	1993-1995	England	Department of Clinical Neurology, National Hospital for Neurology and Neurosurgery, London, UK.	No	Retrospective	Nested case-control with individual patient data
Adam (1996)	30	1991-1994	France	Service de Neurophysiologie, Hopital de la Pitie-Salpetriere, Paris, France.	No	Prospective	Nested case-control with individual patient data
Goldstein (1996)	33	1985-1993	United States	Comprehensive Epilepsy Center, University of Miami School of Medicine, FL, USA.	No	Retrospective	Nested case-control
Holmes (1996)	45	1982-1986	United States	Department of Medicine (Neurology), University of Washington, School of Medicine, Seattle, USA.	No	Prospective	Case series
Rose (1996)	56	1992-1994	Canada	Department of Psychology, University Hospital, London, Ontario, Canada.	No	Prospective	Case series
Sirven (1996)	174	1985-1992	United States	Comprehensive Epilepsy Center, Graduate Hospital, Philadelphia, PA 19146, USA.	No	Retrospective	Case series
Acciarri (1995)	10	1975-1992	Italy	2nd Division of Neurosurgery, Bellaria Hospital, Bologna, Italy.	No	Retrospective	Nested case-control with individual patient data
Berkovic (1995)	135	1986-1991	Australia	Department of Neurology, Austin Hospital, Heidelberg, Melbourne, Australia.	No	Not reported	Case series
Davies (1995)	12	1969-1988	England	Department of Neurosurgery, University Hospital of Wales, Cardiff, UK.	No	Retrospective	Case series
Jooma (1995a)	30	1985-1992	United States	Department of Neurosurgery, University of Cincinnati College of Medicine, Ohio, USA.	No	Retrospective	Nested case-control with individual patient data
Jooma (1995b)	62	1992-1994	United States	Department of Neurosurgery, University of Cincinnati College of Medicine, Ohio, USA.	No	Retrospective	Case series

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Liu (1995)	12	1983-1990	United States	Department of Neurosurgery, University of Cincinnati College of Medicine, Mayfield Neurological Institute, OH 45267-0515.	No	Retrospective	Nested case-control with individual patient data
Renowden (1995)	67	1983-1992	England	Department of Neuroradiology, Radcliffe Infirmary NHS Trust, Oxford, United Kingdom.	No	Retrospective	Case series
Sperling (1995)	73	1986-1990	United States	Comprehensive Epilepsy Center, Graduate Hospital, Philadelphia, PA 19146, USA.	No	Retrospective	Case series
Thadani (1995)	22	1983-1992	United States	Section of Neurology, Dartmouth-Hitchcock Medical Center, Lebonon, NH 03756.	No	Retrospective	Case series
Vossler (1995)	31	1979-1989	United States	Epilepsy Center, Swedish Medical Center, 801 Broadway,Seattle, WA 98122. United States	No	Retrospective	Nested case-control with individual patient data
Wyler (1995)	70	1990-1992	United States	Epilepsy Center, Swedish Medical Center, Seattle, Washington, USA.	No	Prospective	RCT
Blume (1994)	125	1974-1989	Canada	Epilepsy Unit, University Hospital, The University of Western Ontario, London, Ontario, Canada	No	Retrospective	Nested case-control
Guldvog (1994b)	79	1949-1988	Norway	Foundation for Health Services Research, Nordbyhagen, Norway.	Yes	Retrospective	Case series
Guldvog (1994a)	35	1952-1988	Norway	Foundation for Health Services Research, Nordbyhagen, Norway.	Yes	Retrospective	Case series
Naylor (1994)	37	1987-1991	Denmark	Department of Psychiatry, Rigshospitalet, Blegdamsvej 9,DK-2100 Copenhagen O. Denmark	No	Retrospective	Case series
Chelune (1993)	96	1990-1991	United States		No	Prospective	Case series
Bladin (1992)	115	1975-1991	Australia	Comprehensive Epilepsy Program, Austin Hospital, Melbourne, Australia.	No	Retrospective	Case series

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Berkovic (1991)	10	1985-1986	Canada	Montreal Neurological Institute and Hospital, Quebec, Canada.	No	Retrospective	Nested case-control with individual patient data
Elwes (1991)	108	1976-1987	England	Institute of Psychiatry, De Crespigny Park, London, UK.	No	Prospective	Case series
Hopkins (1991)	11	1978-1988	Australia	Royal Children's Hospital, Melbourne, Australia.	No	Retrospective	Nested case-control with individual patient data
Rasmussen (1991)	100	1961-1980	Canada	Montreal Neurology Institute and Hospital, Department of Neurology and Neurosurgery, McGill University, Quebec, Canada.	No	Retrospective	Case series
Wieser (1991)	215	1975-1990	Switzerland	Department of Neurology, University Hospital, Zurich, Switzerland.	No	Retrospective	Case series
Bidzinski (1990)	320	1957-1988	Poland	Department of Neurosurgery, Warsaw Medical Academy, Poland.	No	Retrospective	Case series
Mackenzie (1990)	30	1983-1989	Australia	Prince Henry Hospital, Little Bay, NSW.	No	Retrospective	Case series
Mizrahi (1990)	22	1980-1986	United States	Department of Neurology, Baylor College of Medicine, Houston, TX 77030.	No	Retrospective	Nested case-control with individual patient data
Walczak (1990)	100	1964-1985	United States	Department of Medicine, Duke University Medical Center, Durham, NC 27710.	No	Retrospective	Case series
Yeh (1990)	12	1982-1986	Japan	Department of Neurosurgery, University of Cincinnati College of Medicine, Ohio.	No	Retrospective	Nested case-control with individual patient data
So (1989)	48	1973-1987	Canada	Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada.	No	Retrospective	Nested case-control
Sperling (1989)	39	1976-1983	United States	Department of Neurology, University of Pennsylvania, Philadelphia.	No	Retrospective	Case series

Evidence Table 103. Studies of temporal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Estes (1988)	46	1979-1984	United States		No	Retrospective	Nested case-control with individual patient data
Ivnik (1988)	142	1972-1987	United States	Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN 55905.	No	Retrospective	Case series
Bladin (1987)	63	1985-1987	Australia	Department of Neurology, Austin Hospital, Melbourne, Vic.	No	Retrospective	Case series
Cutfield (1987)	26	1961-1980	New Zealand	North Shore Hospital.	No	Retrospective	Nested case-control
Drake (1987)	16	1974-1986	Canada	Division of Neurosurgery, Hospital for Sick Children, Toronto, Ontario.	No	Retrospective	Nested case-control with individual patient data
King (1986)	23	1981-1983	United States		No	Prospective	Case series
Lieb (1986)	75	1961-1977	United States		No	Retrospective	Case series
Meyer (1986)	50	1970-1983	United States		No	Retrospective	Case series
Carey (1985)	24	1975-1984	Ireland		No	Retrospective	Case series
Delgado-Escueta (1985)	15	1972-1983	United States		No	Retrospective	Nested case-control with individual patient data
Ojemann (1985)	14	1983-1983	United States		No	Not reported	Case series
Powell (1985)	59	1973-1984	England		No	Prospective	Case series

Evidence Table 104. Studies of frontal lobe surgery – general study information

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Ferrier (2001)	35	1975-1996	England	Institute of Epileptology, King's College Hospital, London, UK.	No	Retrospective	Nested case-control
Kral (2001)	32	1989-2000	Germany	Department of Neurosurgery, University of Bonn, Medical Center, Sigmund Freud Strasse 25, 53105 Bonn, Germany.	No	Retrospective	Case series
Siegel (2001)	14	1992-1999	United States	Sections of Neurology, Neurosurgery, and Nuclear Medicine, Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, U.S.A; and Department of Neurology, University Hospital Zurich, Switzerland.	No	Retrospective	Case series
Hong (2000)	18	1995-1999	South Korea	Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. schong@smc.samsung.co.kr	No	Retrospective	Nested case-control with individual patient data
Mosewich (2000)	68	1987-1994	United States	Department of Neurology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.	No	Retrospective	Case series
Chassoux (1999)	120	1964-1995	France	Department of Neurosurgery, Sainte Anne Hospital Center, Paris, France.	No	Retrospective	Case series
Eriksson (1999)	25	1987-1995	Sweden	Institute of Clinical Neuroscience, Dept. of Neurology, Sahlgrenska University Hospital, Goteborg, Sweden.	No	Retrospective	Case series
Ferrier (1999)	42	1975-1996	England	Institute of Epileptology, King's College Hospital, London, UK.	No	Retrospective	Case series
Wennberg (1999)	22	1970-1994	Canada	Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Quebec, Canada.	No	Retrospective	Nested case-control with individual patient data
Helmstaedter (1998)	33	1995-1996	Germany	University Hospital of Epileptology, Bonn, Germany. psych@mailer.meb.uni-bonn.de	No	Retrospective	Case series

Evidence Table 104. Studies of frontal lobe surgery – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Swartz (1998)	19	1986-1995	United States	B.E. Swartz, UCLA Neurology Department, W127B Epilepsy Center, 11301 Wilshire Blvd., Los Angeles, CA 90073. United States	No	Retrospective	Nested case-control with individual patient data
Cappabianca (1997)	13	1985-1994	Italy	Department of Neurosurgery, University Federico II School of Medicine, Naples, Italy.	No	Retrospective	Case series
Smith (1997)	53	1995-1997	United States	Section of Neurosurgery, Medical College of Georgia, Augusta, USA. depatientsurg.jsmith@mail.mcg.edu	No	Retrospective	Nested case-control
Acciarri (1995)	13	1975-1992	Italy	2nd Division of Neurosurgery, Bellaria Hospital, Bologna, Italy.	No	Retrospective	Nested case-control with individual patient data
Adler (1991)	14	1972-1987	United States	Department of Surgery, (Neurosurgery), Stanford University Medical School, Calif.	No	Retrospective	Case series
Garcia Sola (1991)	18	1978-1990	Spain	Department of Clinical Neurophysiology, Hospital Puerta de Hierro, Madrid, Spain.	No	Retrospective	Case series
Palmini (1991)	12	1975-1990	Canada	Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada.	No	Retrospective	Case series
Rasmussen (1991)	283	1928-1980	Canada	Montreal Neurological Institute and Hospital, Quebec, Canada.	No	Retrospective	Case series

Evidence Table 105. Studies of multiple subpial transection – general study information

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Mulligan (2001)	12	1990-1999	United States	Department of Neurosurgery, Yale University School of Medicine, New Haven, CT 06520, U.S.A.	No	Retrospective	Case series
Orbach (2001)	54	1992-2000	United States	Dr. O. Devinsky, NYU-Mt. Sinai Compreh. Epilepsy Ctr., 403 E. 34th St., New York, NY 10016. United States	No	Retrospective	Case series
Shimizu (2000)	31	1983-1998	Japan	Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Japan. smz-h@qb3.so-net.ne.jp	No	Retrospective	Case series
Smith (1998)	84		United States	Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois 60612-3824, USA.	No	Retrospective	Case series
Hufnagel (1997)	22	1993-1996	Germany	Dr. A. Hufnagel, Department of Neurology, University of Essen, Hufelandstr. 55, D-45122 Essen. Germany	No	Retrospective	Nested case-control with individual patient data
Pacia (1997)	21	1992-1994	United States	Departments of Neurology and Neurosurgery, New York University School of Medicine, Hospital for Joint Diseases, New York, NY, USA	No	Retrospective	Nested case-control with individual patient data
Patil (1997)	19	1991-1995	United States	Epilepsy Care Center, Immanuel Medical Center, Omaha, Nebraska, USA.	No	Retrospective	Nested case-control with individual patient data
Morrell (1995)	14	1987-1994	United States	Department of Neurological Science, Rush-Presbyterian-St Luke's Medical Center, Chicago, IL 60612, USA.	No	Retrospective	Nested case-control with individual patient data
Sawhney (1995)	21	1989-1993	England	Department of Clinical Neurophysiology, Maudsley Hospital, London UK.	No	Retrospective	Nested case-control with individual patient data
Shimizu (1991)	12	1989-1990	Japan	Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Japan.	No	Retrospective	Case series

Evidence Table 106. Studies of hemispherectomy – general study information

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Carreno (2001)	13	1992-1999	United States	Departments of Neurology (Drs. Carreno, Wyllie, and Kotagal), Neurosurgery (Drs. Bingaman and Comair), and Neuroradiology (Dr. Ruggieri), The Cleveland Clinic Foundation, OH.	No	Retrospective	Case series
Schramm (2001)	20	1991-1999	Germany	Dr. J. Schramm, Department of Neurosurgery, University of Bonn Medical Center, Sigmund-Freud-Strasse 25, 53105 Bonn. Germany	No	Retrospective	Case series
Di Rocco (2000)	15	1985-1996	Italy	Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy. cdirocco@RM.Unicatt.it	No	Retrospective	Nested case-control with individual patient data
Shimizu (2000)	34	1993-1999	Japan	Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Japan. smzh@tmnh.fuchu.tokyo.jp	No	Retrospective	Case series
Battaglia (1999)	10	1987-1998	Italy	Child Neurology and Psychiatry Unit, UCSC, Rome, Italy.	No	Retrospective	Case series
Wyllie (1998)	16	1990-1996	United States	Department of Neurology, The Cleveland Clinic Foundation, OH 44195, USA.	No	Retrospective	Case series
Vining (1997)	58	1968-1996	United States	Pediatric Epilepsy Center, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA.	No	Retrospective	Case series
Peacock (1996)	58	1986-1995	United States	Department of Surgery, UCLA Medical Center 90095-7039, USA.	No	Retrospective	Case series
Schramm (1995)	13	1992-1994	Germany	Neurosurgical Department, University of Bonn, Germany.	No	Retrospective	Case series
Tinuper (1988)	14	1974-1987	Canada	Montreal Neurological Hospital and Institute, McGill University, Quebec, Canada.	No	Retrospective	Nested case-control with individual patient data
Lindsay (1987)	17	1948-1986	England	National Centre for Children with Epilepsy, Park Hospital for Children, Headington, Oxford.	No	Retrospective	Nested case-control with individual patient data

Evidence Table 107. Studies of corpus callosotomy – general study information

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Hodaie (2001)	17	1992-1999	Canada	Division of Neurosurgery, Hospital for Sick Children and University of Toronto, Ont., Canada.	No	Retrospective	Case series
Kwan (2001)	61	1989-1996	Taiwan	Section of Epilepsy, Neurological Institute, Taipei Veterans General Hospital, Taiwan, ROC. sykwan@vghtpe.gov.tw	No	Retrospective	Nested case-control
Maehara (2001)	52	1991-1998	Japan	Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Fuchu, Tokyo, Japan. maehara.nsrg@tmd.ac.jp	No	Retrospective	Nested case-control
Fandino-Franky (2000)	97	1989-1997	Colombia	Neurological Hospital, Colombian League Against Epilepsy, Cartagena.	No	Prospective	Case series
Matsuzaka (1999)	22	1989-1994	Japan	Department of Pediatrics, Nagasaki University School of Medicine, Sakamoto, Japan. neuro@net.nagasaki-u.ac.jp	No	Retrospective	Case series
McInerney (1999)	47	1972-1999	United States	Sections of Neurosurgery and Neurology, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, USA.	No	Retrospective	Case series
Pinard (1999)	17	1989-1995	France	Unite de Neurochirurgie Pediatrique, Fondation Rothschild, Hopital Saint Vincent de Paul, Paris, France.	No	Retrospective	Nested case-control with individual patient data
Carmant (1998)	28	1989-1993	United States	Department of Neurology, Harvard Medical School, Children's Hospital, Boston, Massachusetts	No	Retrospective	Case series
Sorenson (1997)	23	1991-1994	United States	Department of Neurology, Texas Comprehensive Epilepsy Program, University of Texas, Houston 77225-0708, USA.	No	Retrospective	Case series
Andersen (1996)	20	1988-1994	Denmark	University Clinic of Neurology, Hvidovre Hospital, Denmark.	No	Retrospective	Case series
Rossi (1996)	20	1988-1995	Italy	Institute of Neurosurgery, Catholic University School of Medicine, Rome, Italy.	No	Retrospective	Case series
Sakas (1996)	20	1984-1993	Ireland	National Centre for Neurosurgery, Beaumont Hospital, Dublin, Ireland.	No	Retrospective	Nested case-control

Evidence Table 107. Studies of corpus callosotomy – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Claverie (1995)	20	1983-1993	France	University of Bordeaux 2, B. P. 40 Carreire,F33076 Bordeaux Cedex. France	No	Retrospective	Nested case-control with individual patient data
Reutens (1993)	64	1973-1991	Australia	Department of Neurology, Austin Hospital,Heidelberg, Vic. 3084. Australia	Yes	Retrospective	Case series
Cohen (1991)	10	1987-1989	United States	Section of Pediatric Neurology, Medical College of Georgia, 1120 15th Street, Augusta, GA 30912.United States	No	Prospective	Nested case-control
Fuiks (1991)	80	1985-1990	United States	EpiCare Center, Baptist Memorial Hospital, University of Tennessee, Memphis.	No	Retrospective	Nested case-control
Nordgren (1991)	18	1972-1987	United States	Section of Neurology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.	No	Retrospective	Nested case-control with individual patient data
Oguni (1991)	43	1981-1989	Canada	Montreal Neurological Hospital, Canada.	No	Retrospective	Case series
Marino (1990)	28	1978-1985	Brazil	Division of Functional Neurosurgery, Hospital das Clinicas, Sao Paulo, Brazil.	No	Retrospective	Nested case-control with individual patient data
Provinciali (1990)	15	1987-1988	Italy	Neurological Clinic, University of Ancona, Italy.	No	Prospective	Case series
Sass (1990)	32	1985-1987	United States	Section Neurological Surgery, Yale Univ. School of Medicine, 333 Cedar Street,New Haven, CT 06510. United States	No	Retrospective	Case series
Murro (1988)	25	1980-1986	United States	Department of Neurology, Medical College of Georgia, Augusta 30912.	No	Retrospective	Nested case-control with individual patient data
Purves (1988)	24	1977-1987	Canada	Division of Neurosciences and Neurology, University of British Columbia, Vancouver, Canada.	No	Retrospective	Nested case-control with individual patient data
Spencer (1988)	22	1979-1983	United States	Department of Neurology, Yale University School of Medicine, New Haven, CT 06510.	No	Retrospective	Nested case-control with individual patient data

Evidence Table 107. Studies of corpus callosotomy – general study information (continued)

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Garcia-Flores (1987)	14	1980-1986	Mexico	Osler Clinic, Monterrey, Mexico.	No	Retrospective	Case series
Gates (1987)	24	1979-1985	United States	Comprehensive Epilepsy Program and Department of Neurosurgery, University of Minnesota, Minneapolis, Minnesota, U.S.A.	No	Retrospective	Nested case-control

Evidence Table 108. Studies with epilepsy surgery control patients – general study information

Reference	Number of Patients	Years	Country	Author Affiliation	Multicenter Study	Method of Patient Selection	Study Design
Bauer (2001)	63	1970-1989	Germany	Department of Epileptology, University of Bonn, Germany	No	Retrospective	Case series
Kumlien (2001)	47	1993-1999	United States	Minnesota Epilepsy Group, St. Paul, MN, U.S.A.	No	Retrospective	Case series
Wiebe (2001)	40	1996-2000	Canada	Department of Clinical Neurological Sciences, University of Western Ontario, and London Health Sciences Centre, Canada. swiebe@uwo.ca	No	Prospective	RCT
Markand (2000)	37	1994-1997	United States	Department of Neurology, Division of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana, USA. omarkand@iupui.edu	No	Prospective	Controlled
Holmes (1998)	35	1977-1997	United States	Department of Neurology, University of Washington, Seattle, USA.	No	Prospective	Case series
Wolf (1998)	15	1987-1992	Germany	Epilepsiezentrum Bethel, Bielefeld, Germany.	No	Prospective	Case series
McLachlan (1997)	21	1992-1995	Canada	Department of Clinical Neurological Sciences, University of Western Ontario, London, Canada.	No	Prospective	Controlled
Hermanns (1996)	74	1992-1994	Germany	Bethel Epilepsy Centre, Bielefeld, Germany.	No	Prospective	Case series
Vickrey (1995)	46	1974-1990	United States	Department of Neurology, University of California, Los Angeles, USA.	No	Retrospective	Case series
Guldvog (1991)	185	1960-1989	Norway	National Center for Epilepsy, Sandvika, Norway.	Yes	Retrospective	Matched controls
Huttenlocher (1990)	155	1970-1989	United States	Department of Pediatrics, University of Chicago, IL 60637.	No	Retrospective	Case series
Harbord (1987)	38	1969-1985	Australia	Department of Neurology, Adelaide Children's Hospital, South Australia.	No	Retrospective	Case series

Evidence Table 109. Studies excluded from the evidence base for seizure-free outcomes after temporal lobe surgery

Reference	N	Reason for Exclusion
So (1989)	48	Only patients with bitemporal epileptiform abnormalities were enrolled in this study. Because foci are seen in both temporal lobes, surgery for this condition can be expected to produce poor results compared to patients in whom only one lobe is involved

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements

Reference	Type of Surgery	Pathology	Mean Age at Treatment (Years)	SD of Age at Treatment	Mean Age at First Seizure (Years)	SD of Age at First Seizure	Mean Duration of Condition Before Surgery (Years)	SD of Duration Before Surgery (Years)
Bouilleret (2002)	Standard	MTS	26.4	7.1	8.6	3.8	17.9	9.1
Alsaadi (2001)	Not Described	Not reported						
Boling (2001)	AH	Various (no tumors)	54		18		34.9	12.1
Hennessy (2001)	Standard	MTS	24					
Hennessy (2001)	Standard	Non-MTS focal lesions	19					
Jan (2001)	Not Described	Various	28	6.9				
Kanemoto (2001)	Standard	Not reported	27.1	5.9	9.7	5.3	17.5	7.8
Schramm (2001)	Neocortex	Various	27.9		14.4		13.6	
Sotero de Menezes (2001)	Tailored	Various	8.3	3.1				
Verma (2001)	Standard	Various	34.3	11.7	8.5	8.9	25.8	14.1
Wilson (2001)	Standard	Not reported	32.7	11.3	11.1	9.5		
Dupont (2000)	Partial	Various	29					
Eberhardt (2000)	Tailored	Various	34.6	7.8				
Foldvary (2000)	Tailored	Various	23.9	9			12.9	8.5
Holmes (2000)	Tailored	Various	33		16		17	
Iannelli (2000)	Neocortex	Tumor	9.1	5			2.8	
Markand (2000)	Tailored	Not reported	31	10.8	12.3	9.7	18.7	11.7
Rao (2000)	Standard	Various	25.6				16.1	

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Type of Surgery	Pathology	Mean Age at Treatment (Years)	SD of Age at Treatment	Mean Age at First Seizure (Years)	SD of Age at First Seizure	Mean Duration of Condition Before Surgery (Years)	SD of Duration Before Surgery (Years)
Robinson (2000)	AH	Various	15.4		5.2		10.3	
Assaf (1999)	Partial	Various						
Eriksson (1999)	Tailored	Various	34		14		18	
	Tailored	Various	9.9		1.5		5.5	
Henry (1999)	Not Described	Not reported						
Holmes (1999)	Not Described	Various	35.2	10.9				
Mathern (1999)	Tailored	Various	11.7	0.8	5.3	0.8	6.4	0.7
Mitchell (1999)	Not Described	Various	31					
Rossi (1999)	Not Described	Tumor	20.8				7	
Salanova (1999)	Tailored	Various	30.4		10.5		19.7	
Son (1999)	Standard	MTS	28.9					
Maher (1998)	Not Described	Various	32	10				
Radhakrishnan (1998)	Tailored	Various	31		8		19	
Szabo (1998)	Standard	Various	9.4	1.7	3.6	2.2	5.8	2.3
Bizzi (1997)	Partial	Various	11.9	4.6				
Cappabianca (1997)	Neocortex	Vascular malformation	28.8					
Casazza (1997)	Neocortex	Tumor	30.9	8.9	21	9.6	9.9	6.8
Ho (1997)	Partial	Various	31	10				
Keene (1997)	Neocortex	Various	13	3.6	6	4.6		
Kilpatrick (1997)	Standard	Various	36.8	11.5	15			

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Type of Surgery	Pathology	Mean Age at Treatment (Years)	SD of Age at Treatment	Mean Age at First Seizure (Years)	SD of Age at First Seizure	Mean Duration of Condition Before Surgery (Years)	SD of Duration Before Surgery (Years)
McLachlan (1997)	Tailored	Various	31.9	10.9	12.1	9.8		
Schwartz (1997)	Partial	MTS	26.8	10.2				
Silander (1997)	Tailored	Various	32				18	
	Tailored	Various	14				7.5	
Sisodiya (1997)	Standard	MTS	28.2	6.9				
Adam (1996)	Standard	MTS			9.4	4.1		
Goldstein (1996)	Tailored	Various	9.3		3.2		6.1	
Holmes (1996)	Tailored	Various	29.6					
Sirven (1996)	Standard	Various						
Acciarri (1995)	Neocortex	Vascular malformation	34.8	12.5	33.3	12.8	1.6	1.2
Berkovic (1995)	Partial	Various	29	10				
Davies (1995)	Tailored	Various	23				8	
Jooma (1995b)	Tailored	Various					19	
Jooma (1995a)	Tailored	Tumor	34.1	10	14.4	7.3	19.7	7.7
	Neocortex	Tumor	26.5	17.3	23.8	18.6	2.7	3.1
Liu (1995)	Tailored	Other	37.2	13.7	17.8	9.5	19.3	8.2
Renowden (1995)	AH	MTS	23.6				12	
	Standard	MTS	21.3				12	
Thadani (1995)	Standard	MTS	33		10			
Vossler (1995)	Tailored	Various	14.3	3.9	5	4.4	9.3	4.4

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Type of Surgery	Pathology	Mean Age at Treatment (Years)	SD of Age at Treatment	Mean Age at First Seizure (Years)	SD of Age at First Seizure	Mean Duration of Condition Before Surgery (Years)	SD of Duration Before Surgery (Years)
Blume (1994)	Standard	Various						
Guldvog (1994a)	Standard	Various					8	
Guldvog (1994b)	Standard	Various					11.5	
Berkovic (1991)	Standard	MTS	22.5	6	6.3	4.1	16.2	5.9
Hopkins (1991)	Standard	Various	5.5	2.2	2	1.4	3.6	2.1
Rasmussen (1991)	Standard	Not reported						
Wieser (1991)	AH	Various	29.7	13.7	18.8	15.3	11	10.2
Bidzinski (1990)	Standard	Not reported	23		8		13	
Mizrahi (1990)	Tailored	Various	21	8.4	5.9	2.3	15.1	8.1
Walczak (1990)	Standard	Not reported	25				15	
Yeh (1990)	Neocortex	Vascular malformation	36.3	11.9	25.3	8.3	11	8.2
Sperling (1989)	Standard	Not reported						
Estes (1988)	Tailored	Various						
Bladin (1987)	Standard	Not reported						
Cutfield (1987)	Tailored	Various	22				12	
Drake (1987)	Tailored	Tumor	12.7	2.7	6.3	4.3	6.5	3.9
Lieb (1986)	Standard	Not reported						
Meyer (1986)	Tailored	Not reported	15.8		7.5		8.3	
Delgado-Escueta (1985)	Standard	Various	26.5	6.9	15.8	8	10.7	4.9

AH Amygdalohippocampectomy
MTS Mesial temporal sclerosis

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Males	Females	Number of Patients With Simple Partial Seizures	Number of Patients With Complex Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Bouilleret (2002)	10	8	5	13	16	18	
Alsaadi (2001)						49	12
Boling (2001)			9	9			
Hennessy (2001)							
Hennessy (2001)	42	38	39	41	23	73	31
Jan (2001)	14	15	13	16			
Kanemoto (2001)	22	30	28	24			
Schramm (2001)	26	35	27	34	14	57	33
Sotero de Menezes (2001)	9	5			10	14	
Verma (2001)	7	6	7	6			
Wilson (2001)			38	52		90	
Dupont (2000)			13	17			
Eberhardt (2000)	9	11	12	8			
Foldvary (2000)	34	45	45	34	62	79	48
Holmes (2000)	7	16	8	15			
Iannelli (2000)	16	21	27	10	2	21	2
Markand (2000)	26	27	33	20		53	48
Rao (2000)			60	59		119	
Robinson (2000)	8	14	13	9		22	
Assaf (1999)							
Eriksson (1999)	Adults		31	29			
	Children		7	8			
Henry (1999)						38	

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Males	Females	Number of Patients With Simple Partial Seizures	Number of Patients With Complex Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Holmes (1999)	8	5	3	10			
Mathern (1999)	16	15	22	9			
Mitchell (1999)							
Rossi (1999)							
Salanova (1999)	71	74					
Son (1999)			45	26			
Maher (1998)	50	43	45	48			
Radhakrishnan (1998)	68	107	77	98		175	
Szabo (1998)	7	7	7	7		14	
Bizzi (1997)			11	8			
Cappabianca (1997)							
Casazza (1997)					35	33	16
Ho (1997)	28	35	30	33		63	
Keene (1997)	29	15	28	16			
Kilpatrick (1997)	8	10	11	7			
McLachlan (1997)	26	25	24	27		51	
Schwartz (1997)	6	7	9	4		13	
Silander (1997)	Adults		34	34	20	63	32
	Children		11	13	5	27	11
Sisodiya (1997)	16	11	11	16			
Adam (1996)	7	8					
Goldstein (1996)	16	17	17	16			
Holmes (1996)						45	
Sirven (1996)					174	174	
Acciarri (1995)	5	5	5	5		10	0
Berkovic (1995)							

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Males	Females	Number of Patients With Simple Partial Seizures	Number of Patients With Complex Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Davies (1995)							
Jooma (1995b)							
Jooma (1995a)	Tailored					12	6
	Neocortex					12	6
Liu (1995)	5	7	5	7	0	12	8
Renowden (1995)	3	14	6	11			
	33	17	26	24			
Thadani (1995)	11	11			19	22	4
Vossler (1995)	13	17	19	11			
Blume (1994)			64	61		125	
Guldvog (1994a)	25	10					
Guldvog (1994b)							
Berkovic (1991)	3	7	5	5	1	10	4
Hopkins (1991)	5	6	8	3		11	
Rasmussen (1991)							
Wieser (1991)	114	101	120	95			
Bidzinski (1990)							
Mizrahi (1990)	10	12					
Walczak (1990)	45	55	59	41		100	
Yeh (1990)	3	9	8	4	3	9	10
Sperling (1989)						39	
Estes (1988)	12	13					

Evidence Table 110. Patient characteristics for studies of temporal lobe surgery reporting seizure-free outcome measurements (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Males	Females	Number of Patients With Simple Partial Seizures	Number of Patients With Complex Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Bladin (1987)							
Cutfield (1987)	17	9	11	15		26	
Drake (1987)			8	3	3	11	7
Lieb (1986)	46	29	40	35		75	
Meyer (1986)	27	23	29	21			
Delgado-Escueta (1985)	5	10	12	3	1	15	12

Evidence Table 111. Studies of temporal lobe surgery that reported patients as seizure-free with no auras[a]

Reference	N	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients Seizure Free with No Auras	Percentage	Cohen's h Effect Sizes	Effect Size CI	P Values for Effect Sizes	Standardized Residuals for Effect Sizes
Bouilleret (2002)	18	4.8	2	7	12	66.7	1.91	1.26—2.56	<0.000001	0.73
Wilson (2001)	90		2		47	52.2	1.62	1.32—1.91	<0.000001	-0.40
Dupont (2000)	30	3.5	2.1	5.3	14	46.7	1.50	1.00—2.01	<0.000001	-0.66
Eberhardt (2000)	20	3	2.2	3.7	7	35.0	1.27	0.65—1.89	0.000062	-1.30
Holmes (2000)	23	3	2	6	11	47.8	1.53	0.95—2.11	<0.000001	-0.50
Markand (2000)	51		2		30	58.8	1.75	1.36—2.14	<0.000001	0.40
Rao (2000)	68		2		46	67.6	1.93	1.60—2.27	<0.000001	1.59
Holmes (1999)	13	3	2	5	7	53.8	1.65	0.88—2.42	0.000027	-0.06
Rossi (1999)	28		2		21	75.0	2.09	1.57—2.62	<0.000001	1.62
Maher (1998)	93		2		53	57.0	1.71	1.42—2.00	<0.000001	0.29
Szabo (1998)	14	2.8	2	4	10	71.4	2.01	1.27—2.75	<0.000001	0.92
Casazza (1997)	40	4.6	2		19	47.5	1.52	1.08—1.96	<0.000001	-0.69
McLachlan (1997)	40	2	2	2	18	45.0	1.47	1.03—1.91	<0.000001	-0.92
Schwartz (1997)	13	2.4	2	3.3	7	53.8	1.65	0.88—2.42	0.000027	-0.06
Sisodiya (1997)	27	2.5	2	4	15	55.6	1.68	1.15—2.22	<0.000001	0.04

[a] Seizure-free with no auras means that patients are free of complex and simple partial seizures

Evidence Table 111. Studies of temporal lobe surgery that reported patients as seizure-free with no auras[a] (continued)

Reference	N	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients Seizure Free with No Auras	Percentage	Cohen's h Effect Sizes	Effect Size CI	P Values for Effect Sizes	Standardized Residuals for Effect Sizes
Adam (1996)	15	2.7	2	3.7	7	46.7	1.50	0.79—2.22	0.000038	-0.46
Holmes (1996)	45	4.5	4	5	27	60.0	1.77	1.36—2.19	<0.000001	0.50
Renowden (1995)	17 - AH		2		8	47.1	1.51	0.84—2.18	0.000010	-0.47
	50 – Standard lobectomy		2		25	50.0	1.57	1.18—1.96	<0.000001	-0.52
Meyer (1986)	24	5	5		10	41.7	1.40	0.84—1.97	0.000001	-0.94
Delgado-Escueta (1985)	15	6	2	11	9	60.0	1.77	1.06—2.49	0.000001	0.28

[a] Seizure-free with no auras means that patients are free of complex and simple partial seizures

AH Amygdalohippocampectomy

Evidence Table 112. Studies of temporal lobe surgery that reported patients as seizure-free with auras[a]

Reference	N	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients Seizure Free With Auras	Percentage	Cohen's h Effect Sizes	Effect Size CI	P Values for Effect Sizes	Standardized Residuals for Effect Sizes
Hennessy (2001)	116	5	2		78	67.2	1.92	1.67—2.18	<0.000001	-0.21
Hennessy (2001)	80		2		52	65.0	1.88	1.57—2.19	<0.000001	-0.48
Jan (2001)	29		2		23	79.3	2.2	1.68—2.71	<0.000001	0.95
Sotero de Menezes (2001)	14	5	2	10	6	42.9	1.43	0.69—2.17	0.000159	-1.39
Verma (2001)	13		2		9	69.2	1.97	1.20—2.73	0.000001	0.04
Wilson (2001)	90		2		60	66.7	1.91	1.62—2.20	<0.000001	-0.27
Eberhardt (2000)	20	3	2.2	3.7	13	65.0	1.88	1.26—2.50	<0.000001	-0.23
Markand (2000)	51		2		37	72.5	2.04	1.65—2.43	<0.000001	0.46
Assaf (1999)	75		2		52	69.3	1.97	1.65—2.29	<0.000001	0.12
Eriksson (1999)	15 – children		2		9	60.0	1.77	1.06—2.49	0.000001	-0.49
	60 - adults				34	56.7	1.70	1.35—2.06	<0.000001	-1.37
Mitchell (1999)	45		2		26	57.8	1.73	1.31—2.14	<0.000001	-1.07
Radhakrishnan (1998)	175	3.6	2	5.7	134	76.6	2.13	1.92—2.34	<0.000001	1.82
Ho (1997)	63	4.1	2	6.2	38	60.3	1.78	1.43—2.13	<0.000001	-0.98

[a] Seizure-free with auras means the patients are free of complex seizures but may have simple partial seizures

Evidence Table 112. Studies of temporal lobe surgery that reported patients as seizure-free with auras[a] (continued)

Reference	N	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients Seizure Free With Auras	Percentage	Cohen's h Effect Sizes	Effect Size CI	P Values for Effect Sizes	Standardized Residuals for Effect Sizes
Kilpatrick (1997)	18	2.5	2	3.2	13	72.2	2.03	1.38—2.68	<0.000001	0.25
Reeves (1997)	134	4.2	2.5	6.5	107	79.9	2.21	1.97—2.45	<0.000001	2.25
Schwartz (1997)	13	2.4	2	3.3	9	69.2	1.97	1.20—2.73	0.000001	0.04
Sisodiya (1997)	27	2.5	2	4	16	59.3	1.76	1.22—2.29	<0.000001	-0.71
Adam (1996)	15	2.7	2	3.7	12	80.0	2.21	1.50—2.93	<0.000001	0.73
Liu (1995)	12	5.3	2.2	8.5	6	50.0	1.57	0.77—2.37	0.000119	-0.93
Vossler (1995)	30	6.4	2.3	14.8	20	66.7	1.91	1.40—2.42	<0.000001	-0.15
Blume (1994)	125	5.5	2	16	87	69.6	1.97	1.73—2.22	<0.000001	0.20
Walczak (1990)	100		2		63	63.0	1.83	1.56—2.11	<0.000001	-0.85
Yeh (1990)	12	3.7	2	6	10	83.3	2.30	1.50—3.10	<0.000001	0.86
Estes (1988)	25	4.1	2.2	7	9	36.0	1.29	0.73—1.84	0.000005	-2.36
Meyer (1986)	24	5	5		18	75.0	2.09	1.53—2.66	<0.000001	0.51
Delgado-Escueta (1985)	15	6	2	11	11	73.3	2.06	1.34—2.77	<0.000001	0.29

[a] Seizure-free with auras means the patients are free of complex seizures but may have simple partial seizures

Evidence Table 113. Studies of surgery control patients reporting seizure-free outcome measurements

Reference	N	Years	Country	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients and Percentage							
							Seizure-Free (undefined)	%	Seizure-Free (no auras)	%	Seizure-Free (with auras)	%	Engel Class I	%
Bauer (2001)	63	1970-1989	Germany	8.7	3.7	19	9	14.3						
Kumlien (2001)	47	1993-1999	USA	3.4	2		11	23.4						
Wiebe (2001)	40	1996-2000	Canada		1				1	2.5	3	7.5		
Markand (2000)	33	1994-1997	USA		1				0	0.0				
Holmes (1998)	35	1977-1997	USA		10		2	5.7						
Wolf (1998)	15	1987-1992	Germany		4				3	20.0	4	26.7	4	26.7
McLachlan (1997)	21	1992-1995	Canada		2		0	0.0						
Hermanns (1996)	74	1992-1994	Germany	1.3	0.9	2	0	0.0						
Vickrey (1995)	43	1974-1990	USA	5.7	1	17			2	4.7	4	9.3		
Guldvog (1991)	185	1960-1989	Norway	9	2	31	Reported changes in seizure frequency only							
Huttenlocher (1990)	155	1970-1989	USA	13	5	20	0	0.0						
Harbord (1987)	38	1969-1985	Australia	6.6	2	15	4	10.5						

Evidence Table 114. Studies with epilepsy surgery control patients – reasons for patients not to receive surgery

Reference	Number of Patients	Control Group	Number of Patients Who Refused Surgery	Number of Patients Who Were Unsuitable For Surgery	Number of Patients Who Were Actual Surgical Candidates
Bauer (2001)	63	Medical management control			
Kumlien (2001)	47	Temporal lobe - nonsurgical control		47	
Wiebe (2001)	40	Temporal lobe - nonsurgical control	0	0	40
Markand (2000)	37	Temporal lobe - nonsurgical control	5	32	
Holmes (1998)	35	Medical management control	35		
Wolf (1998)	15	Medical management control	15		
McLachlan (1997)	21	Temporal lobe - nonsurgical control	8	13	
Hermanns (1996)	74	Medical management control			
Vickrey (1995)	46	Medical management control	2	44	
Guldvog (1991)	185	Medical management control			38
Huttenlocher (1990)	155	Medical management control			
Harbord (1987)	38	Medical management control			

Evidence Table 115. Comparisons of summary estimates based on study level characteristics for temporal lobe surgery studies reporting seizure-free with no auras [a]

Study Level Characteristics	Number of Studies	Cohen's h Summary Estimate	95% Confidence Intervals		Back-transformed Percentage Estimate	95% Confidence Intervals	
			Lower	Upper		Lower	Upper
United States	8	1.69	1.50	1.89	56%	46%	66%
Other countries	13	1.66	1.54	1.78	54%	48%	60%
Mesial temporal sclerosis only	6	1.63	1.39	1.86	53%	41%	64%
Various other pathologies	15	1.68	1.57	1.79	55%	50%	61%
Standard temporal lobectomy	11	1.74	1.61	1.88	58%	52%	65%
Tailored temporal lobectomy	6	1.59	1.39	1.78	51%	41%	60%
Other surgical procedures	4	1.53	1.25	1.81	48%	34%	62%

[a] Studies were regrouped according to the selected study level characteristics and new summary estimates were calculated.

Evidence Table 116. Comparisons of summary estimates based on study level characteristics for temporal lobe surgery studies reporting seizure-free with auras. [a]

Study Level Characteristics	Number of Studies	Cohen's h Summary Estimate	95% Confidence Intervals		Back-transformed Percentage Estimage	95% Confidence Intervals	
			Lower	Upper		Lower	Upper
United States	13	2.00	1.90	2.11	71%	66%	76%
Other countries	14	1.90	1.79	2.00	66%	61%	71%
Mesial temporal sclerosis only	4	1.93	1.71	2.14	68%	57%	77%
Various other pathologies	23	1.95	1.87	2.03	69%	65%	72%
Standard temporal lobectomy	11	1.97	1.87	2.07	69%	65%	74%
Tailored temporal lobectomy	10	1.93	1.79	2.06	68%	61%	73%
Other surgical procedures	6	1.92	1.74	2.10	67%	58%	75%

[a] Studies were regrouped according to the selected study level characteristics and new summary estimates were calculated.

Evidence Table 117. Studies of temporal lobe surgery that reported patients as Engel class I

Reference	Number of Patients Evaluated	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients in Engel Class I	Percentage	Cohen's h Effect Sizes	Effect Size CI	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Bouilleret (2002)	18	4.8	2	7	16	88.9	1.63	1.32—1.95	<0.000001	1.59
Alsaadi (2001)	49		2		37	75.5	2.09	1.29—2.89	<0.000001	0.87
Boling (2001)	18	5.3	2		11	61.1	1.50	1.18—1.82	<0.000001	-0.42
Kanemoto (2001)	52	7	2	12	42	80.8	1.43	0.69—2.17	<0.000001	1.56
Schramm (2001)	32	2	2	2	26	81.3	1.66	1.24—2.08	<0.000001	1.26
Sotero de Menezes (2001)	14	5	2	10	6	42.9	1.97	1.73—2.22	0.000159	-1.34
Dupont (2000)	30	3.5	2.1	5.3	24	80.0	1.76	1.52—2.00	<0.000001	1.10
Eberhardt (2000)	20	3	2.2	3.7	13	65.0	1.60	1.15—2.04	<0.000001	-0.18
Foldvary (2000)	79		2		42	53.2	2.62	1.90—3.33	<0.000001	-1.93
Iannelli (2000)	32	6	2	14	26	81.3	2.11	1.71—2.50	<0.000001	1.26
Markand (2000)	51		2		37	72.5	1.79	1.14—2.45	<0.000001	0.54
Robinson (2000)	17	2.7	2	5.5	11	64.7	2.23	1.85—2.62	<0.000001	-0.19
Salanova (1999)	144		2		91	63.2	2.25	1.76—2.74	<0.000001	-0.85
Son (1999)	71	3.2	2	5	66	93.0	1.84	1.61—2.07	<0.000001	4.09
Maher (1998)	93		2		73	78.5	2.01	1.27—2.75	<0.000001	1.71
Szabo (1998)	14	2.8	2	4	10	71.4	2.01	1.27—2.75	<0.000001	0.21
Bizzi (1997)	14	4.8	2	7	10	71.4	1.72	1.28—2.16	<0.000001	0.21

Evidence Table 117. Studies of temporal lobe surgery that reported patients as Engel class I (continued)

Reference	Number of Patients Evaluated	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients in Engel Class I	Percentage	Cohen's h Effect Sizes	Effect Size CI	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Casazza (1997)	40	4.6	2		23	57.5	1.67	1.43—1.91	<0.000001	-0.96
Keene (1997)	44	7.7	2		24	54.5	1.05	0.25—1.85	<0.000001	-1.29
Kilpatrick (1997)	18	2.5	2	3.2	13	72.2	2.56	1.76—3.36	<0.000001	0.30
Sisodiya (1997)	27	2.5	2	4	16	59.3	2.26	1.67—2.85	<0.000001	-0.65
Adam (1996)	15	2.7	2	3.7	15	100.0	2.21	1.34—3.09	<0.000001	3.32
Berkovic (1995)	135	3.7	2	6.8	74	54.8	2.03	1.38—2.68	<0.000001	-2.29
Davies (1995)	12	7.4	2		9	75.0	1.76	1.22—2.29	<0.000001	0.40
Jooma (1995b)	62		2		40	64.5	3.14	2.43—3.86	<0.000001	-0.39
Jooma (1995a)	12 – lesionectomy	3.4	2	7	3	25.0	1.87	1.51—2.22	0.010315	-2.18
	12 – tailored surgery	5	2.5	7	11	91.7	2.46	1.81—3.12	<0.000001	1.53
Thadani (1995)	22	4	3	9	18	81.8	2.25	1.76—2.74	<0.000001	1.09
Blume (1994)	125	5.5	2	16	87	69.6	2.21	1.71—2.72	<0.000001	0.33
Berkovic (1991)	10	2.8	2.4	3.3	8	80.0	1.88	1.26—2.50	0.000001	0.63
Wieser (1991)	138		2		82	59.4	2.04	1.65—243	<0.000001	-1.51
Sperling (1989)	39	5.7	3	9	20	51.3	1.87	1.20—2.54	<0.000001	-1.51
Lieb (1986)	75	8	2	21	35	46.7	2.60	2.28—2.93	<0.000001	-2.70
Delgado-Escueta (1985)	15	6	2	11	14	93.3	2.18	1.89—2.46	<0.000001	1.89

Evidence Table 118. Studies of temporal lobe surgery reporting Engel class I – data used in meta-regression

Reference	N	Cohen's h Effect Size	Weight	Year Study Started	Year Study Ended	United States
Bouilleret (2002)	18	2.46	9	1993	2000	No
Alsaadi (2001)	49	2.11	24.5	1989	1994	Yes
Boling (2001)	18	1.79	9	1981	1999	No
Kanemoto (2001)	52	2.23	26	1987	1999	No
Schramm (2001)	32	2.25	16	1993	1999	No
Sotero de Menezes (2001)	14	1.43	7	1978	1993	Yes
Dupont (2000)	30	2.21	15	1994	1999	No
Eberhardt (2000)	20	1.88	10	1995	1999	No
Foldvary (2000)	79	1.63	39.5	1962	1984	Yes
Iannelli (2000)	32	2.25	16	1981	1997	No
Markand (2000)	51	2.04	25.5	1994	1997	Yes
Robinson (2000)	17	1.87	8.5	1993	1998	Yes
Salanova (1999)	144	1.84	72	1984	1995	Yes
Son (1999)	71	2.60	35.5	1994	1999	No
Maher (1998)	93	2.18	46.5	1994	1996	No
Szabo (1998)	14	2.01	7	1989	1994	Yes
Bizzi (1997)	14	2.01	7	1990	1994	Yes
Casazza (1997)	40	1.72	20	1988	1994	No
Keene (1997)	44	1.66	22	1975	1996	No
Kilpatrick (1997)	18	2.03	9	1993	1995	No
Sisodiya (1997)	27	1.76	13.5	1993	1995	No
Adam (1996)	15	3.14	7.5	1991	1994	No
Berkovic (1995)	135	1.67	67.5	1986	1991	No
Davies (1995)	12	2.09	6	1969	1988	No
Jooma (1995b)	62	1.87	31	1992	1994	Yes
Jooma (1995a)	12 – lesionectomy	1.05	6	1985	1992	Yes
	12 – tailored surgery	2.56	6	1985	1992	Yes

Evidence Table 118. Studies of temporal lobe surgery reporting Engel class I – data used in meta-regression (continued)

Reference	N	Cohen's h Effect Size	Weight	Year Study Started	Year Study Ended	United States
Thadani (1995)	22	2.26	11	1983	1992	Yes
Blume (1994)	125	1.97	62.5	1974	1989	No
Berkovic (1991)	10	2.21	5	1985	1986	No
Wieser (1991)	138	1.76	69	1975	1990	No
Sperling (1989)	39	1.60	19.5	1976	1983	Yes
Lieb (1986)	75	1.50	37.5	1961	1977	Yes
Delgado-Escueta (1985)	15	2.62	7.5	1972	1983	Yes

Evidence Table 119. Results of meta-regression of studies of temporal lobe surgery reporting Engel class I

Parameter	Qe	p value for Qe	Intercept	CI of Intercept	p Value for Intercept	Coefficient	CI of Coefficient	p Value for Coefficient
One predictor models								
Year study ended	55.7	0.006	-58.5	-83.7 — –33.3	.0000006	0.030	0.017 — 0.044	0.000009
Year study started	56.7	0.005	-30.7	-44.6 — -16.7	0.000016	0.016	0.009 — 0.024	0.00001
United States	72.1	0.00006	1.8	1.7 — 1.9	<0.000001	0.174	0.030 — 0.318	0.018
Two predictor models								
Year study ended,	54.4	0.006	-50.4	-79.1 — -21.7	0.006	0.019	-0.005 — 0.042	0.12
Year study started						0.008	-0.006 — 0.021	0.26
Year study started,	54.8	0.005	-28.4	-42.7 — -14.1	0.0001	0.015	0.007 —0.002	0.00007
United States						-0.105	-0.250 — 0.040	0.16
Year study ended,	55.0	0.005	-54.5	-81.3 — -27.7	0.00007	0.028	-0.220 — 0.090	0.39
United States						0.028	0.020 — 0.040	0.00003
Three predictor model								
Year study started,	53.4	0.005	-44.9	-75.6 — -14.3	0.004	0.015	-0.01 — 0.04	0.24
Year study started,						0.008	-0.005 — 0.020	0.21
United States						-0.079	-0.07 — 0.23	0.31

Evidence Table 120. Studies of temporal lobe surgery that reported patients as seizure-free undefined

Reference	Number of Patients Evaluated	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients Seizure Free Undefined	Percentage	Cohen's h Effect Sizes	Effect Size CI	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Henry (1999)	38	6.2	5	7.2	27	71.1	2.01	1.56—2.46	<0.000001	0.90
Mathern (1999)	20		2		13	65.0	1.88	1.26—2.50	<0.000001	0.23
Cappabianca (1997)	10		2		8	80.0	2.21	1.34—3.09	0.000001	0.92
Silander (1997)	25 children		2		12	48.0	1.64	1.28—1.99	<0.000001	-0.97
	62 adults				33	53.2	1.53	0.98—2.09	<0.000001	-0.98
Goldstein (1996)	33	4.7	2	10	15	45.5	1.48	1.00—1.96	<0.000001	-1.34
Sirven (1996)	174	2.7	2.3	8	136	78.2	2.17	1.96—2.38	<0.000001	3.76
Acciarri (1995)	10	5.2	2	14	10	100.0	3.14	2.27—4.02	<0.000001	3.01
Guldvog (1994b)	53 adults	7	2	26	29	54.7	1.67	1.28—2.05	<0.000001	-0.73
Guldvog (1994a)	34 children	7	2		23	67.6	1.93	1.46—2.41	<0.000001	0.54
Hopkins (1991)	11	3.6	2	7.5	8	72.7	2.04	1.21—2.88	0.000002	0.56
Rasmussen (1991)	100	12	2	24	55	55.0	1.67	1.39—1.95	<0.000001	-0.99
Bidzinski (1990)	286	16	2	30	140	49.0	1.55	1.39—1.71	<0.000001	-3.61
Mizrahi (1990)	22	5.3	2	8	14	63.6	1.85	1.26—2.44	<0.000001	0.15
Bladin (1987)	63		2		51	81.0	2.24	1.89—2.59	<0.000001	2.52
Cutfield (1987)	25	12	5	17	13	52.0	1.61	1.06—2.17	<0.000001	-0.69
Drake (1987)	11	2.7	2	5	7	63.6	1.85	1.01—2.68	0.000015	0.10

Evidence Table 121. Studies of temporal lobe surgery reporting seizure-free undefined – data used in meta-regression.

Reference	N	Cohen's h Effect Size	Weight	Year Study Started	Year Study Ended	United States
Henry (1999)	38	2.01	19	1991	1994	Yes
Mathern (1999)	20	1.88	10	1986	1997	Yes
Cappabianca (1997)	10	2.21	5	1985	1994	No
Silander (1997)	25 children	1.64	31	1980	1990	No
	62 adults	1.53	12.5	1980	1990	No
Goldstein (1996)	33	1.48	16.5	1985	1993	Yes
Sirven (1996)	174	2.17	87	1985	1992	Yes
Acciarri (1995)	10	3.14	5	1975	1992	No
Guldvog (1994b)	53 adults	1.67	26.5	1949	1988	No
Guldvog (1994a)	34 children	1.93	17	1952	1988	No
Hopkins (1991)	11	2.04	5.5	1978	1988	No
Rasmussen (1991)	100	1.67	50	1961	1980	No
Bidzinski (1990)	286	1.55	143	1957	1988	No
Mizrahi (1990)	22	1.85	11	1980	1986	Yes
Bladin (1987)	63	2.24	31.5	1985	1987	No
Cutfield (1987)	25	1.61	12.5	1961	1980	No
Drake (1987)	11	1.85	5.5	1974	1986	No

Evidence Table 122. Results of meta-regression of studies of temporal lobe surgery reporting seizure-free undefined

Parameter	Q_e	p value for Q_e	Intercept	CI of Intercept	p value for Intercept	Coefficient	CI of Coefficient	p value for Coefficient
One predictor models								
Year study started	26.2	0.036	-24.7	-37.3 — -12.2	0.0001	0.013	0.007 — 0.019	0.000008
United States	33.6	0.004	1.7	1.6 — 1.8	<0.000001	0.311	0.116 — 0.506	0.002
Year study ended	37.8	0.001	-51.9	-96.2 — -7.6	0.022	0.027	0.004 — 0.049	0.017
Two predictor models								
Year study started	26.1	0.025	-23.3	-41.2 — -5.4	0.011	0.013	0.004 — 0.021	0.004
United States						0.032	-0.247 — 0.310	.824
Year study started	26.2	0.025	-24.9	-71.8 — 22.0	.298	0.013	0.006 — 0.020	0.0002
Year study ended						0.0001	-0.027 — 0.027	0.996
Year study ended	33.3	0.003	-14.1	-70.6 — 42.5	0.626	0.008	-0.020 — 0.036	0.579
United States						0.267	0.018 — 0.516	0.036
Three predictor model.								
Year study started	26.1	0.016	-21.0	-77.8 — 35.8	0.469	0.036	-0.264 — 0.337	0.812
Year study started						0.013	0.003 — 0.002	0.010
United States						-0.001	-0.028 — 0.030	0.932

Evidence Table 123. Studies of temporal lobe surgery reporting relationships between patient or study characteristics and treatment outcome

Reference	N	Seizure Outcome Measurement	Statistical Method	Patient or Study Characteristics Examined									
				Age at Surgery	Age at Seizure Onset	Duration of Epilepsy Prior to Surgery	Length of Followup	Gender	Side of Surgery	Complex Partial Seizures	Simple Partial Seizures	Secondarily Generalized Seizures	Mesial Temporal Sclerosis
Hennessy (2001)	80	Seizure-free with auras	Univariate	Sig.	NS	Sig.		NS	NS	NS	NS	NS	
Hennessy (2001)	116	Seizure-free with auras	Univariate	NS	NS	NS						Sig.	
Foldvary (2000)	79	Engel class I	Univariate	NS		NS		NS	NS				
Holmes (2000)	23	Seizure-free no auras	Univariate	NS	NS	NS		NS	NS				NS
Robinson (2000)	22	Engel class I	Univariate	NS	NS	NS			NS				
Radhakrishnan (1998)	175	Seizure-free with auras	Univariate	NS	NS	NS	NS						Sig.
Goldstein (1996)	33	Seizure-free (undefined)	Univariate	NS	NS	NS			NS				NS
Blume (1994)	125	90% Reduction in Seizure Frequency	Multiple regression	Sig.									NS
Cutfield (1987)	26	Seizure-free (undefined)	Multiple regression		NS	NS							NS

Sig. Statistically significant according to authors
NS Not statistically significant according to authors

Evidence Table 124. Studies of temporal lobe surgery reporting relationships between patient characteristics and treatment outcome – other study variables

Reference	Number of Patients	Seizure Outcome Measurement	Statistical Method	Other Study Variables
Alsaadi (2001)	49	Engel class I	Univariate	Ictal and postictal clinical manifestations (NS)
Hennessy (2001)	80	Seizure-free with auras	Univariate	Special schooling (Sig.), Developmental dysplastic lesions (Sig.), Perinatal complications (NS), Delayed developmental milestones (NS), Family history of epilepsy (NS), Febrile convulsion (NS), EEG spikes confined to temporal lobe (NS), Neoplasms (NS)
Hennessy (2001)	116	Seizure-free with auras	Univariate	Perinatal complications (Sig.), EEG interictal spikes confined to operated temporal lobe (Sig.), Febrile convulsion (NS), Developmental delay (NS), Special schooling (NS), Psychiatric history (NS), Family history of epilepsy (NS), Lateralized abnormality on physical examination (NS)
Dupont (2000)	30	Seizure-free no auras	Multiple regression	PET determined metabolism of the temporal pole, basofrontal cortex, anterior part of the lateral temporal neocortex, and medial temporal cortex (Sig.)
Foldvary (2000)	79	Engel class I	Univariate	Monthly frequency of CPS less than 20 (Sig.), Recorded seizures during routine or prolonged EEG (NS)
Holmes (2000)	23	Seizure-free no auras	Univariate	EEG finding of basal-temporal ictal onset (Sig.), EEG finding of unilateral basal-temporal interictal epileptiform patterns (Sig.)
Robinson (2000)	22	Engel class I	Univariate	History of febrile seizures (NS), IAP memory localization (NS), Unilateral hypometabolism (Sig.)
Salanova (1999)	144	Engel class I	Univariate	History of febrile seizures (Sig.), MTS or discrete lesion (Sig.), Availability of PET scan and volumetric MRI (Sig.), Unitemporal interictal spiking (NS), Bitemporal interictal spiking (NS)
Radhakrishnan (1998)	175	Seizure-free with auras	Univariate	Scalp interictal epileptiform discharges concordant with ictal onset (Sig.), Seizure-free during first year (Sig.), No epileptiform discharge at 3 mo (Sig.), Symptomatic epilepsy etiology (NS), History of febrile seizure (NS), Lesions other than MTS on neuroimaging (NS), No epileptiform discharge at 1 wk (NS),
Goldstein (1996)	33	Seizure-free (undefined)	Univariate	Generalized motor seizures (NS) Mental retardation (NS), Unitlateral temporal interictal activity (NS), Unilateral temporal ictal activity (NS), Significant etiological history (NS)
Blume (1994)	115	Seizure-free with auras	Multiple regression	Febrile convulsions as etiology (NS), No generalized motor seizures (Sig.), Lateralized temporal spikes (Sig.), No extra-anterior temporal spikes on any record (Sig.), No postoperative seizures within one week of surgery (Sig.)
So (1989)	48	Engel class I	Univariate	Stereotactic depth EEG unilateral (seizure onset in the resected lobe) (Sig.), History of early convulsion (<3 yr) (Sig.), Extent of hippocampal removal (Sig.), Residual ECoG epileptiform abnormalities (Sig.), Early postoperative seizures (<2 mo) (Sig.), Pathology (NS), Major etiological factor (NS)
Cutfield (1987)	26	Seizure-free (undefined)	Multiple regression	EEG findings (NS)

Sig. Statistically significant according to authors NS Not statistically significant according to authors

Evidence Table 125. Studies of temporal lobe surgery reporting individual patient age at surgery

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation [a]	95% Confidence Interval		Standardized Residuals for Effect Sizes
				Lower	Upper	
Bouilleret (2002)	18	Seizure-free no auras	0.27	-0.23	0.65	0.97
Sotero de Menezes (2001)	14	Seizure-free with auras	-0.37	-0.75	0.20	-1.42
Verma (2001)	13	Seizure-free with auras	-0.29	-0.73	0.31	-1.07
Eberhardt (2000)	20	Seizure-free no auras	0.07	-0.39	0.49	0.15
Holmes (1999)	13	Seizure-free no auras	0.23	-0.37	0.69	0.65
Szabo (1998)	14	Seizure-free with auras	-0.03	-0.55	0.51	-0.20
Kilpatrick (1997)	18	Seizure-free with auras	-0.16	-0.58	0.33	-0.75
Schwartz (1997)	13	Seizure-free no auras	0.05	-0.52	0.58	0.06
Sisodiya (1997)	27	Engel class I	-0.07	-0.44	0.32	-0.52
Jooma (1995a)	12 lesionectomy	Seizure-free with auras	-0.19	-0.69	0.43	-0.64
	12 tailored		-0.03	-0.59	0.55	-0.14
Liu (1995)	12	Seizure-free with auras	0.37	-0.26	0.78	1.09
Vossler (1995)	30	Seizure-free with auras	0.15	-0.22	0.48	0.66
Berkovic (1991)	10	Seizure-free (undefined)	0.31	-0.40	0.79	0.77
Hopkins (1991)	11	Seizure-free (undefined)	0.34	-0.33	0.78	0.93
Mizrahi (1990)	22	Seizure-free (undefined)	0.16	-0.28	0.55	0.61
Yeh (1990)	12	Seizure-free with auras	-0.23	-0.71	0.40	-0.79
Drake (1987)	11	Seizure-free (undefined)	-0.23	-0.73	0.43	-0.74
Delgado-Escueta (1985)	15	Seizure-free no auras	-0.21	-0.65	0.34	-0.85

[a] A positive correlation indicates more successful surgeries with an older age at surgery.

Evidence Table 126. Sensitivity analysis of studies of temporal lobe surgery reporting individual patient age at surgery for successful and nonsuccessful patients

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	0.02	-0.11	0.14	0.814	10.71	0.906
Removing study with largest negative correlation	0.03	-0.09	0.16	0.601	8.84	0.945
Removing study with largest positive correlation	0.00	-0.13	0.13	0.991	9.41	0.926
Removing study with smallest N	0.01	-0.12	0.13	0.926	10.04	0.902
Removing study with largest N	0.00	-0.14	0.13	0.978	10.15	0.897

[a] A positive correlation indicates more successful surgeries with an older age at surgery.

Evidence Table 127. Studies of temporal lobe surgery reporting individual age at seizure onset

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation [a]	95% Confidence Interval		Standardized Residuals for Effect Sizes
				Lower	Upper	
Bouilleret (2002)	18	Seizure-free no auras	-0.18	-0.60	0.31	-0.16
Verma (2001)	13	Seizure-free with auras	0.21	-0.38	0.68	1.16
Szabo (1998)	14	Seizure-free with auras	-0.34	-0.74	0.23	-0.74
Adam (1996)	15	Seizure-free no auras	0.01	-0.51	0.52	0.53
Jooma (1995a)	12 lesionectomy	Seizure-free with auras	-0.18	-0.68	0.44	-0.22
	12 tailored		0.06	-0.53	0.61	0.53
Liu (1995)	12	Seizure-free with auras	0.13	-0.48	0.65	0.84
Vossler (1995)	30	Seizure-free with auras	-0.16	-0.49	0.22	-0.09
Berkovic (1991)	10	Seizure-free (undefined)	-0.48	-0.85	0.22	-1.02
Hopkins (1991)	11	Seizure-free (undefined)	-0.11	-0.66	0.53	0.10
Mizrahi (1990)	22	Seizure-free (undefined)	-0.15	-0.54	0.29	-0.06
Yeh (1990)	12	Seizure-free with auras	-0.35	-0.77	0.28	-0.69
Drake (1987)	11	Seizure-free (undefined)	0.42	-0.24	0.81	1.70
Delgado-Escueta (1985)	15	Seizure-free no auras	-0.20	-0.64	0.35	-0.21

[a] A positive correlation indicates more successful surgeries with an older age at seizure onset.

Evidence Table 128. Sensitivity analysis of studies of temporal lobe surgery reporting individual patient age at seizure onset

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	-0.11	-0.26	0.04	0.158	7.23	0.890
Removing study with largest negative correlation [b]	-0.09	-0.24	0.06	0.249	6.00	0.916
Removing study with largest positive correlation	-0.14	-0.29	0.02	0.083	4.64	0.969
Removing study with smallest N	-0.09	-0.24	0.06	0.249	6.00	0.916
Removing study with largest N	-0.10	-0.26	0.07	0.238	7.16	0.847

[a] A positive correlation indicates more successful surgeries with an older age at seizure onset.
[b] The study with the largest negative effect size also had the smallest N.

Evidence Table 129. Studies of temporal lobe surgery reporting individual patients duration of epilepsy prior to surgery

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation[a]	95% Confidence Interval		Standardized Residuals for Effect Sizes
				Lower	Upper	
Bouilleret (2002)	18	Seizure-free no auras	0.28	-0.21	0.66	0.21
Verma (2001)	13	Seizure-free with auras	-0.38	-0.77	0.22	-2.08
Szabo (1998)	14	Seizure-free with auras	0.31	-0.26	0.72	0.29
Jooma (1995a)	12 lesionectomy	Seizure-free with auras	-0.01	-0.58	0.57	-0.50
	12 tailored		-0.10	-0.63	0.51	-0.77
Liu (1995)	12	Seizure-free with auras	0.47	-0.15	0.82	0.82
Vossler (1995)	30	Seizure-free with auras	0.29	-0.08	0.59	0.36
Berkovic (1991)	10	Seizure-free (undefined)	0.64	0.02	0.90	1.40
Hopkins (1991)	11	Seizure-free (undefined)	0.42	-0.24	0.82	0.62
Mizrahi (1990)	22	Seizure-free (undefined)	0.21	-0.23	0.58	-0.11
Yeh (1990)	12	Seizure-free with auras	0.03	-0.56	0.59	-0.66
Drake (1987)	11	Seizure-free (undefined)	-0.62	-0.89	-0.03	-2.79
Delgado-Escueta (1985)	15	Seizure-free no auras	0.03	-0.49	0.53	-0.75

[a] A positive correlation indicates more successful surgeries with a longer duration of epilepsy prior to surgery.

Evidence Table 130. Sensitivity analysis of studies of temporal lobe surgery reporting individual patient duration of epilepsy prior to surgery

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	0.15	-0.01	0.30	0.058	15.90	0.195
Removing study with largest negative correlation	0.20	0.04	0.35	0.015	9.44	0.581
Removing study with largest positive correlation [b]	0.12	-0.04	0.28	0.133	13.24	0.278
Removing study with smallest N	0.12	-0.04	0.28	0.133	13.24	0.278
Removing study with largest N	0.12	-0.05	0.29	0.172	15.19	0.174

[a] A positive correlation indicates more successful surgeries with a longer duration of epilepsy prior to surgery.
[b] The study with the largest effect size also had the smallest N.

Evidence Table 131. Studies of temporal lobe surgery reporting number of male and female patients with successful and nonsuccessful surgery

Reference	Seizure Outcome Measurement	Number of Male Patients	Number of Male Successes	Number of Female Patients	Number of Female Successes	Cohen's h Effect Sizes	95% Confidence Interval		p Values for Effect Sizes	Standardized Residuals for Effect Sizes
							Lower	Upper		
Bouilleret (2002)	Seizure-free no auras	5	4	13	8	0.41	-0.62	1.44	0.435201	0.92
Hennessy (2001)	Seizure-free with auras	39	27	41	25	0.17	-0.26	0.61	0.438003	1.23
Verma (2001)	Seizure-free with auras	7	5	6	4	0.10	-0.99	1.19	0.853018	0.30
Eberhardt (2000)	Seizure-free no auras	12	1	8	6	-1.51	-2.40	-0.61	0.000948	-3.29
Holmes (1999)	Seizure-free no auras	3	1	10	6	-0.54	-1.83	0.75	0.411001	-0.74
Szabo (1998)	Seizure-free with auras	7	6	7	4	0.65	-0.40	1.70	0.222367	1.37
Kilpatrick (1997)	Seizure-free with auras	11	9	7	4	0.55	-0.40	1.49	0.258407	1.29
Schwartz (1997)	Seizure-free no auras	9	4	4	3	-0.63	-1.81	0.54	0.290693	-0.98
Sisodiya (1997)	Engel class I	11	6	16	9	-0.03	-0.80	0.73	0.930230	0.07
Liu (1995)	Seizure-free with auras	5	1	7	5	-1.09	-2.23	0.06	0.063539	-1.79
Vossler (1995)	Seizure-free with auras	19	12	11	8	-0.21	-0.95	0.54	0.587416	-0.41
Berkovic (1991)	Seizure-free (undefined)	5	3	5	5	-1.37	-2.61	-0.13	0.030367	-2.11
Yeh (1990)	Seizure-free with auras	8	7	4	3	0.32	-0.88	1.52	0.596218	0.64
Drake (1987)	Seizure-free (undefined)	8	6	3	1	0.86	-0.46	2.19	0.202175	1.39
Delgado-Escueta (1985)	Seizure-free no auras	12	8	3	1	0.68	-0.59	1.94	0.292366	1.17

Evidence Table 132. Studies of temporal lobe surgery reporting number of male and female patients with successful and nonsuccessful surgery – data used in meta-regression

Reference	Number of Patients	Cohen's h Effect Size	Weight	Mesial Temporal Sclerosis Patients Only	Tumor Patients Only	Standard Temporal Lobectomy	Tailored Temporal Lobectomy
Bouilleret (2002)	18	0.4106	3.6111	Yes	No	Yes	No
Hennessy (2001)	80	0.1735	19.9875	No	No	Yes	No
Verma (2001)	13	0.1031	3.2308	No	No	Yes	No
Eberhardt (2000)	20	-1.5087	4.8	No	No	No	Yes
Holmes (1999)	13	-0.5412	2.3077	No	No	Yes	No
Szabo (1998)	14	0.6523	3.5	No	No	Yes	No
Kilpatrick (1997)	18	0.5464	4.2778	No	No	Yes	No
Schwartz (1997)	13	-0.6349	2.7692	Yes	No	No	No
Sisodiya (1997)	27	-0.0343	6.5185	Yes	No	Yes	No
Liu (1995)	12	-1.0864	2.9167	No	No	No	Yes
Vossler (1995)	30	-0.2056	6.9667	No	No	No	Yes
Berkovic (1991)	10	-1.3694	2.5	Yes	No	Yes	No
Yeh (1990)	12	0.3245	2.6667	No	Yes	No	No
Drake (1987)	11	0.8634	2.1818	No	Yes	No	Yes
Delgado-Escueta (1985)	15	0.6797	2.4	No	No	Yes	No

Evidence Table 133. Results of meta-regression of studies of temporal lobe surgery reporting percentage of male and female patients among patients with successful and nonsuccessful surgery

One predictor models Bolded = statistically significant coefficient						
Covariate	**Intercept (CI)**	**P (intercept) =**	**Coefficient (CI)**	**P (coefficient)**	**Q_e =**	**P (Q_e) =**
Start year (centered)	-0.11 (-0.35 to 0.13)	0.359016	-0.03 (-0.31 to 0.26)	0.853727	24.615	0.026
End year (centered)	-0.04 (-0.28 to 0.20)	0.726323	-0.02 (-0.07 to 0.04)	0.592742	27.642	0.010
Mesial temporal sclerosis (MTS=0)	-0.26 (-0.75 to 0.24)	0.316342	0.25 (-0.32 to 0.81)	0.387887	27.177	0.009
Tumor (Tumor = 0)	0.57 (-0.32 to 1.46)	0.211983	-0.67 (-1.60 to 0.25)	0.152673	25.882	0.018
Standard (St = 0)	**0.14 (-0.14 to 0.42)**	**0.340748**	**-0.62 (-1.13 to – 0.12)**	**0.014820**	**21.985**	**0.056**
Tailored (Tailored = 0)	**-0.59 (-1.07 to – 0.11)**	**0.015064**	**0.70 (0.15 to 1.24)**	**0.0124402**	**21.683**	**0.060**
Treatment age (centered)	**-0.12 (-0.36 to 0.12)**	**0.338682**	**-0.03 (-0.05 to 0.00)**	**0.053711**	**24.239**	**0.029**
United States (USA = 0)	-0.14 (-0.54 to 0.26)	0.491480	0.12 (-0.37 to 0.61)	0.629453	27.693	0.010
Left side (centered)	**-0.09 (-0.33 to 0.15)**	**0.454805**	**-0.02 (-0.03 to 0.01)**	**0.075197**	**24.697**	**0.025**

Average start year = 1985.7
Average end year = 1992.3
Average treatment age = 26.68
Average left = 50.6

Evidence Table 133. Results of meta-regression of studies of temporal lobe surgery reporting percentage of male and female patients among patients with successful and nonsuccessful surgery (continued)

Two predictor models: Standard and year plus one other variable Bolded in this table = homogeneous									
Covariate: B_1	**Covariate: B_2**	**Intercept (CI)**	**P (intercept) =**	**Coefficient B_1 (CI)**	**P (B_1) =**	**Coefficient B_2 (CI)**	**P(B_2)**	**Q_e =**	**P (Q_e) =**
Standard (St = 0)	Start year (centered)	0.08 (-0.21 to 0.37)	0.579398	-0.60 (-1.10 to –0.10)	0.019348	-0.02 (-0.05 to 0.00)	0.097903	19.135	0.084
Standard (St = 0)	End year (centered)	0.23 (-0.08 to 0.54)	0.146365	-0.76 (-1.29 to –0.22)	0.005391	-0.04 (-0.10 to 0.02)	0.149786	19.870	0.070
Standard (St = 0)	MTS (MTS=0)	-0.13 (-0.64 to 0.38)	0.607917	-0.67 (-1.18 to –0.17)	0.009323	0.37 (-0.20 to 0.94)	0.208745	20.405	0.060
Standard (St = 0)	**Tumor (tumor = 0)**	**1.48 (0.44 to 2.53)**	**0.005361**	**-0.92 (-1.46 to –0.37)**	**0.001012**	**-1.35 (-2.35 to –0.34)**	**0.008741**	**15.108**	**0.236**
Standard (St = 0)	Tailored (tailored = 0)	-0.29 (-1.30 to 0.72)	0.573474	-0.30 (-1.19 to 0.58)	0.504500	0.43 (-0.54 to 1.39)	0.387611	21.238	0.047
Standard (St = 0)	Treatment age (centered)	0.07 (-0.22 to 0.76)	0.618834	-0.58 ()-1.09 to –0.08)	0.023037	-0.02 (-0.05 to 0.00)	0.093667	19.076	0.087
Standard (St = 0)	United States (USA = 0)	0.20 (-0.28 to 0.69)	0.413259	-0.65 (-1.18 to –0.12)	0.015872	-0.09 (-0.61 to 0.43)	0.745048	21.880	0.039
Standard (St = 0)	Left (left = 0)	0.09 (-0.21 to 0.40)	0.561171	-0.52 (-1.08 to 0.04)	0.067680	-0.08 (-0.09 to –0.06)	<0.000001	21.368	0.045
Tailored (Tailored = 0)	**Start year (centered)**	**-0.65 (-1.13 to –0.17)**	**0.008273**	**0.70 (0.16 to 0.00)**	**0.011632**	**-0.30 (-0.06 to 0.00)**	**0.061406**	**18.245**	**0.108**
Tailored (Tailored = 0)	End year (centered)	-0.61 (-1.09 to –0.13)	0.012149	0.77 (0.21 to 1.34)	0.007076	-0.03 (-0.09 to 0.02)	0.255782	20.376	0.060
Tailored (Tailored = 0)	MTS (MTS=0)	-1.10 (-1.86 to –0.34)	0.004654	0.84 (0.27 to 1.42)	0.003879	0.51 (-0.08 to 1.10)	0.092632	18.861	0.092
Tailored (Tailored = 0)	Tumor (tumor = 0)	0.15 (-0.79 to 1.09)	0.760981	0.77 (0.21 to 1.32)	0.006644	-0.85 (-1.78 to 0.09)	0.074982	18.507	0.101
Tailored (Tailored = 0)	**Treatment age (centered)**	**-0.67 (-1.16 to –0.19)**	**0.006435**	**0.72 (0.18 to 1.27)**	**0.009648**	**-0.03 (-0.06 to 0.00)**	**0.042434**	**17.518**	**0.131**

Evidence Table 133. Results of meta-regression of studies of temporal lobe surgery reporting percentage of male and female patients among patients with successful and nonsuccessful surgery (continued)

Two predictor models: Standard and year plus one other variable					Bolded in this table = homogeneous				
Covariate: B_1	**Covariate: B_2**	**Intercept (CI)**	**P (intercept)=**	**Coefficient B_1 (CI)**	**P (B_1) =**	**Coefficient B_2 (CI)**	**P(B_2)**	**Q_e =**	**P (Q_e) =**
Tailored (Tailored = 0)	United States (USA = 0)	0.56 (-1.09 to –0.04)	0.034766	0.72 (0.15 to 1.29)	0.013569	-0.07 (-0.58 to 0.45)	0.801865	21.620	0.042
Tailored (Tailored = 0)	Left (centered)	-0.54 (-1.02 to –0.05)	0.029525	0.60 (0.03 to 1.17)	0.038490	-0.01 (-0.03 to 0.01)	0.269959	20.490	0.060
Treatment age (centered)	Start year (centered)	-0.13 (-0.37 to 0.11)	0.300278	-0.02 (-0.05 to 0.02)	0.289714	-0.02 (-0.05 to 0.02)	0.403631	23.516	0.024
Treatment age (centered)	End year (centered)	-0.11 (-0.36 to 0.14)	0.386278	-0.03 (-0.05 to 0.00)	0.060675	0.00 (-0.06 to 0.05)	0.883014	24.217	0.019
Treatment age (centered)	MTS (MTS=0)	-0.26 (-0.76 to 0.24)	0.312923	-0.03 (-0.05 to 0.00)	0.069978	0.18 (-0.39 to 0.75)	0.531492	23.846	0.021
Treatment age (centered)	Tumor (tumor = 0)	0.54 (-0.35 to 1.43)	0.235524	-0.03 (-0.06 to 0.00)	0.049363	-0.71 (-1.63 to 0.22)	0.133582	21.989	0.038
Treatment age (centered)	United States (USA = 0)	-0.22 (-0.63 to 0.19)	0.257560	-0.03 (-0.06 to 0.00)	0.057296	0.16 (0.34 to 0.65)	0.5432915	23.851	0.021
Treatment age (centered)	Left (centered)	-0.17 (-0.42 to 0.07)	0.168086	-0.03 (-0.06 to –0.01)	0.016665	-0.02 (-0.04 to 0.00)	0.020548	18.996	0.089
Left (centered)	**Start year (centered)**	**-0.19 (-0.43 to 0.06)**	**0.138223**	**-0.02 (-0.04 to –0.01)**	**0.007930**	**-0.04 (-0.07 to –0.01)**	**0.008234**	**17.845**	**0.120**
Left (centered)	End year (centered)	0.85 (0.60 to 1.10)	<0.000001	-0.02 (-0.04 to 0.00)	0.022466	-1.02 (-1.99 to 0.05)	0.038476	20.411	0.0597
Left (centered)	MTS (MTS=0)	-0.28 (-0.79 to 0.22)	0.269997	-0.02 (-0.03 to 0.00)	0.070488	0.25 (-0.32 to 0.82)	0.390991	23.952	0.020
Left (centered)	Tumor (tumor = 0)	-0.04 (-0.28 to 0.20)	0.717057	-0.02 (-0.05 to 0.00)	0.017863	-0.06 (-0.12 to 0.01)	0.086814	21.3701	0.041
Left (centered)	United States (USA = 0)	-0.10 (-0.50 to 0.31)	0.641064	-0.02 (-0.03 to 0.00)	0.089033	0.01 (-0.50 to 0.52	0.971889	24.695	0.016

Evidence Table 134. Studies of temporal lobe surgery reporting the number of left-sided and right-sided operations with successful and nonsuccessful surgery outcome measurements

Reference	N	Seizure Outcome Measurement	Left Side	Left Side Successes	Right Side	Right Side Successes	Cohen's h Effect Sizes	95% Confidence Interval		p Values for Effect Sizes	Standardized Residuals for Effect Sizes
								Lower	Upper		
Bouilleret (2002)	18	Seizure-free no auras	8	7	10	5	0.85	-0.08	1.78	0.073797	1.98
Hennessy (2001)	80	Seizure-free with auras	38	25	42	27	0.03	-0.41	0.47	0.887980	0.50
Sotero de Menezes (2001)	14	Seizure-free with auras	5	2	9	4	-0.09	-1.18	1.00	0.871789	-0.04
Verma (2001)	13	Seizure-free with auras	6	3	7	6	-0.80	-1.89	0.29	0.152705	-1.33
Eberhardt (2000)	20	Seizure-free no auras	11	3	9	4	-0.36	-1.24	0.52	0.422490	-0.66
Holmes (1999)	13	Seizure-free no auras	5	2	8	5	-0.45	-1.57	0.66	0.425779	-0.69
Szabo (1998)	14	Seizure-free with auras	7	5	7	5	0.00	-1.05	1.05	1.000000	0.13
Kilpatrick (1997)	18	Seizure-free with auras	10	6	8	7	-0.65	-1.58	0.28	0.172765	-1.25
Schwartz (1997)	13	Seizure-free no auras	7	4	6	3	0.14	-0.95	1.23	0.796671	0.39
Sisodiya (1997)	27	Engel class I	11	7	16	8	0.28	-0.49	1.04	0.480658	0.91
Adam (1996)	15	Seizure-free no auras	8	4	7	3	0.14	-0.87	1.16	0.781800	0.42
Goldstein (1996)	33	Seizure-free (undefined)	17	6	16	9	-0.42	-1.11	0.26	0.223648	-1.06
Liu (1995)	12	Seizure-free with auras	7	4	5	2	0.34	-0.80	1.49	0.556065	0.72
Vossler (1995)	30	Seizure-free with auras	17	12	13	8	0.19	-0.53	0.91	0.603189	0.74
Berkovic (1991)	10	Seizure-free (undefined)	7	5	3	3	-1.13	-2.48	0.22	0.102162	-1.55

Evidence Table 134. Studies of temporal lobe surgery reporting the number of left-sided and right-sided operations with successful and nonsuccessful surgery outcome measurements (continued)

Reference	N	Seizure Outcome Measurement	Left Side	Left Side Successes	Right Side	Right Side Successes	Cohen's h Effect Sizes	95% Confidence Interval		p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Mizrahi (1990)	22	Seizure-free (undefined)	12	6	10	8	-0.64	-1.48	0.20	0.132866	-1.38
Yeh (1990)	12	Seizure-free with auras	9	8	3	2	0.55	-0.76	1.86	0.408278	0.94
Estes (1988)	25	Seizure-free with auras	13	4	12	5	-0.23	-1.01	0.56	0.570101	-0.41
Delgado-Escueta (1985)	15	Seizure-free no auras	10	7	5	2	0.61	-0.46	1.69	0.263161	1.27

Evidence Table 135. Sensitivity analysis of studies of temporal lobe surgery reporting the number of left side and right side surgeries among patients with successful and nonsuccessful surgery

Sensitivity Adjustment	Cohen's h Summary Estimate [a]	95% Confidence Interval		p value for Summary Estimate	Q	p value for Q	Back-transformed Percentage Estimate [b]	95% Confidence Interval	
		Lower	Upper					Lower	Upper
Original analysis	-0.07	-0.27	0.13	0.49	17.88	0.46	0%	-2%	0%
Removing study with smallest effect size [c]	-0.05	-0.25	0.15	0.65	15.47	0.56	0%	-2%	1%
Removing study with largest effect size	-0.11	-0.32	0.09	0.27	13.96	0.67	0%	-3%	0%
Removing study with smallest N	-0.05	-0.25	0.15	0.65	15.47	0.56	0%	-2%	1%
Removing study with largest N	-0.10	-0.32	0.13	0.40	17.62	0.41	0%	-3%	0%

[a] A positive summary estimate favors left side surgery patients achieving more successful surgeries.
[b] The back-transformed percentage estimate is the difference between the percentage of left side surgery patients who achieved successful surgery and the percentage of right side surgery patients who achieved successful surgery. A positive percentage favors left side surgeries and a negative percentage favors right side surgeries. A difference of 0% indicates no differences between left side and right side patients in achieving successful surgery.
[c] The study with the smallest effect size also had the smallest N.

Evidence Table 136. Studies of temporal lobe surgery reporting number of simple partial seizure (SPS) patients with successful and nonsuccessful surgery.

Reference	N	Seizure Outcome Measurement	SPS Patients	SPS Successes	Non-SPS Patients	Non-SPS Successes	Cohen's h Effect Sizes	95% Confidence Interval		p Values for Effect Sizes	Standardized Residuals for Effect Sizes
								Lower	Upper		
Bouilleret (2002)	18	Seizure-free no auras	16	10	2	2	-1.32	-2.79	0.15	0.078835	-1.97
Hennessy (2001)	80	Seizure-free with auras	23	18	57	34	0.41	-0.08	0.89	0.099855	2.24
Berkovic (1991)	10	Seizure-free (undefined)	9	7	1	1	-0.98	-3.05	1.08	0.351655	-1.05
Yeh (1990)	12	Seizure-free with auras	3	2	9	8	-0.55	-1.86	0.76	0.408278	-1.03
Drake (1987)	11	Seizure-free (undefined)	3	2	8	5	0.09	-1.24	1.41	0.897564	-0.02

Evidence Table 137. Sensitivity analysis of studies of temporal lobe surgery reporting the percentage of patients with simple partial seizures among patients with successful and nonsuccessful surgery

Sensitivity Adjustment	Cohen's h Summary Estimate [a]	95% Confidence Interval		p value for Summary Estimate	Q	p value for Q	Back-transformed Percentage Estimate [b]	95% Confidence Interval	
		Lower	Upper					Lower	Upper
Original analysis	0.10	-0.30	0.51	0.62	7.12	0.13	0%	-2%	6%
Removing study with smallest effect size	0.22	-0.20	0.64	0.31	3.25	0.36	1%	-1%	10%
Removing study with largest effect size [c]	-0.60	-1.34	0.13	0.11	2.08	0.55	-9%	-39%	0%
Removing study with smallest N	0.14	-0.27	0.56	0.49	6.02	0.11	0%	-2%	8%
Removing study with largest N [c]	-0.60	-1.34	0.13	0.11	2.08	0.55	-9%	-39%	0%

[a] A positive summary estimate favors patients who have simple partial seizures achieving more successful surgeries.
[b] The back-transformed percentage estimate is the difference between the percentage of patients with simple partial seizures who achieved successful surgery and the percentage of patients without simple partial seizures who achieved successful surgery. A positive percentage favors patients with simple partial seizures and a negative percentage favors patients without simple partial seizures. A difference of 0% indicates no differences between patients with or without simple partial seizures in achieving successful surgery.
[c] The study with the largest effect size also had the largest N.

Evidence Table 138. Studies of temporal lobe surgery reporting number of secondarily generalized seizure (SGS) patients with successful and nonsuccessful surgery

Reference	N	Seizure Outcome Measurement	SGS Patients	SGS Successes	Non-SGS Patients	Non-SGS Successes	Cohen's h Effect Sizes	95% Confidence Interval		p Values for Effect Sizes	Standardized Residuals for Effect Sizes
								Lower	Upper		
Hennessy (2001)	80	Seizure-free with auras	31	22	49	30	0.21	-0.24	0.66	0.368647	2.15
Hennessy (2001)	116	Seizure-free with auras	57	31	59	47	-0.55	-0.91	-0.18	0.003215	-2.61
Liu (1995)	12	Seizure-free with auras	8	3	4	3	-0.78	-1.98	0.42	0.204920	-0.96
Berkovic (1991)	10	Seizure-free (undefined)	4	4	6	4	1.23	-0.03	2.50	0.056521	2.26
Yeh (1990)	12	Seizure-free with auras	10	8	2	2	-0.93	-2.45	0.59	0.231255	-0.95
Drake (1987)	11	Seizure-free (undefined)	7	3	4	4	-1.71	-2.94	-0.49	0.006241	-2.47
Delgado-Escueta (1985)	15	Seizure-free no auras	12	9	3	0	2.09	0.83	3.36	0.001176	3.63

Evidence Table 139. Studies of temporal lobe surgery reporting number of secondarily generalized seizure (SGS) patients with successful and nonsuccessful surgery – data used in meta-regression

Reference	Number of Patients	Cohen's h Effect Size	Weight	Mesial Temporal Sclerosis Patients Only	Tumor Patients Only	Standard Temporal Lobectomy	Tailored Temporal Lobectomy
Hennessy (2001)	80	0.2063	18.9875	No	No	Yes	No
Hennessy (2001)	116	-0.5472	28.9914	Yes	No	Yes	No
Liu (1995)	12	-0.7763	2.6667	No	No	No	Yes
Berkovic (1991)	10	1.231	2.4	Yes	No	Yes	No
Yeh (1990)	12	-0.9273	1.6667	No	Yes	No	No
Drake (1987)	11	-1.7141	2.5455	No	Yes	No	Yes
Delgado-Escueta (1985)	15	2.0944	2.4	No	No	Yes	No

Evidence Table 140. Results of meta-regression of studies of temporal lobe surgery reporting the number of patients with secondarily generalized seizures among patients with successful and nonsuccessful surgery

One predictor variable Bolded = statistically significant coefficient						
Covariate	**Intercept (CI)**	**P (intercept)**	**Coefficient (CI)**	**P (coefficient)**	**Q_e =**	**P (Q_e) =**
Start year (centered)	-1.96 (-2.28 to -1.64)	<0.000001	0.00 (-0.09 to 0.09)	0.966950	31.779	<0.0000017
End year (centered)	0.06 (-0.35 to 0.47)	0.780259	-0.06 (-0.13 to 0.01)	0.116190	29.312	0.000020
MTS (MTS=0)	**-0.41 (-0.76 to -0.06)**	**0.021420**	**0.45 (-0.06 to 0.95)**	**0.086312**	**28.831**	**0.000020**
Tumor (Tumor = 0)	**-1.40 (-2.36 to -0.45)**	**0.003970**	**1.29 (0.30 to 2.28)**	**0.010444**	**25.277**	**0.000126**
Standard (St = 0)	**-0.08 (-0.34 to 0.19)**	**0.584601**	**-1.09 (-1.88 to -0.29)**	**0.007470**	**24.620**	**0.000165**
Tailored (Tailored = 0)	**-1.23 (-2.09 to -0.38)**	**0.004862**	**1.13 (0.23 to 2.03)**	**0.013471**	**25.674**	**0.000103**
Treatment age (centered)	-0.24 (-0.52 to 0.05)	0.101922	-0.01 (-0.07 to 0.04)	0.574820	31.462	0.000008
United States (USA = 0)	**0.58 (-0.29 to 1.45)**	**0.189245**	**-0.86 (-1.77 to 0.05)**	**0.065196**	**28.380**	**0.000031**
Percent male (centered)	-0.23 (-0.50 to 0.04)	0.096627	-0.01 (-0.04 to 0.02)	0.543944	31.413	0.000008
Percent simple partial seizures	-0.20 (-0.47 to 0.08)	0.164976	0.00 (-0.03 to 0.03)	0.916759	31.770	0.000007
Percent generalized seizures	-0.29 (-0.65 to 0.06)	0.107075	-0.01 (-0.03 to 0.01)	0.462774	31.251	0.000008

Evidence Table 140. Results of meta-regression of studies of temporal lobe surgery reporting the number of patients with secondarily generalized seizures among patients with successful and nonsuccessful surgery (continued)

Two predictor variables: start year plus one variable

Bolded in this table = both coefficients significant, Italicized and bolded = both coefficients significant and MR homogeneous

Covariate: B_1	Covariate: B_2	Intercept (CI)	P (intercept)	Coefficient B_1 (CI)	P (B_1) =	Coefficient B_2 (CI)	P(B_2)	Q_e =	P (Q_e) =
MTS (MTS = 0)	**Tumor (Tumor = 0)**	**-2.10 (-3.19 to –1.01)**	**0.000166**	**0.70 (0.17 to 1.23)**	**0.010168**	**1.69 (0.65 to 2.72)**	**0.001381**	**18.611**	**0.000937**
MTS (MTS = 0)	Standard (St = 0)	-0.41 (-0.76 to –0.06)	0.021115	0.83 (0.28 to 1.38)	0.003086	-1.58 (-2.44 to –0.72)	0.000318	15.869	0.0032
MTS (MTS = 0)	**Tailored (Tailored = 0)**	**-1.97 (-2.98 to –0.95)**	**0.000143**	**0.73 (0.19 to 1.27)**	**0.007651**	**1.56 (0.60 to 2.57)**	**0.001340**	**18.594**	**0.000964**
MTS (MTS = 0)	Treatment age (centered)	-0.42 (-0.78 to –0.06)	0.022014	0.43 (-0.09 to 0.95)	0.101515	-0.01 (-0.06 to 0.05)	0.834629	28.787	0.000009
MTS (MTS = 0)	United States (USA = 0)	0.26 (-0.76 to 1.28)	0.621027	0.33 (-0.221 to 0.86)	0.235274	-0.67 (-1.63 to 0.29)	0.172392	26.968	0.000020
MTS (MTS = 0)	Percent male (centered)	-0.41 (-0.76 to –0.06)	0.021216	0.44 (-0.10 to 0.97)	0.107418	0.00 (-0.03 to 0.03)	0.936807	28.824	0.000009
MTS (MTS = 0)	Percent simple	-0.42 (-0.77 to –0.07)	0.018427	0.62 (0.03 to 1.20)	0.0404442	-0.02 (-0.06 to 0.02)	0.266268	27.575	0.000015
MTS (MTS = 0)	Percent CGE	-0.52 (-0.96 to –0.09)	0.019117	0.46 (-0.05 to 0.97)	0.077299	-0.01 (-0.03 to 0.01)	0.401950	28.129	0.000012
MTS (MTS = 0)	Start year (centered)	-0.41 (-0.81 to –0.01)	0.046672	0.45 (-0.06 to 0.95)	0.086060	0.00 (-0.09 to 0.09)	0.980949	28.830	0.000009
MTS (MTS = 0)	End year (centered)	-0.18 (-0.72 to 0.36)	0.521359	0.36 (-0.18 to 0.89)	0.189704	-0.04 (-0.12 to 0.003)	0.267427	27.596	0.000015
Tumor (Tumor = 0)	Standard (St = 0)	0.70 (-2.26 to 0.85)	0.376850	0.63 (-0.91 to 2.16)	0.423728	-0.70 (-1.93 to 0.53)	0.264120	23.979	0.000081
Tumor (Tumor = 0)	Tailored (Tailored = 0)	-1.69 (-2.73 to –0.65)	0.001444	0.89 (-0.26 to 2.04)	0.128514	0.73 (-0.32 to 1.77)	0.172070	23.361	0.000107

Evidence Table 140. Results of meta-regression of studies of temporal lobe surgery reporting the number of patients with secondarily generalized seizures among patients with successful and nonsuccessful surgery (continued)

Two predictor variables: start year plus one variable (continued)

Bolded in this table = both coefficients significant, Italicized and bolded = both coefficients significant and MR homogeneous

Covariate: B_1	Covariate: B_2	Intercept (CI)	P (intercept)	Coefficient B_1 (CI)	P (B_1) =	Coefficient B_2 (CI)	P(B_2)	Q_e =	P (Q_e) =
Tumor (Tumor = 0)	Treatment age (centered)	-1.46 (-2.43 to –0.49)	0.003117	1.31 (0.32 to 2.30)	0.009589	-0.02 (-0.07 to 0.03)	0.490667	24.753	0.000056
Tumor (Tumor = 0)	United States (USA = 0)	-0.64 (-1.96 to 0.68)	0.341773	1.22 (0.23 to 2.22)	0.015783	-0.76 (-1.68 to 0.15)	0.102166	22.554	0.000156
Tumor (Tumor = 0)	Percent male (centered)	-1.50 (-2.52 to –0.49)	0.003679	1.44 (0.33 to 2.54)	0.010665	0.01 (-0.02 to 0.04)	0.563892	24.896	0.000053
Tumor (Tumor = 0)	Percent simple	-1.49 (-2.50 to –0.48)	0.003880	1.36 (0.34 to 2.38)	0.009061	0.01 (-0.02 to 0.04)	0.608476	24.964	0.000051
Tumor (Tumor = 0)	Percent CGE	-1.52 (-2.52 to –0.52	0.002871	1.55 (0.37 to 2.72)	0.010040	0.01 (-0.02 to 0.04)	0.434255	24.625	0.000060
Tumor (Tumor = 0)	Start year (centered)	-1.39 (-2.35 to –0.43)	0.004522	1.32 (0.32 to 2.32)	0.00961	0.02 (-0.07 to 0.11)	0.697709	25.077	0.000049
Tumor (Tumor = 0)	**End year (centered)**	**-1.83 (-2.77 to –0.89)**	**0.000142**	**2.52 (1.38 to 3.67)**	**0.000016**	**-0.16 (-0.24 to –0.08)**	**0.000140**	**12.157**	**0.016221**
Standard (St = 0)	Tailored (Tailored = 0)	-0.38 (-2.15 to 1.38)	0.671466	-0.85 (-2.39 to 0.69)	0.278810	0.31 (-1.44 to 2.05)	0.730062	24.501	0.000063
Standard (St = 0)	Treatment age (centered)	-0.04 (-0.36 to 0.29)	0.830962	-1.16 (-2.01 to –0.30)	0.007991	0.01 (-0.04 to 0.07)	0.655440	24.423	0.000066
Standard (St = 0)	**United States (USA = 0)**	**1.44 (0.46 to 2.42)**	**0.004075**	**-1.63 (-2.49 to –0.76)**	**0.000222**	**-1.59 (-2.58 to –0.60)**	**0.001663**	**14.728**	**0.005300**
Standard (St = 0)	Percent male (centered)	-0.09 (-0.38 to 0.20)	0.529649	-1.07 (-1.87 to –0.27)	0.008599	0.00 (-0.04 to 0.03)	0.745227	24.513	0.000063
Standard (St = 0)	Percent simple	-0.04 (-0.34 to 0.25)	0.781214	-1.12 (-1.92 to –0.31	0.006384	-0.01 (-0.04 to 0.02)	0.596896	24.337	0.000068

Evidence Table 140. Results of meta-regression of studies of temporal lobe surgery reporting the number of patients with secondarily generalized seizures among patients with successful and nonsuccessful surgery (continued)

Two predictor variables: start year plus one variable (continued)

Bolded in this table = both coefficients significant, Italicized and bolded = both coefficients significant and MR homogeneous

Covariate: B_1	Covariate: B_2	Intercept (CI)	P (intercept)	Coefficient B_1 (CI)	P (B_1) =	Coefficient B_2 (CI)	P(B_2)	Q_e =	P (Q_e) =
Standard (St = 0)	Percent CGE	0.20 (-0.29 to 0.68)	0.426228	-1.54 (-2.59 to –0.50)	0.003776	-0.02 (-0.05 to 0.01)	0.179913	22.870	0.00134
Standard (St = 0)	Start year (centered)	0.13 (-0.26 to 0.51)	0.521675	-1.39 (-2.29 to –0.49)	0.002344	0.07 (-0.03 to 0.18)	0.147246	22.531	0.000157
Standard (St = 0)	**End year (centered)**	**0.82 (0.28 to 1.35)**	**0.002696**	**-2.17 (-3.14 to –1.20)**	**0.000012**	**-0.17 (-0.25 to –0.08)**	**0.000146**	**22.531**	**0.038118**
Tailored (Tailored = 0)	Treatment age (centered)	-1.24 (-2.09 to 0.38)	0.004783	1.12 (0.21 to 2.03)	0.015741	-0.01 (-0.06 to 0.05)	0.836505	25.631	0.000038
Tailored (Tailored = 0)	**United States (USA = 0)**	**-0.35 (-1.35 to 0.64)**	**0.487119**	**1.98 (0.96 to 3.00)**	**0.000147**	**-1.81 (-2.84 to –0.77)**	**0.000619**	**13.960**	**0.007424**
Tailored (Tailored = 0)	Percent male (centered)	-1.26 (-2.13 to –0.40)	0.004135	1.13 (0.23 to 2.03)	0.013545	-0.01 (-0.04 to 0.02)	0.548722	25.317	0.000043
Tailored (Tailored = 0)	Percent simple	-1.27 (-2.13 to –0.41)	0.003935	1.22 (0.29 to 2.15)	0.010041	-0.01 (-0.05 to 0.02)	0.461415	25.137	0.000047
Tailored (Tailored = 0)	Percent CGE	-1.26 (-2.13 to –0.39)	0.004449	1.22 (0.22 to 2.22)	0.016733	0.00 (-0.2 to 0.03)	0.698106	25.521	0.000040
Tailored (Tailored = 0)	Start year (centered)	-1.26 (-2.12 to –0.40)	0.004139	1.26 (0.31 to 2.20)	0.009042	0.04 (-0.05 to 0.13)	0.400510	24.967	0.000051
Tailored (Tailored = 0)	**End year (centered)**	**-1.32 (-2.18 to –0.45)**	**0.002739**	**1.83 (0.82 to 2.84)**	**0.000369**	**-0.12 (-0.20 to –0.40)**	**0.002625**	**16.626**	**0.00285**
United States (USA = 0)	**Treatment age (centered)**	**1.00 (0.03 to 1.96)**	**0.042543**	**-1.48 (-2.59 to –0.38)**	**0.008544**	**-0.06 (-0.12 to 0.00)**	**0.051456**	**24.549**	**0.000062**
United States (USA = 0)	Percent male (centered)	0.58 (-0.29 to 1.45)	0.190020	-0.90 (-1.81 to 0.02)	0.054632	-0.01 (-0.04 to 0.02)	0.412989	27.716	0.000014

Evidence Table 140. Results of meta-regression of studies of temporal lobe surgery reporting the number of patients with secondarily generalized seizures among patients with successful and nonsuccessful surgery (continued)

Two predictor variables: start year plus one variable (continued)

Bolded in this table = both coefficients significant, Italicized and bolded = both coefficients significant and MR homogeneous

Covariate: B_1	Covariate: B_2	Intercept (CI)	P (intercept)	Coefficient B_1 (CI)	P (B_1) =	Coefficient B_2 (CI)	P(B_2)	Q_e =	P (Q_e) =
United States (USA = 0)	Percent simple	0.96 (-0.06 to 1.99)	0.066008	-1.38 (-2.55 to –0.20)	0.021714	0.03 (-0.01 to 0.07)	0.169206	26.506	0.000025
United States (USA = 0)	**Percent CGE**	**1.05 (0.10 to 1.99)**	**0.029933**	**-1.81 (-2.99 to –0.62)**	**0.002728**	**-0.04 (-0.07 to –0.01)**	**0.014582**	**22.274**	**0.000177**
United States (USA = 0)	Start year (centered)	0.58 (-0.29 to 1.45)	0.191861	-0.89 (-1.83 to 0.04)	0.060169	-0.02 (-0.11 to .007)	0.715934	28.248	0.000011
United States (USA = 0)	End year (centered)	0.53 (-0.36 to 1.41)	0.245352	-0.65 (-1.75 to 0.45)	0.244482	-0.03 (-0.11 to 0.06)	0.516362	27.956	0.000013

Evidence Table 141. Studies of temporal lobe surgery reporting quality of life outcome measurements

Epilepsy Surgery Inventory					
Reference	Number of Patients	Surgery	Followup (Years)	Mean Overall Quality of Life Score	SD of Overall Score
Rose (1996)	47	Standard temporal lobectomy	0	60.5	19.0
			2	57.7	20.7

The study found no significant difference in overall quality of life scores measured prior to or 2 years after surgery, but reported that patients with low preoperative scores showed the greatest improvement in postoperative scores.

Quality of Life in Epilepsy					
Reference	Number of Patients	Surgery	Followup (Years)	Mean Global Score	SD of Global Score
Markand (2000)	53	Tailored temporal lobectomy	0	47	10
	51		2	54	12
	37	Control	0	42	10.1
	33		2	40	12

The study found that the baseline overall score was significantly higher in the surgery group. At 2 years after surgery the overall score was significantly improved in the surgery group compared to baseline and the control group. The improvement in the surgery group was almost entirely due to patients who became completely seizure-free. Patients who were free of complex partial seizures but still had auras or who still experienced complex partial seizures had no significant improvement in overall score after surgery.

Evidence Table 142. Studies of temporal lobe surgery reporting employment data

Reference	Number of Patients Evaluated	Mean Followup Time in Years	Minimum Followup	Maximum Followup	Number of Patients Not Able to Obtain Work Prior to Surgery	Number of Patients Able to Obtain Work After Surgery	Number of Patients Working Prior to Surgery	Number of Patients Able to Remain at Work After Surgery
Boling (2001)	18	5.3	2		1	0	13	9
Reeves (1997)	134	4.2	2.5	6.5	20	7	67	57
Sperling (1995)	73	2			28	15	33	30
Mizrahi (1990)	22	5.3	2	8	5	3	4	3
Delgado-Escueta (1985)	15	6	2	11	3	3	8	7

Evidence Table 143. Studies of temporal lobe surgery reporting the ability to attend or remain in school after surgery

Reference	N	Surgery	Followup (Years)	Minimum Followup	Maximum Followup	Number of Patients			
						Did Not Attend School Prior to Surgery	Able to Attend School After Surgery	Attending School Prior to Surgery	Able to Remain in School or Obtain Employment After Surgery
Mizrahi (1990)	22	Tailored temporal lobectomy	5.3	2	8	0	0	11	11
Delgado-Escueta (1985)	15	Standard temporal lobectomy	6	2	11	1	1	2	2

In Mizrahi, all eleven patients attending school at the time of surgery showed improvement in school or obtained employment at the time of followup. In Delgado-Escueta, only three patients were of school age; all showed improvement in schoolwork after surgery.

Evidence Table 144. Studies of temporal lobe surgery reporting ability to obtain a driver's license after surgery

Reference	Number of Patients	Surgery	Followup (Years)	Minimum Followup Time	Maximum Followup Time	Number of Patients Able to Obtain a Drivers License After Surgery
Reeves (1997)	134	Standard	4.2	2.5	6.5	89 (66%)

The number of patients who were driving increased significantly after surgery; 16% compared to 66%.

Evidence Table 145. Studies reporting new cases of depression after temporal lobe surgery

Reference	Number of Patients	Years	Country	Method of Diagnosis
Kanemoto (2001)	52	1987-1999	Japan	Mood disorder due to a general medical condition that fulfilled the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) criteria
Kohler (2001)	58	1986-1999	United States	Neurologic and neuropsychological evaluations were used to determine the presence of psychiatric symptoms meeting the severity criteria for mood and anxiety disorders as classified in the DSM-IV, including major depression and depression not otherwise specified.
Nees (2001)	50	1992-1994	England	Data derived from standard interviews on all patients by a clinical psychiatrist were used to make a diagnosis of depression.
Wiebe (2001)	36	1996-2000	Canada	Depression was assessed with the depression scale of the Center for Epidemiological Studies-Depression Scale (CES-D)
Anhoury (2000)	109	1988-1997	England	Clinical diagnoses of mood disorders were made by experienced psychiatrists with an interest in epilepsy.
Derry (2000)	39	1996-1998	Canada	The CES-D was used to define clinical depression for the purposes of this study.
Altshuler (1999)	49	1974-1990	United States	Patients were administered the Structured Clinical Interview for DSM-III-R that assesses current and past psychopathology for evidence of depression.
Ring (1998)	60	1995-1996	England	Depression was defined according to DSM-IV criteria, but as if there were no associated general medical condition.
Naylor (1994)	37	1987-1991	Denmark	Patients were diagnosed as having moderate or severe depressive episodes before or after surgery using the criteria of the International Classification of Diseases-10th revision.
Bladin (1992)	107	1975-1991	Australia	DSM-III criteria were used to diagnose depression.

Evidence Table 146. Patient characteristics for studies of temporal lobe surgery reporting new cases of depression

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Kanemoto (2001)	52	Standard	Not reported	27.1	5.9	9.7	5.3	17.5	7.8
Kohler (2001)	58	Standard	Various	32.3	10.6			17.7	10.3
Nees (2001)	50	Not described	Various	26		8.8			
Wiebe (2001)	36	Standard	Various	34.4	9.9	16.2	10		
Anhoury (2000)	109	Not described	Various	30.1	7.4				
Derry (2000)	39	Standard	Not reported	31.2	1	12.1	10	18.8	9.2
Altshuler (1999)	49	Standard	Mesial temporal sclerosis	40	5.5	11.4	8.3	17.6	4.3
Ring (1998)	60	Not described	Not reported	27	7.4				
Naylor (1994)	37	AH	Various	29.1	9.1	11.5	10.3	17.6	8.2
Bladin (1992)	107	Standard	Not reported						

AH Amygdalohippocampectomy

Evidence Table 146. Patient characteristics for studies of temporal lobe surgery reporting new cases of depression (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females	Number of Patients With Simple Partial Seizures
Kanemoto (2001)	22	30	28	24	
Kohler (2001)	27	31	20	38	44
Nees (2001)	31	19	17	33	
Wiebe (2001)	12	24	21	19	
Anhoury (2000)			50	71	
Derry (2000)	18	21	16	23	
Altshuler (1999)	23	26	23	26	
Ring (1998)	36	24	21	39	
Naylor (1994)			22	15	
Bladin (1992)	62	48	46	64	

Evidence Table 147. Results of meta-analysis of studies of temporal lobe surgery reporting new cases of depression after surgery

Reference	Number of Patients	Number of New Cases of Depression After Treatment	Percentage	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Kanemoto (2001)	52	2	3.8	0.39	0.01—0.78	0.044109	-1.66
Kohler (2001)	58	6	10.3	0.65	0.29—1.02	0.000421	-0.29
Nees (2001)	50	14	28.0	1.12	0.72—1.51	<0.000001	2.14
Wiebe (2001)	36	7	19.4	0.91	0.45—1.38	0.000107	0.91
	40 – control patients	8	20.0	---	---	---	---
Anhoury (2000)	109	26	23.9	1.02	0.76—1.29	<0.000001	2.57
Derry (2000)	39	4	10.3	0.65	0.21—1.10	0.003988	-0.25
Altshuler (1999)	49	5	10.2	0.65	0.25—1.05	0.001288	-0.29
Ring (1998)	60	7	11.7	0.70	0.34—1.06	0.000134	-0.05
Naylor (1994)	37	2	5.4	0.47	0.01—0.92	0.043542	-1.05
Bladin (1992)	107	5	4.7	0.44	0.17—0.70	0.001436	-2.18

Evidence Table 148. Studies of temporal lobe surgery reporting new cases of depression after surgery – data used in meta-regression

Reference	Number of Patients	Cohen's h Effect Size	Weight	Year Study Started	Year Study Ended	Mesial Temporal Sclerosis Patients Only	Standard Temporal Lobectomy	Age at Surgery	Conducted in the United States
Kanemoto (2001)	52	0.3948	26	1987	1999	No	Yes	27.1	No
Kohler (2001)	58	0.6549	29	1986	1999	No	Yes	32.3	Yes
Nees (2001)	50	1.1152	25	1992	1994	No	Yes	26	No
Wiebe (2001)	36	0.9133	18	1996	2000	No	Yes	34.4	No
Anhoury (2000)	109	1.0205	54.5	1988	1997	No	Yes	30.1	No
Derry (2000)	39	0.652	19.5	1996	1998	No	Yes	31.2	No
Altshuler (1999)	49	0.6503	24.5	1974	1990	Yes	Yes	40	Yes
Ring (1998)	60	0.6972	30	1995	1996	No	Yes	27	No
Naylor (1994)	37	0.4693	18.5	1987	1991	No	No	29.1	No
Bladin (1992)	107	0.4358	53.5	1975	1991	No	Yes	30.8	No

Evidence Table 149. Results of meta-regression of studies of temporal lobe surgery reporting new cases of depression after surgery

One predictor variable Bolded = statistically significant coefficient						
Covariate	**Intercept (CI)**	**P (intercept) =**	**Coefficient (CI)**	**P (coefficient)**	**Q_e =**	**P (Q_e) =**
Start year (centered)t	**0.73 (0.61 to 0.84)**	**<0.000001**	**0.02 (0.00 to 0.03)**	**0.034561**	**13.400**	**0.099**
End year (centered)	0.71 (0.60 to 0.83)	<0.000001	0.02 (-0.01 to 0.06)	0.163850	16.060	0.042
Mesial temporal sclerosis (MTS=0)	0.65 (0.25 to 1.05)	0.001318	0.06 (-0.35 to 0.47)	0.773529	17.940	0.022
Standard (St = 0)	0.72 (0.60 to 0.84)	<0.000001	-0.25 (-0.72 to 0.22)	0.293673	16.910	0.031
Treatmet age (centered)	0.71 (0.59 to 0.82)	<0.000001	-0.01 (-0.04 to 0.03)	0.689034	17.964	0.021
United States (USA = 0)	0.65 (0.39 to 0.92)	0.000002	0.06 (-0.23 to 0.36)	0.666754	17.8370	0.022
% Males (centered)	0.70 (0.58 to 0.81)	<0.000001	-0.01 (-0.02 to 0.01)	0.347664	17.0790	0.029

Evidence Table 149. Results of meta-regression of studies of temporal lobe surgery reporting new cases of depression after surgery (continued)

Two predictor variables: Start year plus one variable

Bolded = homogeneous only (2nd predictor variable not significant)

Covariate: B_1	Covariate: B_2	Intercept (CI)	P (intercept)	Coefficient B_1 (CI)	P (B_1) =	Coefficient B_2 (CI)	P(B_2)	Q_e =	P (Q_e) =
Start year (centered)	End year (centered)	0.73 (0.62 to 0.84)	<0.000001	0.02 (0.00 to 0.04)	0.094916	-0.01 (-0.05 to 0.04)	0.821843	13.4900	0.061
Start year (centered)	MTS (MTS=0)	0.92 (0.46 to 1.38)	0.000084	0.02 (0.00 to 0.04)	0.025968	-0.20 (-0.67 to 0.27)	0.397550	12.6830	0.080
Start year (centered)	Standard (St = 0)	0.75 (0.63 to 0.86)	<0.000001	0.02 (0.00 to 0.03)	0.029075	-0.27 (-0.74 to 0.21)	0.268487	12.1720	0.095
Start year (centered)	Treatmet age (centered)	0.74 (0.62 to 0.85)	<0.000001	0.02 (0.00 to 0.04)	0.028560	0.01 (-0.02 to 0.05)	0.464442	12.8680	0.075
Start year (centered)	United States (USA = 0)	0.78 (0.49 to 1.07)	<0.000001	0.02 (0.00 to 0.03)	0.030205	-0.06 (-0.37 to 0.26)	0.729666	13.2810	0.066
Start year (centered)	% Males (centered)	0.72 (0.61 to 0.84)	<0.000001	0.02 (0.00 to 0.03)	0.032570	-0.01 (-0.02 to 0.01)	0.430557	12.7630	0.078

Evidence Table 150. Studies reporting new cases of psychosis after temporal lobe surgery

Reference	N	Years	Country	Exclusion from Surgery	Method of Diagnosis
Kanemoto (2001)	52	1987-1999	Japan	Patients were excluded from surgery if they had chronic psychosis	Psychotic disorder due to a general medical condition that fulfilled the Diagnostic and Statistical Manual of Mental Disorders-4th edition (DSM-IV) criteria
Wiebe (2001)	36	1996-2000	Canada	Patients were excluded from surgery if they had chronic psychosis	Psychopathology was assessed with the General Health Questionnaire
Anhoury (2000)	109	1988-1997	England	Patients were not excluded for psychiatirc disorders	Clinical diagnoses of psychosis were made by experienced psychiatrists with an interest in epilepsy.
Blumer (1998)	44	1994-1995	United States	Patients were not excluded for psychiatirc disorders	Patients were evaluated by a psychiatrist using a standardized psychiatric evaluation developed specifically for patients with epilepsy
Naylor (1994)	37	1987-1991	Denmark	Patients were not excluded for psychiatirc disorders	Patients were diagnosed as having acute psychotic disorder before or after surgery using the criteria of the International Classification of Diseases-10th revision.
Bladin (1992)	107	1975-1991	Australia	Patients were not excluded for psychiatirc disorders	DSM-III criteria were used to diagnose psychoses.

Evidence Table 151. Patient characteristics for studies of temporal lobe surgery reporting new cases of psychosis

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Kanemoto (2001)	52	Standard	Not reported	27.1	5.9	9.7	5.3	17.5	7.8
Wiebe (2001)	36	Standard	Various	34.4	9.9	16.2	10		
Anhoury (2000)	109	Not described	Various	30.1	7.4				
Blumer (1998)	44	Not described	Various	36				20.5	13.2
Naylor (1994)	37	AH	Various	29.1	9.1	11.5	10.3	17.6	8.2
Bladin (1992)	107	Standard	Not reported						

AH Amygdalohippocampectomy

Patient characteristics for studies of temporal lobe surgery reporting new cases of psychosis (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females
Kanemoto (2001)	22	30	28	24
Wiebe (2001)	12	24	21	19
Anhoury (2000)			50	71
Blumer (1998)	22	22	19	25
Naylor (1994)			22	15
Bladin (1992)	62	48	46	64

Evidence Table 152. Studies of temporal lobe surgery reporting new cases of psychosis after surgery

Reference	Number of Patients	New Cases of Psychosis After Treatment	Percentage	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Kanemoto (2001)	52	7	13.5	0.75	0.37—1.14	0.000128	2.09
Wiebe (2001)	36	1	2.8	0.33	-0.13—0.80	0.155362	-0.16
	40 – control patients	1	2.5	---	---	---	---
Anhoury (2000)	109	3	2.8	0.33	0.07—0.60	0.013860	-0.32
Blumer (1998)	44	2	4.5	0.43	0.01—0.85	0.043855	0.30
Naylor (1994)	37	0	0.0	0.00	-0.46—0.46	1.000000	-1.67
Bladin (1992)	107	3	2.8	0.34	0.07—0.60	0.013852	-0.29

Evidence Table 153. Studies of temporal lobe surgery reporting both the number of patients with IQ changes after surgery and the pre-treatment and post-treatment mean IQ

Reference	N	Years	Country	Test Used to Determine IQ	Method Used to Determine Significant Change in IQ
Miranda (2001)	50	1976-1998	Canada	Wechsler Intelligence Scale for Children—Revised, Wechsler Intelligence Scale for Children—III, Wechsler Adult Intelligence Scale—Revised. Used Verbal IQ data for analysis.	A significant change following surgery for epilepsy was defined as two times the value of the average standard error of measurement for each scale.
Robinson (2000)	21	1993-1998	United States	Wechsler Intelligence Scale for Children—III, Wechsler Adult Intelligence Scale—Revised. Used Verbal IQ data for analysis.	A significant individual change was defined as a difference between pre- and postoperative scores greater than 0.5 SDs (>8 points)
Westerveld (2000)	82		United States	Wechsler Intelligence Scale for Children. Used Verbal IQ data for analysis.	The frequency of changes in IQ exceeding two times the value of the standard error of the measurement from each scale was used to determine significant changes (seven points for VIQ).
Chelune (1993)	96	1990-1991	United States	Wechsler Adult Intelligence Scale—Revised. Used Verbal IQ data for analysis.	A significant individual change between pretest and posttest scores was defined as exceeding the reliable change interval of 90% after correction for expected practice effects.
Ivnik (1988)	141	1972-1987	United States	Wechsler Adult Intelligence Scale—Revised. Used Verbal IQ data for analysis.	Changes that are larger than the standard error of the measuring instrument represent cases in which true cognitive change occurred for a specific patient.
Powell (1985)	59	1973-1984	England	Wechsler Adult Intelligence Scale—Revised. Used Verbal IQ data for analysis.	Change in pretest to posttest scores of more than 10 points.

Evidence Table 154. Patient characteristics for studies of temporal lobe surgery reporting individual patient changes in IQ

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Miranda (2001)	50	Not described	Various	13.3	3.4	6.1	4.6	7.3	4.5
Robinson (2000)	22	AH	Various	15.4		5.2		10.3	
Westerveld (2000)	82	Not described	Various	14.4		5.4			
Chelune (1993)	96	Standard	Not reported	29.4	7.4	13.2	9.2	16.5	8.4
Ivnik (1988)	141	Tailored	Not reported	28	7.8	12.9	9.4		
Powell (1985)	59	Standard	Not reported	25.5	9.6	9.6	8		

AH Amygdalohippocampectomy

Patient characteristics for studies of temporal lobe surgery reporting individual patient changes in IQ (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females	Patients With Secondarily Generalized Seizures
Miranda (2001)	25	25	21	29	
Robinson (2000)	8	14	13	9	
Westerveld (2000)			48	34	
Chelune (1993)	49	47	60	36	
Ivnik (1988)			68	74	54
Powell (1985)	30	29	34	15	

Evidence Table 155. Studies of temporal lobe surgery reporting individual patient changes in verbal IQ after surgery

Reference	Number of Patients	Significant Decrease in IQ					Significant Increase in IQ				
		N	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes	N	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Miranda (2001)	50	7	0.77	0.37—1.16	0.000126	0.61	7	0.77	0.37—1.16	0.000126	0.12
Robinson (2000)	21	1	0.44	-0.16—1.04	0.153959	-0.71	4	0.90	0.30—1.51	0.003424	0.53
Westervel d (2000)	82	8	0.64	0.33—0.94	0.000047	-0.12	7	0.59	0.29—0.90	0.000146	-1.07
Chelune (1993)	96 surgery	8	0.59	0.30—0.87	0.000050	-0.52	8	0.59	0.30—0.87	0.000050	-1.24
	40 control	2	---	---	---	---	2	---	---	---	---
Ivnik (1988)	141	13	0.62	0.38—0.85	<0.000001	-0.36	27	0.91	0.67—1.14	<0.000001	1.63
Powell (1985)	59	10	0.85	.049—1.21	0.000004	1.14	8	0.75	0.39—1.12	0.000042	0.06

Evidence Table 156. Studies of temporal lobe surgery reporting individual patient changes in verbal IQ – changes in mean IQ

Reference	Number of Patients	Mean Pre-surgery IQ	SD of the Pre-surgery IQ	Mean Post-surgery IQ	SD of the Post-surgery IQ	Hedges' d Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Miranda (2001)	50	86	17	87	16	-0.06	-0.45—0.33	0.763796	-0.05
Robinson (2000)	21	87	9	89	12	-0.09	-0.70—0.51	0.764497	-0.14
Westerveld (2000)	82	93	16	93	14	0.00	-0.31—0.31	1.000000	0.38
Chelune (1993)	96 surgery	90	11	91	12	-0.17	-0.46—0.11	0.231396	-1.02
	40 control	92.1	12.9	93.0	12.8	---	---	---	---
Ivnik (1988)	141	95	NR	96	NR	---	---	---	---
Powell (1985)	59	100	20	98	19	0.10	-0.26—0.46	0.580321	0.92

Evidence Table 157. Sensitivity analysis of studies of temporal lobe surgery reporting mean IQ

Sensitivity Adjustment	Hedges' d Summary Estimate	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	-0.05	-0.21	0.11	0.53	1.53	0.82
Removing study with smallest effects size [a]	0.00	-0.19	0.20	0.96	0.48	0.92
Removing study with largest effect size	-0.09	-0.26	0.09	0.34	0.68	0.88
Removing study with smallest N	-0.05	-0.21	0.12	0.57	1.51	0.68
Removing study with largest N	0.00	-0.19	0.20	0.96	0.48	0.92

[a] The study with the smallest effect size also had the largest N.

Evidence Table 158. Studies of temporal lobe surgery reporting individual changes in patient memory after surgery

Reference	Number of Patients	Years	Country	Wechsler Memory Scale Used in Study
Canizares (2000)	33	1998-1999	Spain	General Memory Score
Chelune (1993)	96	1990-1991	United States	Verbal
Ivnik (1988)	141	1972-1987	United States	Memory quotient
Ojemann (1985)	13	1983-1983	United States	Verbal
Powell (1985)	59	1973-1984	England	Logical Memory percent Recall

Evidence Table 159. Studies of temporal lobe surgery reporting individual patient changes in memory function

Reference	Number of Patients	Wechsler Memory Scale Used in Study	Number of Patients With a Significant Decrease in Memory Score	Percentage of Patients Experiencing a Decrease	Number of Patients With a Significant Increase in Memory Score	Percentage of Patients Experiencing an Increase	Baseline Mean Memory Score	Baseline SD of the Mean Memory Score	Mean Memory Score After Surgery	SD of the Mean Memory Score After Surgery
Canizares (2000)	33	General Memory Score	3	9.1%	10	30.3%	80	15	88	19
Chelune (1993)	96 surgery patients	Verbal	28	29.2%	1	1.0%	90	14	87	14
	40 control patients	Verbal	1	2.5%	2	5%	94.5	17.4	102.5	18.3
Ivnik (1988)	141	Memory quotient	48	34.0%	48	34.0%	100		100	
Ojemann (1985)	13	Verbal	8	61.5%	3	23.1%	23		17	
Powell (1985)	59	Logical Memory percent Recall	8	13.6%	13	22.0%	70	28	74	25

Evidence Table 160. Patient characteristics for studies of temporal lobe surgery reporting complications due to surgery

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Epilepsy Before Surgery (Years)
Boling (2001)	18	AH	Various (no tumors)	54		18		34.9	12.1
Schramm (2001)	61	Neocortex	Various	27.9		14.4		13.6	
Sotero de Menezes (2001)	15	Tailored	Various	8.3	3.1				
Wiebe (2001)	36	Standard	Various	34.4	9.9	16.2	10		
Iannelli (2000)	37	Neocortex	Tumor	9.1	5			2.8	
Rao (2000)	164	Standard	Various	25.6				16.1	
Robinson (2000)	21	AH	Various	15.4		5.2		10.3	
Wurm (2000)	16	AH	Various	35.7					
Altshuler (1999)	49	Standard	MTS	40	5.5	11.4	8.3	17.6	4.3
Leung (1999)	11	Standard	MTS	28				17.2	
Parrent (1999)	19	AH	Not reported	34.1					
Salanova (1999)	145	Tailored	Various	30.4		10.5		19.7	
Son (1999)	71	Standard	MTS	28.9					
Visudhiphan (1999)	14	Standard	Various	13.1	3.6	6.7	3.8	6.4	4.5
Radhakrishnan (1998)	175	Tailored	Various	31		8		19	
Wyllie (1998)	72	Standard	Various			4.4			
Bizzi (1997)	14	Partial	Various	11.9	4.6				
Blume (1997)	14	Tailored	Various	8.5		2.6		6	
Kilpatrick (1997)	36	Standard	Various	36.8	11.5	15			
Adam (1996)	30	Standard	MTS	29		9			
Acciarri (1995)	10	Neocortex	Vascular malformation	34.8	12.5	33.3	12.8	1.6	1.2

Evidence Table 160. Patient characteristics for studies of temporal lobe surgery reporting complications due to surgery (continued)

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Epilepsy Before Surgery (Years)
Davies (1995)	12	Tailored	Various	23				8	
Jooma (1995a)	14	Tailored	Tumor	34.1	10	14.4	7.3	19.7	7.7
	16	Neocortex	Tumor	26.5	17.3	23.8	18.6	2.7	3.1
Liu (1995)	22	Tailored	Other	37.2	13.7	17.8	9.5	19.3	8.2
Wyler (1995)	70	Standard	Various	30.9		10.5			
Blume (1994)	125	Standard	Various						
Guldvog (1994b)	64	Standard	Various					11.5	
Guldvog (1994a)	35	Standard	Various					8	
Hopkins (1991)	11	Standard	Various	5.5	2.2	2	1.4	3.6	2.1
Bidzinski (1990)	320	Standard	Not reported	23		8		13	
Mackenzie (1990)	30	Standard	Not reported						
Mizrahi (1990)	22	Tailored	Various	21	8.4	5.9	2.3	15.1	8.1
Walczak (1990)	100	Standard	Not reported	25				15	
So (1989)	48	Tailored	Bitemporal epileptiform abnormalities	27.5					
Cutfield (1987)	26	Tailored	Various	22				12	
Drake (1987)	16	Tailored	Tumor	12.7	2.7	6.3	4.3	6.5	3.9

Evidence Table 160. Patient characteristics for studies of temporal lobe surgery reporting complications due to surgery (continued)

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Epilepsy Before Surgery (Years)
King (1986)	23	Not described	Various	28.7	9.2	12.9	10.5	15.7	7.6
Meyer (1986)	50	Tailored	Not reported	15.8		7.5		8.3	
Carey (1985)	24	Standard	Various	21		10.8		14.7	
Delgado-Escueta (1985)	15	Standard	Various	26.5	6.9	15.8	8	10.7	4.9

AH Amygdalohippocampectomy
MTS Mesial temporal sclerosis

Evidence Table 160. Patient characteristics for studies of temporal lobe surgery reporting complications due to surgery (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females	Number of Patients With Simple Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Boling (2001)			9	9		
Schramm (2001)	26	35	27	34	14	33
Sotero de Menezes (2001)	9	5			10	
Wiebe (2001)	12	24	21	19		
Iannelli (2000)	16	21	27	10	2	2
Rao (2000)			60	59		
Robinson (2000)	8	14	13	9		
Wurm (2000)	3	13	7	9		
Altshuler (1999)	23	26	23	26		
Leung (1999)	8	3	4	7		
Parrent (1999)	7	12	10	9		
Salanova (1999)	71	74				
Son (1999)			45	26		
Visudhiphan (1999)	4	10	7	7		
Radhakrishnan (1998)	68	107	77	98		
Wyllie (1998)						
Bizzi (1997)			11	8		
Blume (1997)	6	8	7	7	13	
Kilpatrick (1997)	8	10	11	7		
Adam (1996)	15	15	11	19	19	17
Acciarri (1995)	5	5	5	5		0
Davies (1995)						
Jooma (1995b)						6
Liu (1995)	5	7	5	7	0	8
Wyler (1995)	23	47	37	33		
Blume (1994)			64	61		

Evidence Table 160. Patient characteristics for studies of temporal lobe surgery reporting complications due to surgery (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females	Number of Patients With Simple Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Guldvog (1994b)						
Guldvog (1994a)	25	10				
Hopkins (1991)	5	6	8	3		
Bidzinski (1990)						
Mackenzie (1990)					18	19
Mizrahi (1990)	10	12				
Walczak (1990)	45	55	59	41		
Cutfield (1987)	17	9	11	15		
Drake (1987)			8	3	3	7
King (1986)			12	11		
Meyer (1986)	27	23	29	21		
Carey (1985)			11	13	3	12
Delgado-Escueta (1985)	5	10	12	3	1	12

Evidence Table 161. Complications due to surgery reported in studies of temporal lobe surgery

Reference	N	Number of Patients with a Serious Permanent Complication	Percentage of Permanent Complications	List of Permanent Complications [a]	Number of Patients with a Mild or Transient Complication	Percentage of Transient Complications	List of Transient Complications [a]
Boling (2001)	18	0	0.00		1	5.56	Scalp wound infection (1)
Schramm (2001)	61	0	0.00		3	4.92	Meningitis (2), Dysphasia (1)
Sotero de Menezes (2001)	15	1	6.67	Hemiparesis (1)	3	20.00	4th cranial nerve palsy (1), Speech delay (1), Attention-deficit disorder (1)
Wiebe (2001)	36	2	5.56	Sensory abnormality of the thigh due to a small thalamic infarct (1)	1	2.78	Wound infection (1)
Iannelli (2000)	37	1	2.70	Hemiparesis (1)	2	5.41	Skin flap infection (1), Dysphasia (1)
Rao (2000)	164	1	0.61	Hemiplegia due to injury to the anterior choroidal artery (1)			Complications were not reported per patient. Hemiparesis (5), Dysphasia (2), Meningitis (2), Wound infection (2), Oculomotor nerve palsy (1)
Robinson (2000)	41	2	9.09	Partial peripheral nerve palsy (1), Dysnomia (1)	6	14.6	Partial peripheral nerve palsy (2), Dysnomia (2), Facial nerve palsy (1), Dysnomia (1)
Wurm (2000)	16	1	6.25	Hemiparesis (1)	0	0.00	
Altshuler (1999)	49	5	10.20	Hemiparesis (3), Cranial nerve palsy (1), Dysplagia (1)			Not reported
Leung (1999)	11	1	9.09	Paralysis of the frontalis muscle due to facial nerve injury (1)	1	9.09	Vocal cord palsy (1)

Evidence Table 161. Complications due to surgery reported in studies of temporal lobe surgery (continued)

Reference	N	Number of Patients with a Serious Permanent Complication	Percentage of Permanent Complications	List of Permanent Complications [a]	Number of Patients with a Mild or Transient Complication	Percentage of Transient Complications	List of Transient Complications [a]
Parrent (1999)	19	0	0.00		1	5.26	Hematoma
Salanova (1999)	145	2	1.38	Hemiparesis (1), Homonymous hemianopsia (1)	1	0.69	Hemiparesis (1)
Son (1999)	71	2	2.82	Hemiparesis (2)	2	2.82	Surgical wound infection (2)
Visudhiphan (1999)	14	0	0.00		0	0.00	
Radhakrishnan (1998)	175	2	1.14	Hemiparesis (1), Dysphasia (1)			Not reported
Wyllie (1998)	72	0	0.00		2	2.78	Language disturbance after venous infraction (1), Ipsilateral superior oblique paresis (1)
Bizzi (1997)	14	1	7.14	Basal ganglia infarction (1)	3	21.43	Micrographia (1), Hemiparesis (1), Bone flap osteomyelitis (1)
Blume (1997)	14	0	0.00				Not reported
Kilpatrick (1997)	36	0	0.00		3	8.33	Mild dysphasia (3)
Adam (1996)	30	2	6.67	Upper limb deficient due to infarction (1), Hemiparesis (1)	0	0.00	
Acciarri (1995)	10	0	0.00		0	0.00	
Davies (1995)	12	1	8.33	Worsening of preoperative hemiparesis (1)	3	25.00	Persistent mild dysphasia (1), Bone flap infection (2)
Jooma (1995b)	30	2	12.50	Hemiparesis (2)			Not reported
Liu (1995)	22	2	9.09	Moderate increase in preexisting hemiparesis (2)	0	0.00	

Evidence Table 161. Complications due to surgery reported in studies of temporal lobe surgery (continued)

Reference	N	Number of Patients with a Serious Permanent Complication	Percentage of Permanent Complications	List of Permanent Complications [a]	Number of Patients with a Mild or Transient Complication	Percentage of Transient Complications	List of Transient Complications [a]
Wyler (1995)	70	3	4.29	Subgaleal cerebrospinal fluid fistula (3)	1	1.43	Nerve paresis (1)
Blume (1994)	125	1	0.80	Hemiparesis (1)	1	0.80	Hemiparesis (1)
Guldvog (1994a)	35	0	0.00		6	17.14	Minor hemiparesis (3), Minor partial facial paresis (2), Dysphasia (1)
Guldvog (1994b)	64	6	9.38	Memory deficit and Dysphasia (1), Long-term slow cerebration (1), Facial paresis and Dysphasia (1), Memory deficit and Hemiparesis (1), Hemiparesis and Hypalgesia (1), Paresis of the left arm and ataxia (1)	5	7.81	Facial paresis (4), Hemiparesis (1)
Hopkins (1991)	11	0	0.00		2	18.18	Hemiparesis, mild (2)
Bidzinski (1990)	320	2	0.63	Hemiparesis (2)			Not reported
Mackenzie (1990)	30	0	0.00		2	6.67	Mild word-finding difficulty (1), Mild hemiparesis (1)
Mizrahi (1990)	22	0	0.00		0	0.00	
Walczak (1990)	100	1	1.00	Hemiplegia (1)	9	9.00	Bone flap infection (1), Decrease spontaneous speech or anomias (7), Hemiparesis (1)
So (1989)	48	0	0.00		3	6.25	Dysphasia (2), Wound infection (1)

Evidence Table 161. Complications due to surgery reported in studies of temporal lobe surgery (continued)

Reference	N	Number of Patients with a Serious Permanent Complication	Percentage of Permanent Complications	List of Permanent Complications [a]	Number of Patients with a Mild or Transient Complication	Percentage of Transient Complications	List of Transient Complications [a]
Cutfield (1987)	26	0	0.00		1	3.85	Dysphasia (1)
Drake (1987)	16	0	0.00		4	25.00	Mild contralateral hemiparesis (3), Contralateral increase in tone only (1)
King (1986)	23	0	0.00		3	13.04	Dysphasia (3)
Meyer (1986)	50	0	0.00		6	12.00	Infected bone flaps (2), Rhinorrhea (1), Upper-extremity paresis (2), Expressive Dysphasia (1)
Carey (1985)	24	0	0.00		2	8.33	Hemiparesis, mild (1), Dysphasia (1)
Delgado-Escueta (1985)	15	1	6.67	Cerebral anoxic episode causing a drop in mental quotient (1)	2	13.33	Dysphasia and mild right arm clumsiness (1), Mild naming disorder (1)

[a] The number of patients with each specific complication is in parenthesis

Evidence Table 162. Patient characteristics for studies of temporal lobe surgery reporting surgery related mortality

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Boling (2001)	18	AH	Various (no tumors)	54		18		34.9	12.1
Schramm (2001)	61	Neocortex	Various	27.9		14.4		13.6	
Wiebe (2001)	36	Standard	Various	34.4	9.9	16.2	10		
Iannelli (2000)	37	Neocortex	Tumor	9.1	5			2.8	
Rao (2000)	164	Standard	Various	25.6				16.1	
Robinson (2000)	22	AH	Various	15.4		5.2		10.3	
Wurm (2000)	16	AH	Various	35.7					
Altshuler (1999)	49	Standard	MTS	40	5.5	11.4	8.3	17.6	4.3
Leung (1999)	11	Standard	MTS	28				17.2	
Parrent (1999)	19	AH	Not reported	34.1					
Salanova (1999)	145	Tailored	Various	30.4		10.5		19.7	
Son (1999)	71	Standard	MTS	28.9					
Visudhiphan (1999)	14	Standard	Various	13.1	3.6	6.7	3.8	6.4	4.5
Wyllie (1998)	72	Standard	Various			4.4			
Bizzi (1997)	14	Partial	Various	11.9	4.6				
Blume (1997)	14	Tailored	Various	8.5		2.6		6	
Kilpatrick (1997)	36	Standard	Various	36.8	11.5	15			
Adam (1996)	30	Standard	MTS	29		9			

Evidence Table 162. Patient characteristics for studies of temporal lobe surgery reporting surgery related mortality (continued)

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Acciarri (1995)	10	Neocortex	Vascular malformation	34.8	12.5	33.3	12.8	1.6	1.2
Berkovic (1995)	135	Partial	Various	29	10				
Davies (1995)	12	Tailored	Various	23				8	
Liu (1995)	22	Tailored	Other	37.2	13.7	17.8	9.5	19.3	8.2
Wyler (1995)	70	Standard	Various	30.9		10.5			
Blume (1994)	125	Standard	Various						
Guldvog (1994b)	64	Standard	Various					11.5	
Guldvog (1994a)	35	Standard	Various					8	
Bladin (1992)	107	Standard	Not reported						
Elwes (1991)	108	Standard	Various	23					
Hopkins (1991)	11	Standard	Various	5.5	2.2	2	1.4	3.6	2.1
Bidzinski (1990)	320	Standard	Not reported	23		8		13	
Mizrahi (1990)	22	Tailored	Various	21	8.4	5.9	2.3	15.1	8.1
Yeh (1990)	12	Neocortex	Vascular malformation	36.3	11.9	25.3	8.3	11	8.2
So (1989)	48	Tailored	Bitemporal epileptiform abnormalities	27.5					
Cutfield (1987)	26	Tailored	Various	22				12	

Evidence Table 162. Patient characteristics for studies of temporal lobe surgery reporting surgery related mortality (continued)

Reference	N	Surgery	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Drake (1987)	16	Tailored	Tumor	12.7	2.7	6.3	4.3	6.5	3.9
Meyer (1986)	50	Tailored	Not reported	15.8		7.5		8.3	
Carey (1985)	24	Standard	Various	21		10.8		14.7	

AH Amygdalohippocampectomy
MTS Mesial temporal sclerosis

Evidence Table 162. Patient characteristics for studies of temporal lobe surgery reporting surgery related mortality (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females	Number of Patients With Simple Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Boling (2001)			9	9		
Schramm (2001)	26	35	27	34	14	57
Wiebe (2001)	12	24	21	19		
Iannelli (2000)	16	21	27	10	2	21
Rao (2000)			60	59		119
Robinson (2000)	8	14	13	9		22
Wurm (2000)	3	13	7	9		
Altshuler (1999)	23	26	23	26		49
Leung (1999)	8	3	4	7		11
Parrent (1999)	7	12	10	9		
Rossi (1999)						
Salanova (1999)	71	74				
Son (1999)			45	26		
Visudhiphan (1999)	4	10	7	7		14
Wyllie (1998)						
Bizzi (1997)			11	8		
Blume (1997)	6	8	7	7	13	14
Kilpatrick (1997)	8	10	11	7		
Adam (1996)	15	15	11	19	19	30
Acciarri (1995)	5	5	5	5		10
Berkovic (1995)						
Davies (1995)						
Liu (1995)	5	7	5	7	0	12
Wyler (1995)	23	47	37	33		

Evidence Table 162. Patient characteristics for studies of temporal lobe surgery reporting surgery related mortality (continued)

Reference	Right Side Surgeries	Left Side Surgeries	Number of Males	Number of Females	Number of Patients With Simple Partial Seizures	Number of Patients With Secondarily Generalized Seizures
Blume (1994)			64	61		125
Guldvog (1994b)						
Guldvog (1994a)	25	10				
Bladin (1992)	62	48	46	64		
Elwes (1991)	53	49	54	48		
Hopkins (1991)	5	6	8	3		11
Bidzinski (1990)						
Mizrahi (1990)	10	12				
Yeh (1990)	3	9	8	4	3	9
Cutfield (1987)	17	9	11	15		26
Drake (1987)			8	3	3	11
Meyer (1986)	27	23	29	21		
Carey (1985)			11	13	3	20

Evidence Table 163. Corpus callosotomy studies excluded from the evidence base for seizure frequency outcomes

Reference	N	Reason for Exclusion
Pinard (1999)	14	Patients with West Syndrome are different from the patients in the other studies of corpus callosotomy because of the spasms that are characteristic of this syndrome. The main measure of surgical success for these patients is a reduction in spasms and is not comparable to the seizure-free and seizure frequency reduction outcome measurements reported in the other studies in the evidence base.

Evidence Table 164. Patient characteristics in studies of corpus callosotomy reporting seizure frequency outcomes

Reference	N	Pathology	Mean Age at Treatment (Years)	SD of Age at Treatment (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Duration of Condition Before Treatment (Years)	SD of Duration Before Treatment (Years)
Kwan (2001)	61	Lennox-Gastaut	7.9					
Maehara (2001)	52		18		5.1		12.9	
Matsuzaka (1999)	22		19		5.6		13.3	
McInerney (1999)	47		13.6		3.8		9.8	
Sakas (1996)	20		25.7	1.4	8.8	1.4		
Claverie (1995)	20		22.8	9.7				
Reutens (1993)	64		20		5.2		14.8	
Marino (1990)	28		21.4	10.1	6.5	5.7	14.9	8.2
Murro (1988)	25		25.8	11.8	6.2	3.6	19.6	11.3
Purves (1988)	24		25.9	10.9	6.3	6.8	19.6	10.2
Spencer (1988)	22		20.5	6.6	5.6	3.8	14.9	7
Gates (1987)	24							

Evidence Table 164. Patient characteristics in studies of corpus callosotomy reporting seizure frequency outcomes (continued)

Reference	N	Males	Females	Simple Partial Seizures	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Kwan (2001)	61	47	14				
Maehara (2001)	52	34	18	24	5		52
Matsuzaka (1999)	22			9	7		17
McInerney (1999)	47	28	19	18	19		47
Sakas (1996)	20	14	6		8		20
Claverie (1995)	20						
Reutens (1993)	64	38	26	14	20		64
Marino (1990)	28			25	23		25
Murro (1988)	25	7	6	1	5		10
Purves (1988)	24	12	12	8	19	5	12
Spencer (1988)	22	17	5	13	21		22
Gates (1987)	24	15	7	1	19	22	22

Evidence Table 165. Studies of corpus callosotomy reporting a percentage reduction in seizure frequency

Reference	N	Type of Seizure Evaluated	Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients				
						90% or Greater Reduction	75% to 90% Reduction	50% to 75% Reduction	Less than 50% Reduction	No Change or Worse
Kwan (2001)	61	All seizure types		2		11	0	27	7	16
Maehara (2001)	52	Disabling generalized seizures	3.3	2	6.8	32				
Matsuzaka (1999)	22	Most disabling seizures	4.8	2.1	8.4	4	10	3	5	0
McInerney (1999)	43	Most disabling seizures	12.3	2	27	13	11	6	3	10
Sakas (1996)	20	Drop attacks and generalized tonic-clonic seizures	6.7			6	0	10	0	4
Claverie (1995)	15	All seizure types	4.5	2	10	4	1	2	2	6
Reutens (1993)	27	All seizure types		2				14	13	
Marino (1990)	28	All seizure types	8.7	4	11	22	3	2	0	1
Murro (1988)	13	All seizure types	3.1	2.3	5.6	3	4	2	1	3
Purves (1988)	24	All seizure types	5.1	2	11		17			3
Spencer (1988)	22	All seizure types	2			2	5	5	7	3
Gates (1987)	22	All seizure types	3.7	2.1	6.6	8	3	5	5	1

Evidence Table 166. Studies of corpus callosotomy reporting a 90% or greater reduction in frequency of all seizure types

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients With a 90% or Greater Reduction in Seizure Frequency	Percentage	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Kwan (2001)	61		2		11	18.0	0.88	0.52—1.23	0.000001	-0.46
Claverie (1995)	15	4.5	2	10	4	26.7	1.09	0.37—1.80	0.002957	0.43
Murro (1988)	13	3.1	2.3	5.6	3	23.1	1.00	0.23—1.77	0.010616	0.17
Spencer (1988)	22		2		2	9.1	0.61	0.02—1.20	0.042193	-1.18
Gates (1987)	22	3.7	2.1	6.6	8	36.4	1.29	0.70—1.89	0.000018	1.29

Evidence Table 167. Studies of corpus callosotomy reporting patients who received no benefit from surgery

Patients' seizure frequencies were unchanged or become worse; all seizure types were considered

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	No Change or Worse	Percentage	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Kwan (2001)	61		2		16	26.2	1.08	0.72—1.43	<0.000001	1.67
Claverie (1995)	15	4.5	2	10	6	40.0	1.37	0.65—2.09	0.000177	1.55
Marino (1990)	28	8.7	4	11	1	3.6	0.38	-0.14—0.90	0.154803	-1.82
Murro (1988)	13	3.1	2.3	5.6	3	23.1	1.00	0.23—1.77	0.010616	0.46
Purves (1988)	24	5.1	2	11	3	12.5	0.72	0.16—1.29	0.012293	-0.39
Spencer (1988)	22		2		3	13.6	0.76	0.17—1.35	0.012112	-0.25
Gates (1987)	22	3.7	2.1	6.6	1	4.5	0.43	-0.16—1.02	0.154113	-1.41

Evidence Table 168. Studies of corpus callosotomy reporting patients as completely seizure-free

Reference	Number of Patients Evaluated	Type of Seizure Evaluated	Mean Followup Period in Years	Minimum Followup	Maximum Followup	Patients Completely Seizure-Free (No Auras)	Percentage
Marino (1990)	28	All seizure types	8.7	4	11	1	3.6
Murro (1988)	13	All seizure types	3.1	2.3	5.6	0	0.0
Spencer (1988)	22	All seizure types		2		1	4.5
Gates (1987)	22	All seizure types	3.7	2.1	6.6	3	13.6

Evidence Table 169. Studies of corpus callosotomy reporting pre- and postsurgery seizure frequency [a]

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Pre-surgery Seizure Frequency		Post-surgery Seizure Frequency		Results of Paired t-test [b]		
					Mean	SD	Mean	SD	t	df	p value
Murro (1988)	13	3.1	2.3	5.6	110	164.6	20	35	2.0	12	0.065
Spencer (1988)	22		2		159	210	78	130	2.7	21	0.014
Gates (1987)	22	3.7	2.1	6.6	178.3	273.6	40	49	2.6	21	0.015

[a] Seizure frequency is presented as seizures per month
[b] Calculated by ECRI

Evidence Table 170. Studies of corpus callosotomy reporting relationships between patient or study characteristics and treatment outcome

Reference	N	Seizure Outcome Measurement	Statistical Method	Patient Characteristics Examined		
				Age at Treatment	Age at Seizure Onset	Other Study Variables
Kwan (2001)	61	Seizure-free or seizure reduction by more than 50% of all seizure types	Univariate			Bisynchronous anterior-dominant epileptiform discharges vs. posterior-dominant epileptiform discharges (NS)
Maehara (2001)	52	90% reduction in frequency of disabling generalized seizures	Multiple regression			Total callosotomy was independently predictive of satisfactory reduction in drop attacks and disabling generalized seizures (Sig.)
Sakas (1996)	20	Completely free of drop attacks and generalized tonic-clonic seizures or significantly improved	Univariate	NS	Sig. Younger age of onset showed better improvement	Extent of resection (NS), Pre-operative electroencephalographic patterns (NS), Neuro-imaging finding (NS)
Spencer (1988)	22	Seizure-free with auras	Univariate		NS	Full scale IQ scores less than 45 were associated with poor outcome (Sig.), Hemiparetic patients vs. normal physical examine (NS)

NS Not statistically significant
Sig. Statistically significant according to the authors

Evidence Table 171. Studies of corpus callosotomy reporting individual patient age at surgery

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation [a]	95% Confidence Interval		Standardized Residuals for Effect Sizes
				Lower	Upper	
Claverie (1995)	15	90% reduction in seizure frequency	-0.18	-0.63	0.37	-1.19
Nordgren (1991)	18	80% reduction in seizure frequency	0.17	-0.32	0.59	0.13
Marino (1990)	28	90% reduction in seizure frequency	0.20	-0.18	0.54	0.38
Murro (1988)	13	90% reduction in seizure frequency	-0.22	-0.69	0.38	-1.21
Purves (1988)	24	80% reduction in frequency and severity of all seizure types	0.15	-0.27	0.52	0.07
Spencer (1988)	22	Seizure-free with auras	0.39	-0.04	0.69	1.29

[a] A positive correlation coefficient indicates more successful surgeries with an older age at surgery.

Evidence Table 172. Sensitivity analysis of studies of corpus callosotomy reporting individual patient age at surgery

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	0.14	-0.05	0.32	0.16	4.05	0.54
Removing study with largest negative effect size [b]	0.18	-0.03	0.37	0.09	2.59	0.63
Removing study with largest positive effect size	0.13	-0.08	0.33	0.21	4.03	0.40
Removing study with smallest N	0.18	-0.03	0.37	0.09	2.59	0.63
Removing study with largest N	0.14	-0.08	0.34	0.22	4.04	0.40

[a] A positive correlation coefficient indicates more successful surgeries with an older age at surgery.
[b] The study with the largest negative effect size had the smallest N

Evidence Table 173. Studies of corpus callosotomy reporting individual patient age at seizure onset

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation [a]	95% Confidence Interval		Standardized Residuals for Effect Sizes
				Lower	Upper	
Nordgren (1991)	18	80% reduction in seizure frequency	0.26	-0.24	0.65	0.95
Marino (1990)	28	90% reduction in seizure frequency	-0.17	-0.51	0.22	-1.23
Murro (1988)	13	90% reduction in seizure frequency	0.18	-0.42	0.66	0.46
Purves (1988)	24	80% reduction in frequency and severity of all seizure types	0.16	-0.26	0.53	0.63
Spencer (1988)	22	Seizure-free with auras	-0.07	-0.48	0.36	-0.53

[a] A positive correlation coefficient indicates more successful surgeries with an older age at seizure onset.

Evidence Table 174. Sensitivity analysis of studies of corpus callosotomy reporting individual patient age at seizure onset

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	0.04	-0.16	0.24	0.70	2.55	0.64
Removing study with largest negative effect size [b]	0.12	-0.12	0.35	0.33	1.05	0.79
Removing study with largest positive effect size	0.00	-0.23	0.22	0.97	1.65	0.65
Removing study with smallest N	0.02	-0.19	0.24	0.83	2.34	0.51
Removing study with largest N	0.12	-0.12	0.35	0.33	1.05	0.79

[a] A positive correlation coefficient indicates more successful surgeries with an older age at seizure onset.
[b] The study with the largest negative effect size also had the largest N.

Evidence Table 175. Studies of corpus callosotomy reporting individual patient duration of epilepsy prior to surgery

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation [a]	95% Confidence Interval		Standardized Residuals for Effect Sizes
				Lower	Upper	
Nordgren (1991)	18	80% reduction in seizure frequency	-0.14	-0.57	0.35	-1.25
Marino (1990)	28	90% reduction in seizure frequency	0.36	-0.01	0.65	1.35
Murro (1988)	13	90% reduction in seizure frequency	-0.28	-0.72	0.32	-1.49
Purves (1988)	24	80% reduction in frequency and severity of all seizure types	0.06	-0.36	0.45	-0.51
Spencer (1988)	22	Seizure-free with auras	0.40	-0.02	0.70	1.34

[a] A positive correlation coefficient indicates more successful surgeries with a longer duration of epilepsy prior to surgery.

Evidence Table 176. Sensitivity analysis of studies of corpus callosotomy reporting individual patient duration of epilepsy prior to surgery

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	0.15	-0.05	0.34	0.15	6.21	0.18
Removing study with largest negative effect size [b]	0.21	-0.01	0.40	0.06	3.98	0.26
Removing study with largest positive effect size	0.08	-0.15	0.30	0.50	4.41	0.22
Removing study with smallest N	0.21	-0.01	0.40	0.06	3.98	0.26
Removing study with largest N	0.06	-0.18	0.30	0.60	4.40	0.22

[a] A positive correlation coefficient indicates more successful surgeries with a longer duration of epilepsy prior to surgery.
[b] The study with the largest negative effect size also had the smallest N.

Evidence Table 177. Studies of corpus callosotomy reporting patients who were free of their most disabling seizures

Reference	N	Type of Seizures Evaluated	Followup Period in Years	Minimum Followup	Maximum Followup	Number of Patients Free of Disabling Seizures	Percentage	Cohen's h Effect Size	95% Confidence Interval
Matsuzaka (1999)	22	Most disabling seizures	4.8	2.1	8.4	4	18.2	0.88	0.29—1.47
McInerney (1999)	43	Most disabling seizures	12.3	2	27	13	30.2	1.16	0.74—1.59
Sakas (1996)	20	Drop attacks and generalized tonic-clonic seizures	6.7	2		4	20.0	0.93	0.31—1.55
Marino (1990)	23	Drop attacks and generalized tonic-clonic seizures	8.7	4	11	7	30.4	1.17	0.59—1.75
Murro (1988)	13	Tonic, Atonic, Tonic-clonic, Complex partial	3.1	2.3	5.6	1	7.7	0.56	-0.21—1.33
Spencer (1988)	22	Tonic, Atonic, Tonic-clonic, Complex partial		2		9	40.9	1.39	0.80—1.98
Gates (1987)	22	Tonic, Atonic, Tonic-clonic, Complex partial	3.7	2.1	6.6	6	27.3	1.10	0.51—1.69

Evidence Table 178. Studies of corpus callosotomy reporting patients who were free of generalized tonic-clonic seizures.

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Patients with Generalized Tonic-Clonic Seizures			Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
					N	Free	% Free				
Kwan (2001)	61		2		23	3	13.0	0.74	0.16—1.32	0.012206	-2.04
Maehara (2001)	52	3.3	2	6.8	16	2	12.5	0.72	0.03—1.42	0.040934	-1.71
McInerney (1999)	43	12.3	2	27	35	10	28.6	1.13	0.66—1.60	0.000002	-0.80
Sakas (1996)	20	6.7			18	6	33.3	1.23	0.58—1.88	0.000222	-0.21
Marino (1990)	28	8.7	4	11	21	11	52.4	1.62	1.01—2.22	<0.000001	1.12
Murro (1988)	13	3.1	2.3	5.6	10	1	10.0	0.64	-0.23—1.52	0.150175	-1.51
Spencer (1988)	22		2		21	16	76.2	2.12	1.52—2.73	<0.000001	2.87
Gates (1987)	22	3.7	2.1	6.6	15	11	73.3	2.06	1.34—2.77	<0.000001	2.19

Evidence Table 179. Studies of corpus callosotomy reporting patients who were free of generalized tonic-clonic seizures – data used in meta-regression

Reference	Number of Patients	Cohen's h Effect Size	Weight	Year Study Started	Year Study Ended	Conducted in the United States	Mean Age at Surgery
Kwan (2001)	61	0.74	11.50	1989	1996	No	7.9
Maehara (2001)	52	0.72	8.00	1991	1998	No	18
McInerney (1999)	43	1.13	17.50	1972	1999	Yes	13.6
Sakas (1996)	20	1.23	9.00	1984	1993	No	25.7
Marino (1990)	28	1.62	10.50	1978	1985	No	21.4
Murro (1988)	13	0.64	5.00	1980	1986	Yes	25.8
Spencer (1988)	22	2.12	10.50	1979	1983	Yes	20.5
Gates (1987)	22	2.06	7.50	1979	1985	Yes	19

Evidence Table 180. Results of the meta-regression for studies of corpus callosotomy reporting patients who were free of generalized tonic-clonic seizures after surgery

One predictor variables Bolded = statistically significant coefficient						
Covariate	**Intercept (CI)**	**P (intercept) =**	**Coefficient (CI)**	**P (coefficient)**	**Q_e =**	**P (Q_e) =**
Start year (centered)	**1.265 (1.043 to 1.487)**	**<0.000001**	**-0.033 (-0.068 to 0.0009)**	**0.055932**	**17.7957**	**0.006764**
End year (centered)	**1.359 (1.136 to 1.582)**	**<0.000001**	**-0.060 (-0.094 to -0.026)**	**0.000563**	**9.554118**	**0.144729**
United States (USA = 0)	**1.497 (1.189 to 1.805)**	**<0.000001**	**-0.411 (-0.85 to 0.027)**	**0.066393**	**18.07976**	**0.006036**
Age at treatment (centered)	**1.335 (1.111 to 1.560)**	**<0.000001**	**0.034 (-0.004 to 0.072)**	**0.085921**	**18.50058**	**0.005096**
Lennox-Gastaut (all others = 0)	**1.389 (1.152 to 1.627)**	**<0.000001**	**-0.650 (-1.275 to -0.02)**	**0.041219**	**17.28277**	**0.008298**
Percentage male (centered)	1.269 (1.047 to 1.491)	<0.000001	0.029 (-0.006 to 0.065)	0.104512	18.81447	0.004489

Average N = 19.88
Average start year: 1981.5
Average end year: 1990.63
Average age at treatment: 18.987
Average percentage male: 68.106

Evidence Table 180. Results of the meta-regression for studies of corpus callosotomy reporting patients who were free of generalized tonic-clonic seizures after surgery (continued)

Two predictor variables									
Covariate: B_1	**Covariate: B_2**	**Intercept (95% CI's)**	**P (intercept) =**	**Coefficient B_1 (95% CI's)**	**P (B_1) =**	**Coefficient B_2 (95% CI's)**	**P(B_2)**	**Q_e =**	**P (Q_e) =**
End year (centered)	Start year (centered)	1.332 (1.106 to 1.557)	<0.001	-0.058 (-0.092 to -0.023)	0.001	-0.028 (-0.063 to 0.007)	0.112	7.028	0.219
End year (centered)	United States (USA = 0)	1.499 (1.191 to 1.807)	<0.001	-0.057 (-0.092 to -0.022)	0.001	-0.292 (-0.738 to 0.153)	0.198	7.9	0.162
End year (centered)	Age at treatment (centered)	1.353 (1.128 to 1.578)	<0.001	-0.066 (-0.109 to -0.023)	0.003	-0.01 (-0.059 to 0.038)	0.673	9.376	0.095
End year (centered)	Lennox-Gastaut (all others= 0)	1.408 (1.17 to 1.646)	<0.001	-0.055 (-0.091 to -0.019)	0.003	-0.374 (-1.025 to 0.276)	0.26	8.283	0.141
End year (centered)	Percentage male (centered)	1.338 (1.112 to 1.564)	<0.001	-0.058 (-0.092 to -0.023)	0.001	0.02 (-0.016 to 0.057)	0.269	8.332	0.139

Evidence Table 181. Studies of corpus callosotomy reporting patients who became free of atonic seizures after surgery

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Patients with Atonic Seizures			Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
					N	Free	% Free				
Kwan (2001)	61		2		11	6	54.5	1.66	0.83—2.50	0.000097	-0.35
Maehara (2001)	52	3.3	2	6.8	52	42	80.8	2.23	1.85—2.62	<0.000001	2.71
McInerney (1999)	43	12.3	2	27	30	17	56.7	1.70	1.20—2.21	<0.000001	-0.44
Sakas (1996)	20	6.7			13	7	53.8	1.65	0.88—2.42	0.000027	-0.42
Marino (1990)	28	8.7	4	11	18	9	50.0	1.57	0.92—2.22	0.000002	-0.76
Gates (1987)	22	3.7	2.1	6.6	22	8	36.4	1.29	0.70—1.89	0.000018	-1.84

Evidence Table 182. Studies of corpus callosotomy reporting employment data

Reference	Number of Patients	Followup in Years	Number of Patients Not Able to Obtain Employment Prior to Surgery	Number of Patients Able to Obtain Employment or Begin Training After Surgery	Number of Patients With a 50% or Better Reduction in Drop Attacks and Generalized Tonic-Clonic Seizures
Sakas (1996)	20	6.7	20	16	16

Patients in this study were between the ages of 15 and 37 years and no patients had regular employment or training prior to surgery. After surgery, 7 patients had full-time employment and 9 were in training.

Evidence Table 183. Studies of corpus callosotomy reporting changes in IQ

Reference	Number of Patients	Number of Patient With a Decrease in IQ	Number of Patient With an Increase in IQ	Baseline IQ		IQ After Surgery	
				Mean	SD	Mean	SD
Cohen (1991)	10	1	2	43	18	42	19

All patients were 18 years old or younger. The authors concluded that a majority of patients did not appear to experience any significant change in cognitive functioning.

Evidence Table 184. Patient characteristics from studies of corpus callosotomy reporting complications due to surgery

Reference	N	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration Before Surgery (Years)
Hodaie (2001)	17		10.5					
Maehara (2001)	52		18		5.1		12.9	
Fandino-Franky (2000)	97		14					
Pinard (1999)	17	West Syndrome	6.9	3.5	0.5	0.3	6.4	3.5
Carmant (1998)	28		13.8	6.5				
Sorenson (1997)	23		16.6		5.5		12.2	1.5
Andersen (1996)	20		20.8					
Rossi (1996)	20		23				15	
Sakas (1996)	20		25.7	1.4	8.8	1.4		
Reutens (1993)	64		20		5.2		14.8	
Fuiks (1991)	80		18.3		5.3			
Nordgren (1991)	18		13.1	3.2	3.6	3.5	9.1	3.9
Oguni (1991)	43		23.5				18.8	
Marino (1990)	28		21.4	10.1	6.5	5.7	14.9	8.2
Provinciali (1990)	15		26.2	7.6				
Sass (1990)	32		24	6.6	7.4	5	16.7	8.3
Murro (1988)	25		25.8	11.8	6.2	3.6	19.6	11.3
Purves (1988)	24		25.9	10.9	6.3	6.8	19.6	10.2
Garcia-Flores (1987)	14		17.8	9	6.5	8.8		
Gates (1987)	24							

Evidence Table 184. Patient characteristics from studies of corpus callosotomy reporting complications due to surgery (continued)

Reference	Males	Females	Simple Partial Seizures	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Hodaie (2001)	8	9				
Maehara (2001)	34	18	24	5		52
Fandino-Franky (2000)	59	38				
Pinard (1999)						
Carmant (1998)						
Sorenson (1997)						
Andersen (1996)	13	7				
Rossi (1996)	14	6	9	13		20
Sakas (1996)	14	6		8		20
Reutens (1993)	38	26	14	20		64
Fuiks (1991)	44	36		9		69
Nordgren (1991)	11	7	13	8	8	16
Oguni (1991)	20	23	5	8	24	43
Marino (1990)			25	23		25
Provinciali (1990)	9	6				
Sass (1990)	21	11			32	
Murro (1988)	7	6	1	5		10
Purves (1988)	12	12	8	19	5	12
Garcia-Flores (1987)			3	3	3	6
Gates (1987)	15	7	1	19	22	22

Evidence Table 185. Studies of corpus callosotomy reporting complications – list of complications

Reference	N	Years	Country	Number of Patients with a Serious Permanent Complication	List of Permanent Complications	Number of Patients with a Mild or Transient Complication	List of Transient Complications
Hodaie (2001)	17	1992-1999	Canada	0		2	Wound infection (2)
Maehara (2001)	52	1991-1998	Japan	0		17	Acute epidural hematoma without neurological deficit (1), Akinetic state (14), Marked disconnect syndrome (2)
Fandino-Franky (2000)	97	1989-1997	Colombia	0		12	Leg weakness (10), Mutism (2)
Pinard (1999)	17	1989-1995	France	2	Deteriorated language (2)	0	
Carmant (1998)	28	1989-1993	United States	0		3	Acute disconnection problems (3)
Sorenson (1997)	23	1991-1994	United States	1	Right frontal infarction related to venous thrombosis (1)	13	Complications were not identified per patient. Meningitis (3), Diabetes insipidus (1), Postoperative disconnection syndrome (13)
Andersen (1996)	20	1988-1994	Denmark	7	Seven patients had persistent interhemispheric disconnection syndrome with the following symptoms: Mild hemiapraxia (3), Severe cognitive and neurologic sequelae (language impairment, hemisphere competition, apraxia) (4)	5	Interhemispheric disconnection syndrome (5)
Rossi (1996)	20	1988-1995	Italy	1	Mild leg weakness (1)	12	Mutism (8), Mild hemiparesis (2), Dysarthria (2)
Sakas (1996)	20	1984-1993	Ireland	0		7	Hemiparesis (3), Disconnection syndrome (3), Hemiparesis and Akinetism (1)

Evidence Table 185. Studies of corpus callosotomy reporting complications – list of complications (continued)

Reference	N	Years	Country	Number of Patients with a Serious Permanent Complication	List of Permanent Complications	Number of Patients with a Mild or Transient Complication	List of Transient Complications
Reutens (1993)	64	1973-1991	Australia	4	Hemiparesis (2), Persistent disturbance in behavior (2)		Complications were not identified per patient. Meningitis (4), Wound infections (4), Extradural hematoma (1), Hemiparesis (13), Akinesia or mutism (20), Postoperative aggression (6), Persistent mild disconnection syndrome (1)
Fuiks (1991)	80	1985-1990	United States	0		5	Subdural hemotoma (1), Deep wound infection (1), Left hemiparesis (1), Epidural hematoma (2)
Nordgren (1991)	18	1972-1987	United States	1	Hemiparesis worsened (1)	3	Aseptic meningitis (2), hydrocephalus and shut (1)
Oguni (1991)	43	1981-1989	Canada	0		16	Epidural hematoma with hemiparesis (1), Cranial infection (1), Collection of blood between the galea and bone flap (1), Contralateral weakness of the leg (2), Decreased output of speech (4), Minor confusional state (3), Mild fever (2), Drowsiness (2)
Marino (1990)	28	1978-1985	Brazil	1	Hemiplegia (1)	1	Meningitis (1)
Provinciali (1990)	15	1987-1988	Italy	0		8	Broncho-pneumonia (1), Meningitis (1), Deficit in naming objects held in the left hand (1), Hemiparesis (1), Arachnoiditis (1), Apraxia and/or slight paresis of left arm (3)
Sass (1990)	32	1985-1987	United States	4	Clinically significant language impairments (4)	1	Venous hemorrhagic infarction (1)
Murro (1988)	25	1980-1986	United States	0		6	Intracranial hemorrhage (2), Wound infection (2), Bone flap infection (1), Mild hemiparesis (1)

Evidence Table 185. Studies of corpus callosotomy reporting complications – list of complications (continued)

Reference	N	Years	Country	Number of Patients with a Serious Permanent Complication	List of Permanent Complications	Number of Patients with a Mild or Transient Complication	List of Transient Complications
Purves (1988)	24	1977-1987	Canada	0		11	Reduced speech output and left hemiparesis (7), Subdural hematoma (2), Meningitis and abscess (1), Diabetes insipidus (1)
Garcia-Flores (1987)	14	1980-1986	Mexico	0		1	Hemiparesis (1)
Gates (1987)	24	1979-1985	United States	3	Stuttering disorders (2), Lower extremity weakness resulting from cerebral infarction (1)	4	Hematomas (2), Steroid-dependent cerebral edema (1), Bone flap infection (1)

Evidence Table 186. Patient characteristics from studies of frontal lobe surgery reporting seizure outcome measurements

Reference	N	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Epilepsy Before Surgery (Years)
Ferrier (2001)	35		17.3	8.5	6.2	4.1	11.1	7.2
Siegel (2001)	14	Various	31.3		12.2		19.2	
Hong (2000)	18	Cortical dysplasia	18.3	9.8	5.6	4.1	12.6	7.4
Eriksson (1999)	12	Various	34		14		18	
	13	Various	9.9		1.5		5.5	
Wennberg (1999)	22	Foreign tissue lesion	23.2	12.8				
Swartz (1998)	19	Various	31.3	12.3	17.8	13.3	13.5	9.7
Cappabianca (1997)	13		28.8					
Smith (1997)	53	Various						
Acciarri (1995)	13	Vascular malformation	31.7	14.4	27.7	10.2	4	5
Adler (1991)	14	Various	12.2		3		7.8	
Garcia Sola (1991)	18	Various	18.7					
Palmini (1991)	12	Neuronal migration disorder	17.5				11.9	
Rasmussen (1991)	283	Non-tumoral lesion						

Evidence Table 186. Patient characteristics from studies of frontal lobe surgery reporting seizure outcome measurements (continued)

Reference	Right Side Surgery	Left Side Surgery	Males	Females	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Ferrier (2001)							
Siegel (2001)							
Hong (2000)	3	8	7	4			
Eriksson (1999)	Adults		6	6			
	Children		6	7			
Wennberg (1999)	10	9					
Swartz (1998)	6	7					
Cappabianca (1997)							
Smith (1997)							
Acciarri (1995)	3	8	7	4	1	2	8
Adler (1991)	11	3	8	6			
Garcia Sola (1991)							
Palmini (1991)							
Rasmussen (1991)							

Evidence Table 187. Studies of frontal lobe surgery reporting seizure-free undefined

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Patients Seizure Free Undefined	Percentage	Cohen's h Effect Sizes	95% Confidence Interval	p Values for Effect Sizes	Standardized Residuals for Effect Sizes
Ferrier (2001)	35	6	2	19.5	21	60.0	1.77	1.30—2.24	<0.000001	2.26
Cappabianca (1997)	13		2		11	84.6	2.34	1.57—3.10	<0.000001	2.80
Smith (1997)	24		2		15	62.5	1.82	1.26—2.39	<0.000001	2.03
Acciarri (1995)	11	6.7	2	13	11	100.0	3.14	2.31—3.98	<0.000001	4.48
Garcia Sola (1991)	18	9	5	12.5	6	33.3	1.23	0.58—1.88	0.000222	-0.08
Rasmussen (1991)	283	16	2	49	68	24.0	1.02	0.86—1.19	<0.000001	-5.40

Evidence Table 188. Studies of frontal lobe surgery reporting patients who were seizure-free undefined – data used in meta-regression

Reference	N	Cohen's h Effect Size	Weight	Year Study Started	Year Study Ended	Conducted in the United States	Vascular Malformation Patients Only
Ferrier (2001)	35	1.77	17.5	1975	1996	No	No
Cappabianca (1997)	13	2.34	6.5	1985	1994	No	No
Smith (1997)	24	1.82	12	1995	1997	Yes	No
Acciarri (1995)	11	3.14	5.5	1975	1992	No	Yes
Garcia Sola (1991)	18	1.23	9	1978	1990	No	No
Rasmussen (1991)	283	1.02	141.5	1928	1980	No	No

Evidence Table 189. Results of the meta-regression for studies of frontal lobe surgery reporting patients who were seizure-free undefined

One predictor variable Bolded = statistically significant coefficient						
Covariate	**Intercept (CI)**	**P (intercept) =**	**Coefficient (CI)**	**P (coefficient)**	**Q_e =**	**P (Q_e) =**
Start year (centered)	**1.743 (1.514 to 1.973)**	**<0.000001**	**0.015 (0.010 to 0.0218)**	**<0.000001**	**15.33792**	**0.004049**
End year (centered)	**1.711 (1.492 to 1.930)**	**<0.000001**	**0.059 (0.037 to 0.080)**	**<0.000001**	**14.93439**	**0.004839**
United States (USA = 0)	**1.823 (1.257 to 2.389)**	**<0.000001**	**-0.603 (-1.188 to -0.019)**	**0.042828**	**39.13536**	**<0.000001**
Tumor (all others=0)	**3.141 (2.305 to 3.977)**	**<0.000001**	**-1.939 (-2.787 to -1.091)**	**0.000007**	**23.13496**	**0.000119**

Two predictor variables									
Covariate: B_1	**Covariate: B_2**	**Intercept (CI)**	**P (intercept)**	**Coefficient B_1 (CI)**	**P (B_1) =**	**Coefficient B_2 (CI)**	**P(B_2)**	**Q_e =**	**P (Q_e) =**
Start year (centered)	End year (centered)	1.726 (1.492 to 1.961)	<0.001	0.005 (-0.024 to 0.035)	0.725	0.04 (-0.068 to 0.148)	0.468	14.81	0.002
Start year (centered)	United States (USA = 0)	1.412 (0.824 to 2)	<0.001	0.018 (0.011 to 0.026)	<0.001	0.436 (-0.275 to 1.147)	0.23	13.894	0.003
Start year (centered)	Tumor (all others=0)	3.11 (2.274 to 3.946)	<0.001	0.013 (0.007 to 0.02)	<0.001	-1.483 (-2.356 to -0.611)	0.001	4.239	0.237
End year (centered)	USA (USA = 0)	1.466 (0.883 to 2.049)	<0.001	0.065 (0.04 to 0.091)	<0.001	0.312 (-0.374 to 0.998)	0.373	14.14	0.003
End year (centered)	Tumor (all others=0)	3.116 (2.28 to 3.952)	<0.001	0.051 (0.028 to 0.073)	<0.001	-1.513 (-2.381 to -0.644)	0.001	3.278	0.351
United States (USA = 0)	Tumor (all others=0)	3.806 (2.786 to 4.826)	<0.001	-0.664 (-1.249 to -0.079)	0.026	-1.983 (-2.831 to -1.134)	<0.001	18.178	<0.001

Average N = 64
Average year started = 1972.67
Average year ended = 1991.5

Evidence Table 190. Studies of frontal lobe surgery reporting patients with seizure-free outcomes

Reference	Number of Patients	Followup Period in Years	Minimum Followup	Maximum Followup	Seizure Free Outcome	Number of Patients with Outcome	Percentage
Siegel (2001)	14		2		Engel Class I	8	57.1
Hong (2000)	11	3.5	2.1	4.7	Engel Class I	6	54.5
Eriksson (1999)	12 - adults	2			Seizure-free with auras	3	25.0
	13 - children					4	30.8
Wennberg (1999)	19	6.5	2	17	Engel Class I	11	57.9
Swartz (1998)	14	4.1	2	9	Seizure-free with no auras	8	57.1
Adler (1991)	14	8.2	3.6	19	Seizure-free with no auras	8	57.1
Palmini (1991)	12	5.8	2	15	Seizure-free with auras	2	16.7

Evidence Table 191. Studies of frontal lobe surgery reporting relationships between patient or study characteristics and treatment outcome

Reference	N	Seizure Outcome Measurement	Statistical Method	Patient or Study Characteristic Examined				
				Age at Treatment	Age at Seizure Onset	Duration of Epilepsy Prior to Treatment	Length of Followup	Other Study Variables
Ferrier (2001)	35	Seizure-free with auras	Univariate					Abolition of seizure patterns (Sig.), Abolition of sporadic spikes or their presence in the postsurgery electrocorticograms (NS), Location of residual sporadic discharges (NS), Incomplete removal of abnormal tissue (NS)
Smith (1997)	53	Seizure-free (undefined)	Univariate	NS	NS	NS	NS	Seizure frequency (NS), Completeness of lesion resection (NS), Lesional cases had better outcomes than nonlesional cases (Sig.)

Sig. Statistically significant
NS Not statistically significant

Evidence Table 192. Patient characteristics from studies of frontal lobe surgery reporting complications due to surgery

Reference	N	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration of Epilepsy Before Surgery (Years)
Kral (2001)	32	Various	10.8		4.6		6.1	
Mosewich (2000)	68		28.5	12.4	12.1	9.9	16.5	10.6
Chassoux (1999)	120	Various	21	8.2	9.2	7.3	11.9	7.3
Ferrier (1999)	42	Various	16.8	10.4	6.1	5.2	10.6	7.9
Helmstaedter (1998)	33	Various	29.8	10	15	11	15.2	9
Swartz (1998)	19	Various	31.3	12.3	17.8	13.3	13.5	9.7
Smith (1997)	53	Various						
Acciarri (1995)	13	Vascular malformation	31.7	14.4	27.7	10.2	4	5

Patient characteristics from studies of frontal lobe surgery reporting seizure outcome measurements (continued)

Reference	Right Side Surgery	Left Side Surgery	Males	Females	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Kral (2001)			22	10	20	12	4
Mosewich (2000)	39	29	45	23			
Chassoux (1999)	75	44	77	43			79
Ferrier (1999)			18	19		16	
Helmstaedter (1998)	16	17	21	12			
Swartz (1998)	6	7					
Smith (1997)							
Acciarri (1995)	3	8	7	4	1	2	8

Evidence Table 193. Studies of frontal lobe surgery reporting complications – list of complications

Reference	N	Years	Number of Patients with a Serious Permanent Complication	List of Permanent Complications	Number of Patients with a Mild or Transient Complication	List of Transient Complications
Kral (2001)	32	1989-2000	0			Complications were not identified per patient. Meningitis (1), Wound infection (2), Subdural hygroma (1), Weakness of the contralateral hand (3), Hemiparesis (1)
Mosewich (2000)	68	1987-1994	0		3	Mild to moderate hemiparesis (2), Mild hemiparesis and expressive dyphasia (1)
Chassoux (1999)	120	1964-1995	27	One year or more after surgery: Spastic hemiparesis or pronounced worsening of the preoperative deficit (27)	72	Minor motor deficit or a worsening of the preoperative motor deficit (19), Isolated facial paresis (6), Motor inertia (5), Hemiparesis or hemiplegia (42)
Ferrier (1999)	37	1975-1996	0		19	Complications were not identified per patient, but 18 of 37 patients had no postoperative complications. Hemiparesis (8), Mild dysphasia (2), Bone flap infection (8), CSF leak (1), Buzzing sensation in the left ear (1), Monoplegia with mild weakness (1)
Helmstaedter (1998)	33	1995-1996	0		14	Motor aphasia and paresis (3), transcortical aphasia and paresis (4), Cortical dysarthria (2) Severe psychomotor slowing (3), Anosmia (1)
Swartz (1998)	15	1986-1995	0		6	Decreased verbal fluency (2), Incontinence (1), Abulia (2), Monoparesis (1)
Smith (1997)	53		4	Disabling hemipareses (2), Diabetes insipidus (1), Steroid-induced diabetes mellitus (1)	6	Osteomyelitis (1), Epidural hematoma (1), Hemiparesis (1), Aphasia (1), Aspiration pneumonitis (1), Mild dysnomia (1)
Acciarri (1995)	11	1975-1992	0		0	

Evidence Table 194. Patient characteristics from studies of frontal lobe surgery reporting surgery related mortality

Reference	N	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration of Epilepsy Before Surgery (Years)
Kral (2001)	32	Mixed	10.8		4.6		6.1	
Smith (1997)	53	Mixed						
Acciarri (1995)	13	Vascular malformation	31.7	14.4	27.7	10.2	4	5

Patient characteristics from studies of frontal lobe surgery reporting surgery related mortality (continued)

Reference	Right Side Surgery	Left Side Surgery	Males	Females	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Kral (2001)			22	10	20	12	4
Smith (1997)							
Acciarri (1995)	3	8	7	4	1	2	8

Evidence Table 195. Patient characteristics from studies of hemispherectomy reporting seizure-free outcome measurements

Reference	N	Years	Country	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration of Epilepsy Before Surgery (Years)
Di Rocco (2000)	15	1985-1996	Italy	2.4	2.8				
Tinuper (1988)	14	1974-1987	Canada	14.5	10.2	4.7	5.6	9.8	9.5
Lindsay (1987)	17	1948-1986	England	12	2.9	5.1	2.4	7	2

Patient characteristics from studies of hemispherectomy reporting seizure-free outcome measurements (continued)

Reference	Right Side Surgery	Left Side Surgery	Males	Females	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Di Rocco (2000)	9	6	11	4			
Tinuper (1988)	6	8					
Lindsay (1987)	8	7	7	8			

Evidence Table 196. Studies of hemispherectomy reporting seizure outcome measurements

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Seizure-free With No Auras	Percentage	Seizure Free (Undefined)	Percentage
Di Rocco (2000)	15	5.5	3.5	14	6	40.0	---	---
Tinuper (1988)	14	6.9	4	13	---	---	10	71.4
Lindsay (1987)	15	14.1	2	36	---	---	9	60.0

Studies of hemispherectomy reporting seizure outcome measurements (continued)

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Engel Class I	Percentage	Engel Class IV	Percentage
Di Rocco (2000)	15	5.5	3.5	14	10	66.7	1	6.7
Tinuper (1988)	14	6.9	4	13	---	---	---	---
Lindsay (1987)	15	14.1	2	36	11	73.3	1	6.7

Evidence Table 197. Studies of hemispherectomy reporting education data

Reference	N	Mean Followup in Years	Minimum Followup	Maximum Followup	Number of Patients Going to School Prior to Surgery	Number of Patients Able to Remain at School or Obtain Employment After Surgery
Lindsay (1987)	15	14.1	2	36	1	8

Evidence Table 198. Studies of hemispherectomy reporting changes in IQ

Reference	N	Mean Followup in Years	Minimum Followup	Maximum Followup	Number of Patients with a Decrease in IQ	Number of Patients with an Increase in IQ	Baseline IQ		IQ After Surgery	
							Mean	SD	Mean	SD
Lindsay (1987)	15	14.1	2	36	2	6	59	14	66	Not reported

Evidence Table 199. Patient characteristics from studies of hemispherectomy reporting complications

Reference	N	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration of Epilepsy Before Surgery (Years)
Carreno (2001)	13						
Schramm (2001)	20	14.3	12.4	3.3	3.8	10.5	10.9
Di Rocco (2000)	15	2.4	2.8				
Shimizu (2000)	34	6.9		5.5		5.5	
Battaglia (1999)	10	1.7	1.7				
Wyllie (1998)	16			1.5			
Vining (1997)	58	6.8					
Peacock (1996)	58	4.8		0.8		3.9	
Schramm (1995)	13	12		3.7		9	
Tinuper (1988)	14	14.5	10.2	4.7	5.6	9.8	9.5
Lindsay (1987)	17	12	2.9	5.1	2.4	7	2

Evidence Table 199. Patient characteristics from studies of hemispherectomy reporting complications (continued)

Reference	Number of Patients	Right Side Surgery	Left Side Surgery	Males	Females	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Carreno (2001)	13							
Schramm (2001)	20			11	9			
Di Rocco (2000)	15	9	6	11	4			
Shimizu (2000)	34			21	13			
Battaglia (1999)	10			7	3	9	3	4
Wyllie (1998)	16							
Vining (1997)	58	32	26	18	40			
Peacock (1996)	58	25	33	31	27			
Schramm (1995)	13			11	2			
Tinuper (1988)	14	6	8					
Lindsay (1987)	17	8	7	7	8			

Evidence Table 200. Studies of hemispherectomy reporting complications – list of complications

Reference	N	Years	Country	Number of Patients with a Serious Permanent Complication	List of Permanent Complications	Number of Patients with a Mild or Transient Complication	List of Transient Complications
Carreno (2001)	13	1992-1999	United States	0		4	Bone flap infection (1), Placement of shunt for hydrocephalus (3)
Schramm (2001)	20	1991-1999	Germany	0		3	Subgaleal cerebrospinal fluid effusion (1), Meningitis (1), Deep infection (1)
Di Rocco (2000)	15	1985-1996	Italy	0		12	Five patients had more than one complication. Fever (6), Skin infection (2), Osteomyelitis and meningitis (1), Hemiparesis (2), Dystonia (2), Unilateral third cranial nerve deficit (1), Anemia (1), Hydrocephalus requiring a CSF shunt (5), Subdural hematoma (1)
Shimizu (2000)	34	1993-1999	Japan	1	Severe disability due to bilateral brain swelling (1)	5	Placement of shunts to treat CSF accumulation or hydrocephalus (5)
Battaglia (1999)	10	1987-1998	Italy	0		5	Hydrocephalus (3), Subdural hematoma (1), Hyperthermia (1)
Wyllie (1998)	16	1990-1996	United States	0		2	Deep vein thrombosis with secondary staphylococcus infection (1), Contralateral subdural hematoma (1)
Vining (1997)	58	1968-1996	United States	1	Coma (1)		Complications were not identified per patient. Severe intraoperative bleeding (8), Shunts (16), Septic meningitis (2), Bone infection (1), Deep venous thrombosis in the leg (2)
Peacock (1996)	58	1986-1995	United States	0		6	3 of 27 patients receiving a functional hemispherectomy developed hydrocephalus requiring a shunt (3), Mild cerebrospinal fluid infections treated with antibiotics (3)
Schramm (1995)	13	1992-1994	Germany	0		2	Placement of a shunt (1), Subgaleal cerebrospinal fluid effusion (1)
Tinuper (1988)	14	1974-1987	Canada	0		2	Hydrocephalus corrected with a shunt (1), Abscess in the removal cavity treated with antibiotics (1)

Evidence Table 201. Patient characteristics in studies of multiple subpial transection

Reference	N	Pathology	Mean Age at Surgery (Years)	SD of Age at Surgery (Years)	Mean Age at Seizure Onset (Years)	SD of Age at Seizure Onset (Years)	Mean Duration of Epilepsy Before Surgery (Years)	SD of Duration of Epilepsy Before Surgery (Years)
Mulligan (2001)	12		29.4		12.5		13.8	
Orbach (2001)	54							
Shimizu (2000)	31		9.3					
Smith (1998)	84							
Hufnagel (1997)	22		25.7	10.4	8.7	8.4	17	9.8
Pacia (1997)	21	Various	30.6	8.8				
Patil (1997)	19		21.7	14.1	8.3	6.9	13.3	9.4
Morrell (1995)	14	Landau-Kleffner syndrome	7	2.2	3.8	1.1	3.2	1.4
Sawhney (1995)	21		16	9.4	7	4.3	9	9.3
Shimizu (1991)	12		29					

Patient characteristics in studies of multiple subpial transection (continued)

Reference	Males	Females	Simple Partial Seizures	Complex Partial Seizures	Secondarily Generalized Seizures	Generalized Convulsive Seizures
Mulligan (2001)	4	8				
Orbach (2001)						
Shimizu (2000)	24	7				
Smith (1998)						
Hufnagel (1997)	12	10	8	14		16
Pacia (1997)	13	8				
Patil (1997)	6	13		14	16	
Morrell (1995)	4	10				
Sawhney (1995)	5	16				
Shimizu (1991)	9	3				

Evidence Table 202. Studies of multiple subpial transection reporting seizure frequency outcomes

Reference	N	Followup Period in Years	Minimum Followup	Maximum Followup	Seizure-free Outcome	Number of Patients with Outcome	Percentage
Mulligan (2001)	12	1.5	0.5	3	Seizure-free (undefined)	0	0.0
					90% reduction in seizure frequency	3	25.0
Orbach (2001)	54	4.7	2.3	7.4	Seizure-free with auras	20	37.0
					Engel Class I	20	37.0
					90% reduction in seizure frequency	20	37.0
Shimizu (2000)	25		1		Engel Class I	5	20.0
Smith (1998)	84		2		Engel Class I	42	50.0
Hufnagel (1997)	22	1.5	0.7	3.1	Seizure-free with auras	9	40.9
					90% reduction in seizure frequency	15	68.2
Pacia (1997)	21	1.8	1	2.8	Seizure-free with auras	12	57.1
					Engel Class I	12	57.1
Patil (1997)	19	2.6	1.3	4.5	Seizure-free (undefined)	5	26.3
					90% reduction in seizure frequency	17	89.5
Morrell (1995)	14	3.7	1.1	6.5	Seizure-free (undefined)	11	78.6
Sawhney (1995)	21	2.9	0.8	5	Seizure-free (undefined)	0	0.0

Evidence Table 203. Studies of multiple subpial transection reporting individual patient age at surgery

Reference	Number of Patients	Seizure Outcome Measurement	Point-Biserial Correlation [a]	95% Confidence Intervals		Standardized Residuals for Effect Sizes
				Lower	Upper	
Hufnagel (1997)	22	Seizure-free (undefined)	-0.18	-0.56	0.26	-1.63
Pacia (1997)	21	Seizure-free (undefined)	0.16	-0.29	0.55	0.08
Patil (1997)	19	Seizure-free (undefined)	0.20	-0.28	0.60	0.26
Morrell (1995)	14	Seizure-free (undefined)	0.17	-0.40	0.64	0.09
Sawhney (1995)	21	Improved	0.38	-0.06	0.70	1.25

[a] A positive correlation coefficient indicates more successful surgeries with an older age at surgery.

Evidence Table 204. Sensitivity analysis of studies of multiple subpial transection reporting individual patient age at surgery

Sensitivity Adjustment	Point-Biserial Correlation [a]	95% Confidence Interval		p Value for Summary Estimate	Q	p Value for Q
		Lower	Upper			
Original analysis	0.14	-0.07	0.34	0.196	3.33	0.504
Removing study with larest negative effect size [b]	0.24	-0.01	0.45	0.055	0.68	0.879
Removing study with largest positive effect size	0.07	-0.17	0.30	0.579	1.76	0.63
Removing study with smallest N	0.14	-0.09	0.36	0.243	3.32	0.344
Removing study with largest N	0.24	-0.01	0.45	0.055	0.68	0.879

[a] A positive correlation coefficient indicates more successful surgeries with an older age at surgery.
[b] The same study had the largest negative effect size and the largest N

Evidence Table 205. Studies of multiple subpial transection reporting successful surgery among male and female patients

Reference	N	Seizure Outcome Measurement	Number of Male Patients	Number of Male Successes	Number of Female Patients	Number of Female Successes	Cohen's h Effect Size [a]	95% Confidence Intervals		p Value for the Effect Size	Standardized Residuals for Effect Sizes
								Lower	Upper		
Hufnagel (1997)	22	Seizure-free (undefined)	12	5	10	4	0.03	-0.81	0.87	0.936876	-0.56
Pacia (1997)	21	Seizure-free (undefined)	13	7	8	5	-0.18	-1.06	0.71	0.695827	-1.05
Patil (1997)	19	Seizure-free (undefined)	6	2	13	3	0.23	-0.74	1.20	0.642986	-0.02
Morrell (1995)	14	Seizure-free (undefined)	4	4	10	7	1.16	0.00	2.32	0.050049	1.67
Sawhney (1995)	21	Improved	5	4	16	10	0.39	-0.61	1.40	0.445580	0.33

[a] A positive effect size favors male patients achieving more successful surgeries.

Evidence Table 206. Sensitivity analysis of studies of multiple subpial transection reporting successful surgery among male and female patients

Sensitivity Adjustment	Cohen's h Summary Estimate [a]	95% Confidence Interval		p value for Summary Estimate	Q	p value for Q	Back-transformed Percentage Estimate [b]	95% Confidence nterval	
		Lower	Upper					Lower	Upper
Original analysis	0.24	-0.19	0.66	0.272	3.59	0.464	1%	-1%	11%
Removing study with smallest effect size	0.37	-0.12	0.85	0.141	2.48	0.479	3%	0%	17%
Removing study with largest effect size [c]	0.10	-0.36	0.55	0.684	0.79	0.852	0%	-3%	7%
Removing study with smallest N	0.10	-0.36	0.55	0.684	0.79	0.852	0%	-3%	7%
Removing study with largest N	0.31	-0.18	0.80	0.219	3.28	0.350	2%	-1%	15%

[a] A positive summary estimate favors male patients achieving more successful surgeries.
[b] The back-transformed percentage estimate is the difference between the percentage of malr patients who achieved successful surgery and the percentage of female patients who achieved successful surgery. A positive percentage favors male patients and a negative percentage favors female patients. A difference of 0% indicates no differences between male and female patients in achieving successful surgery.
[c] The same study had the largest effect size and the smallest N

Evidence Table 207. Studies of multiple subpial transection reporting no benefit [a]

Reference	Number of Patients	Followup Period in Years	Minimum Followup	Maximum Followup	No Benefit	Percentage
Mulligan (2001)	12	1.5	0.5	3	5	41.7
Hufnagel (1997)	22	1.5	0.7	3.1	3	13.6
Pacia (1997)	21	1.8	1	2.8	1	4.8
Patil (1997)	19	2.6	1.3	4.5	0	0.0

[a] Patients had no change in seizure frequency or experienced an increase in seizure frequency after surgery

Evidence Table 208. Studies of multiple subpial transection reporting complications

Reference	N	Years	Country	Number of Patients with a Serious Permanent Complication	List of Permanent Complications	Number of Patients with a Mild or Transient Complication	List of Transient Complications
Mulligan (2001)	12	1990-1999	USA	0		0	
Shimizu (2000)	31	1983-1998	Japan	0		0	
Smith (1998)	84		USA	7	Aphasia, weakness, parietal sensory loss, worsening of a preexisting language disorder (7)	8	Eight patients experienced transient complications. Weakness (3), Cortical sensory loss (1), Dyslexia (1), Meningitis (1), Phlebitis (1), Orchitis (1), VIth cranial nerve palsy (1)
Hufnagel (1997)	22	1993-1996	Germany	4	Dysphasia (2), Global aphasia (1), Erethism and hyperkinesia (1)	10	Neurological deficits involving motor impairment (10)
Pacia (1997)	21	1992-1994	USA	1	Moderate dysphasia (1)	9	Mild higher corticosensory loss (1), Decreased left hand proprioception (1), Mild dysnomia and Dyslexia (1), Mild dysnomia (6)
Patil (1997)	19	1991-1995	USA	0		3	Hemiparesis (3)
Morrell (1995)	14	1987-1994	USA	0		2	Two small infarcts with one patient having right arm weakness (2)
Sawhney (1995)	21	1989-1993	England	2	Worsening of existing hemiplegia (2)	12	Neurological deficit (12), Arterial bleeding (1), Pulmonary embolism (1)
Shimizu (1991)	12	1989-1990	Japan	0		1	Intracerebral hematoma (1)

Evidence Table 209. Studies addressing nondrug, nonsurgery interventions

Reference	Country	Vagal-Nerve Stimulation	Ketogenic Diet	Magnetic Therapy	Vitamin B_6 Therapy	Herbal Medicine	Acupuncture	Elecrical Brain Stimulation	Chiropractic Therapy	Crainial Realignment	Hyperbaric Oxygen Therapy
Aldenkamp (2001)	Holland	✓									
Andriola (2001)		✓									
Chayasirisobhon (2001)	United States	✓									
Ergene (2001)	United States	✓									
Hoppe (2001)	Germany	✓									
Liporace (2001)		✓									
Pulsifer (2001)	United States		✓								
DeGiorgio (2000) Followup of ClinicalTrial EO5	United States	✓									
Hosain (2000)	United States	✓									
Ohtsuka (2000)	Japan					✓					
Valesco (2000a)	Mexico							✓			
Velasco (2000b)	Mexico							✓			
Ben-Menachem (1999)	Sweden	✓									
Boon (1999)	Belgium	✓									
Clinical Trial EO4 Labar (1999)	United States	✓									
Kloster (1999)	Norway						✓				
Mak (1999)			✓								
Parker (1999)	United Kingdom	✓									
Sirven (1999)	United States		✓								
Clinical Study EO5 Handforth (1998)	United States	✓									

Evidence Table 209. Table listing studies addressing each nondrug, nonsurgery intervention (continued)

Reference	Country	Vagal-Nerve Stimulation	Ketogenic Diet	Magnetic Therapy	Vitamin B_6 Therapy	Herbal Medicine	Acupuncture	Elecrical Brain Stimulation	Chiropractic Therapy	Crainial Realignment	Hyperbaric Oxygen Therapy
Freeman (1998)	United States		✓								
Lundgren (1998)	Sweden	✓									
Vining (1998)	United States		✓								
Salinski (1996) Followup of ClinicalTrial EO3	Multi-national	✓									
Tiancai (1996)	China					✓					
Clinical Trial EO3 The VNS Group (1995)	Multi-national	✓									
Nagakubo (1993)	Japan					✓					
Fisher (1992)	United States							✓			
Sramka (1990)	Russia							✓			
Ogunmekan (1989)	Canada					✓					
Schwartz (1989)			✓								
Ziyu (1987)	China						✓				
Sills (1986)			✓								
Trauner (1985)	United States		✓								
Total Number of Studies		**16**	**8**	**0**	**0**	**4**	**2**	**4**	**0**	**0**	**0**

Evidence Table 210. Articles addressing vagal nerve stimulation (VNS) excluded for quality reasons

Study	Reason for Exclusion
Liporace (2001)	This study was designed to assess the effects of making program adjustments to the VNS device on side effects without reducing the effectiveness of the device. Patient characteristics poorly described. Seizure type and severity information not presented. Followup time not presented.

Evidence Table 211. Quality of reporting in studies of vagal nerve stimulation

Reference	Sampling methodology described?	Clinical setting clearly described?	Inclusion/exclusion criteria stated?	Criteria used to categorize patients reported?	Basic demographic data for patients presented?	Information on comorbidities presented?	Information on method of data collection presented?	Analytic methods clearly described?	Information on sample size requirements presented?	Outcome data clearly presented?	Individual patient data presnted?
RCTs performed in the United States											
Clinical Study EO5 (1998)	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Clinical Trial EO3 (1995)	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Long-term followups of RCT's performed in the United States											
DiGiorgio (2000) Followup of Clinical Trial EO5	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Salinski (1996) Followup of Clinical Trial EO3	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Case-series performed in the United States											
Chayasirisobhon (2001)	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Ergene (2001)	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Hosain (2000)	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Clinical Trial EO4 Labar (1999)	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Case-series performed outside of the United States											
Aldenkamp (2001)	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No
Hoppe (2001)	No	Yes	Yes	No	No	No	NA	NA	No	Yes	No
Ben-Menachem (1999)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
Boon (1999)	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Parker (1999)	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes
Lundgren (1998)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes

Evidence Table 212. Primary characteristics of included studies on vagal nerve stimulation

Reference	Start	End	Country	N	Longitudinal Study	Number of Study Groups	Number of Treatment Arms	Cross-Over Design	If Cross-Over Design, Was Washout Period Included
Aldenkamp (2001)	NR	NR	Holland	16	Yes	1	1	No	NA
Chayasirisobhon (2001)	1998	1999	United States	24	Yes	1	1	No	NA
Ergene (2001)	NR	NR	United States	17	Yes	1	1	NA	NA
Hoppe (2001)	1998	1999	Germany	36	Yes	1	1	No	NA
DiGiorgio (2000) Follow-up of Clinical Trial EO5	1995	1996	United States	199	Yes	1	1	No	NA
Hosain (2000)	NR	NR	United States	13	Yes	1	1	No	NA
Ben-Menachem (1999)	1992	1997	Sweden	64	Yes	1	1	No	NA
Boon (1999)	1995	1999	Belgium	25	Yes	1	1	No	NA
Clinical Trial EO4 Labar (1999)	NR	NR	United States	25	Yes	1	1	No	NA
Parker (1999)	1995	1996	United Kingdom	16	Yes	1	1	No	NA
Clinical Study EO5 Handforth (1999)	1995	1996	United States	199	Yes	2	2	No	NA
Lundgren (1998)	NR	NR	Sweden	16	Yes	1	1	No	NA
Salinski (1996) Follow-up of Clinical Trial EO3	NR	NR	Multi-national[a]	114	Yes	1	1	No	NA
Clinical Trial EO3 The VNS Group (1995)	NR	NR	Multi-national[a]	114	Yes	2	2	No	NA

[a] United States / Germany / Sweden / Canada / Holland

Evidence Table 212. Primary characteristics of included studies on vagal nerve stimulation (continued)

Reference	Type of Control Group	Randomized	Randomization Method Described	Method of Randomization Acceptable	Patients Blinded	2nd or 3rd Party Raters Blinded	Multi-center	Number of Centers	Industry Funded
Aldenkamp (2001)	NA	NA	NA	NA	No	No	No	1	NR
Chayasirisobhon (2001)	NA	NA	NA	NA	No	No	No	1	Yes
Ergene (2001).	NA	NA	NA	NA	No	No	No	1	NR
Hoppe (2001)	NA	NA	NA	NA	No	No	No	1	Yes
DiGiorgio (2000) Follow-up of Clinical Trial EO5	NA	NA	NA	NA	No	No	Yes	20	Yes
Hosain (2000)	NA	NA	NA	NA	No	No	No	1	NR
Ben-Menachem (1999)	NA	NA	NA	NA	No	No	No	1	No
Boon (1999)	NA	NA	NA	NA	No	No	No	1	No
Clinical Trial EO4 Labar (1999)	NA	NA	NA	NA	No	No	Yes	NR	Yes
Parker (1999)	NA	NA	NA	NA	No	No	No	1	No
Clinical Study EO5 Handforth (1999)	Concurrent Active	Yes	Yes	Yes	Yes	Yes	Yes	20	Yes
Lundgren (1998)	NA	NA	NA	NA	No	No	No	1	NR
Salinski (1996) Follow-up of Clinical Trial EO3	NA	NA	NA	NA	No	No	Yes	17	Yes
Clinical Trial EO3 The VNS Group (1995)	Concurrent Active	Yes	No	NA	Yes	Yes	Yes	17	Yes

Evidence Table 213. Study characteristics: data collection and analysis for studies of vagal nerve stimulation

Reference	Long Term Followup of Previous Controlled Trial	Subgroup Analysis of a Larger Trial	A Priori Power Calculations Performed	Pretreatment Baseline Data Reported	Baseline Observation Period	Method For Seizure Frequency Measurement
RCTs performed in United States [a]						
Clinical Study EO5 Handforth (1999)	No	No	Yes	Yes	12 to 16 weeks	Patient or caregiver maintained seizure diary
Clinical Trial EO3 The VNS Group (1995)	No	No	No	Yes	12 weeks	Patient or caregiver maintained seizure diary
Long-term followup of RCTs performed in United States						
DiGiorgio (2000) Followup of Clinical Trial EO5	Yes	No	No	Yes	12 to 16 weeks	Patient or caregiver maintained seizure diary
Salinski (1996) Followup of Clinical Trial EO3	Yes	No	No	Yes	12 weeks	Patient or caregiver maintained seizure diary
Case series performed in United States						
Chayasirisobhon (2001)	No	No	No	Yes	4 weeks	Patient or caregiver maintained seizure diary
Ergene (2001)	No	No	No	Yes	NR	Patients asked to subjectively describe change in seizure frequency and severity
Hosain (2000)	No	No	No	Yes	1 month	Unclear
Clinical Trial EO4 Labar (1999)	No	Yes	No	Yes	1 month	Patient or caregiver maintained seizure diary
Case series performed outside United States						
Aldenkamp (2001)	No	No	No	Yes	NR	NR
Hoppe (2001)	No	No	No	Yes	None	Patient or caregiver maintained seizure diary

Evidence Table 213. Study characteristics: data collection and analysis for studies of vagal nerve stimulation (continued)

Reference	Long Term Followup of Previous Controlled Trial	Subgroup Analysis of a Larger Trial	A Priori Power Calculations Performed	Pretreatment Baseline Data Reported	Baseline Observation Period	Method For Seizure Frequency Measurement
Ben-Menachem (1999)	No	No	No	Yes	3 months	Patient or caregiver maintained seizure diary (n = 57) Unknown (n = 7)
Boon (1999)	No	No	No	Yes	2 years[c]	Patient or caregiver maintained seizure diary (and for baseline retrospective review of diary plus medical records)
Parker (1999)	No	No	No	Yes	8 weeks	Patient or caregiver maintained seizure diary
Lundgren (1998)	No	No	No	Yes	6 months	Patient or caregiver maintained seizure diary

Evidence Table 213. Study characteristics: data collection and analysis for studies of vagal nerve stimulation (continued)

Reference	Followup [b]			Total Attrition: N (%)	Patient Data Stratified by Seizure Type	Compliance Monitored	Individual Patient Data Presented	Statistical Methods Reported	Statistical Methods Appropriate	AED Regimes Fixed During Followup Period
	Multiple	Longest	Times							
RCTs performed in United States										
Clinical Study EO5 Handforth (1999)	Yes	16 wks	12 to 16 wks	5 (2.5)	No	Yes	No	Yes	Yes	Yes
Clinical Trial EO3 The VNS Group (1995)	No	14 wks	14 wks	0 (0.0)	No	NR	No	Yes	Yes	Yes
Long-term followup of RCTs performed in United States										
DiGiorgio (2000) Followup of Clinical Trial EO5	Yes	1 yr	3 mos 12 mos	31 (15.9)	No	NR	No	Yes	Yes	No
Salinski (1996) Followup of Clinical Trial EO3	Yes	1 yr	3 mos 6 mos 9 mos 12 mos	14 (12.3)	No	NR	No	Yes	Yes	No
Case series performed in United States										
Chayasirisobhon (2001)	No	6 mos	6 mos	0 (0.0)	No	NR	Yes	No (none performed)	NA	Yes
Ergene (2001)	Yes	12 mos	1 to 3 wks 5 to 7 wks 3 mos 6 mos 9 to 12 mos	0 (0.0)	No	NR	No	Yes	Yes	Yes
Hosain (2000)	No	6 mos	6 mos	0 (0.0)	No	NR	Yes	Yes	Yes	No
Clinical Trial EO4 Labar (1999)	No	3 mos	3 mos	1 (4.0)	No	Yes	No	Yes	Yes	Yes

Evidence Table 213. Study characteristics: data collection and analysis for studies of vagal nerve stimulation (continued)

Reference	Followup [b]			Total Attrition: N (%)	Patient Data Stratified by Seizure Type	Compliance Monitored	Individual Patient Data Presented	Statistical Methods Reported	Statistical Methods Appropriate	AED Regimes Fixed During Followup Period
	Multiple	Longest	Times							
Case series performed outside United States										
Aldenkamp (2001)	No	6 mos	6 mos	0 (0.0)	Yes	NR	No	Yes	Yes	No
Hoppe (2001)	No	>6 mos	Mean: 8.0 (SD: 2.8) mos	0 (0.0)	No	NR	No	Yes	Yes	Yes
Ben-Menachem (1999)	No	5 yrs	Mean: 20 mos Rng: 3 to 64 mos	0 (0.0)	Yes	NR	Partial	No (none performed)	NA	NR
Boon (1999)	No	4 yrs 2 mos	Mean: 26 mos Rng: 3 to 64 mos	0 (0.0)	No	NR	Yes	Yes	Yes	No
Parker (1999)	Yes	12 mos	6 mos 12 mos	1 (6.25) 1 (6.25)	No	NR	Yes	Yes	Yes	No [d]
Lundgren (1998)	Yes	24 mos	4 to 6 mos 10 to 12 mos 16 to 18 mos 22 to 24 mos	0 (0.0) 0 (0.0) 5 (31.3) 14 (87.5)	No	NR	Yes	Yes	Yes	No [e]

[a] Multinational studies in which the majority of study centers were based in the United States are included in this section
[b] Followup time refers to time after activation of device or in case of followup studies the followup time refers to time after completion of controlled phase of study
[c] Based on a retrospective review of medical records and patient seizure diaries
[d] Dosage of phenytoin increased in one patient with a >50% increase in seizures at 9 months. Authors report that this had no effect on seizure frequency. Remaining 14 patients maintained on same drugs and dosage for remainder of study.
[e] One patient received concomitant transient add-on treatment with felbamate. The dosage of clonazepam was increased from 1.25 to 1.50 mg daily in patient 1 during the eighth month of VNS treatment. The dosage of lamotrigine was increased in one patient after 11 months of vagal nerve stimulation treatment.
Mos = Months NA = Not applicable Wks = weeks NR = Not reported Rng = Range

Evidence Table 214. Study characteristics: attrition rates in studies of vagal nerve stimulation

Reference	Attrition in the Whole Study (at Longest Followup)[a]							
	Total: N (%)	Due to Death: N (%)	Due to Adverse Event: N (%)	Due to Unrelated Illness: N (%)	Due to Treatment Dissatisfaction: N (%)	Due to Other Treatment: N (%)	Due to Other[b] Causes: N (%)	Due to Censorship[c] N (%)
RCTs performed in United States								
Clinical Study EO5 Handforth (1999)	5 (2.5)[d]	0 (0.0)	3 (1.5)[d]	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)
Clinical Trial EO3 The VNS Group (1995)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Long-term followup of RCTs performed in United States								
DiGiorgio (2000) Followup of Clinical Trial EO5	31 (15.9)	2 (1.0)	2 (1.0)	0 (0.0)	18 (9.2)	0 (0.0)	9 (4.6)	0 (0.0)
Salinski (1996) Followup of Clinical Trial EO3	14 (12.3)	2 (1.8)	0 (0.0)	1 (0.9)	9 (7.9)	0 (0.0)	2 (1.8)	0 (0.0)
Case series performed in United States								
Chayasirisobhon (2001)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ergene (2001)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hosain (2000)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical Trial EO4 Labar (1999)	1 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0 (0.0)
Case series performed outside United S tates								
Aldenkamp (2001)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hoppe (2001)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ben-Menachem (1999)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Boon (1999)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parker (1999)	1 (6.25)	0 (0.0)	1 (6.25)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lundgren (1998)	5 (31.3)[g] 14 (87.5)[h]	NR	NR	NR	NR	NR	NR	NR

Evidence Table 214. Study characteristics: attrition rates in studies of vagal nerve stimulation (continued)

Reference	Attrition in Per Treatment Arm (at Longest Followup)[a]							
	Treatment Arm	Total: N (%)	Due to Death: N (%)	Due to Adverse Event: N (%)	Due to Unrelated Illness: N (%)	Due to Treatment Dissatisfaction: N (%)	Due to Other Treatment: N (%)	Due to Other Causes: N (%)
RCTs performed in United States								
Clinical Study EO5 Handforth (1999)	High	3 (3.2)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)[e]
	Low	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)[f]
Clinical Trial EO3 The VNS Group (1995)	High	NA	NA	NA	NA	NA	NA	NA
	Low	NA	NA	NA	NA	NA	NA	NA

[a] Exact attrition figures at different followup times and for different outcome measures are presented in the results table
[b] "Other" refers to patients lost to followup for unspecified reasons
[c] Censored patients are those who had not yet reached follow-up time at time of analysis
[d] Includes one patient who was not randomized because of surgical infection
[e] Poor compliance (n = 1); Uninterruptible patient diary
[f] Withdrawal of consent (n = 1)
[g] At 18 months
[h] At 24 months
NA = Not applicable
NR = Not reported

Evidence Table 215. Study characteristics: confirmation of diagnosis and definition used in studies of vagal nerve stimulation

Reference	Method(s) Used toEnsure That Patients Were Correctly Diagnosed	Patient Description
RCT's performed in the United States		
Clinical Study EO5 Handforth (1999)	Not reported	Patients with medically refractory seizures defined as a frequency of ≥6 seizures per month
Clinical Trial EO3 The VNS Group (1995)	Not reported	Patients with medically refractory seizures defined as a frequency of ≥6 seizures per month
Long-term followup of RCT's performed in the United States		
DiGiorgio (2000) Followup of Clinical Trial EO5	As Clinical Study EO5 above	As Clinical Study EO5 above
Salinski (1996) Followup of Clinical Trial EO3	As Clinical Study EO3 above	As Clinical Study EO3 above
Case-series performed in the United States		
Chayasirisobhon (2001)	Not reported	Patients with seizures refractory to antiepilpetic drugs given alone or in various combinations
Ergene (2001)	Not reported	Patients with persistant, frequent seizures despite appropriate medical management
Hosain (2000)	Clinical evaluation Routine EEG Video-EEG	Patients with severe, medication resistant mixed seizures
Clinical Trial EO4 Labar (1999)	Retrospective review of clinical notes, EEG data, neroimaging data	Patients with medication resistant generalized epilepsy
Case-series performed outside the United States		
Aldenkamp (2001)	Clinical evaluation EEG evidence	Patients with Lennox-Gestaut syndrome whose seizures were unacceptable to patient because of impact on dailiy function Patients seizures were resistant to treatment with antiepileptic drugs and patients were inelligable for resective surgery
Hoppe (2001)	Not reported	Patients with pharmacoresistant complex-partial seizures
Ben-Menachem (1999)	Clinical evaluation Routine EEG Ictal video-EEG in patients with partial seizures MRI	Patients with seizuers refractory to available antiepileptic drugs

Evidence Table 215. Study characteristics: confirmation of diagnosis and definition used in studies of vagal nerve stimulation (continued)

Reference	Method(s) Used to Ensure That Patients Were Correctly Diagnosed	Patient Description
Boon (1999)	Extensive pre-surgical evaluation which included: Clinical evaluation Video-EEG monitoring (+2 patients underwent intracranial video-EEG monitoring) MRI FDG-PET	Patients with medically refractory partial seizures considered for resective surgery but, following an extensive evaluation, were found not to be suitable candidates because a confined or resectable epileptogenic zone could not be identified
Parker (1999)	Clinical assessment Interictal EEG activity conjusive with generalized seizures Normal MRI (no evidence of focal lesion) PET (no evidence of focal lesion or focal lesion with absence of interical focal abnormality)	Patients with cryptogenic epileptic enecepahlopathy
Lundgren (1998)	Not reported	Patients with intractable epilepsy

Evidence Table 216. Study characteristics: patient selection criteria in studies of vagal nerve stimulation

Reference	Reasons for Patient Selection						Minimum Seizure Rate to be Eligible	Side Effects Included in Definition of Treatment Resistant Epilepsy	Study Reported Prior AEDs Failed at Maximum Tolerated Dose
	Subpopulation of Patients Who Received VNS	Children	Adults	Particular Syndrome	Particular Seizure Type	Mentally Retarded or Have Deveolpmental Disability			
RCTs performed in United States									
Clinical Study EO5 Handforth (1999)	Yes	No	No	No	Yes	No	6 per month	No	No
Clinical Trial EO3 The VNS Group (1995)	Yes	No	No	No	Yes	No	6 per month	No	No
Long-term followup of RCTs performed in United States									
DiGiorgio (2000) Followup of Clinical Trial EO5	Yes	No	No	No	Yes	No	6 per month	No	No
Salinski (1996) Followup of Clinical Trial EO3	Yes	No	No	No	Yes	No	6 per month	No	No
Case series performed in United States									
Chayasirisobhon (2001)	No	No	No	No	No	No	6 per month	No	No
Ergene (2001)	Yes	No	No	No	Yes	No	Not reported	No	No
Hosain (2000)	Yes	No	No	Yes	No	No	Not reported	No	No
Clinical Trial EO4 Labar (1999)	Yes	No	No	No	Yes	No	≥1 per month	No	No
Case series performed outside United States									
Aldenkamp (2001)	Yes	Yes	No	Yes	No	Yes	Not reported	No	No
Hoppe (2001)	Yes	No	Yes	No	Yes	No	Not reported	No	No
Ben-Menachem (1999)	No	No	No	No	No	No	Not reported	No	No
Boon (1999)	Yes	No	No	No	Yes	No	Not reported	No	No
Parker (1999)	Yes	Yes	No	No	No	No	Not reported	No	No
Lundgren (1998)	Yes	Yes	No	No	No	No	Not reported	No	No

[a] See The Vagus Nerve Stimulation Study

Evidence Table 216. Study characteristics: patient selection criteria in studies of vagal nerve stimulation (continued)

Reference	Inclusion Critiera	Excusion Criteira	Patient Sampling Method
RCTs performed in United States			
Clinical Study EO5 Handforth (1999)	≥6 seizures in a 30 day period Age 12 to 65 years Use acceptable AX-contraception if fertile female Take 1 to 3 marketed AEDs on a stable regimen for >1 month	Deteriorating medical or neurological conditions Pregnancy Cardiac or pulmonary disorder Active peptic ulcer History of non-epilpetic seizures >1 episode of status epilepticus in previous 12 mos Prior cervical vagotomy Prior brain stimulation Prior VNS Prior resective epilepsy surgery Inability to perform pulmonary function tests Unable to comply with clinical visits	Not reported
Clinical Trial EO3 The VNS Group (1995)	Partial seizures Seizures not adequatley controlled with medication ≥6 seizures per month Age ≥12 years	Progressive or unstable-medical condition Eitiology best treated by surgery Use of >3 AED's at study entry Use of an experimental AED at time of entry Pregnancy ≥20% variation in serum AED levels during baseline.	Consecutive

Evidence Table 216. Study characteristics: patient selection criteria in studies of vagal nerve stimulation (continued)

Reference	Inclusion Critiera	Excusion Criteira	Patient Sampling Method
Long-term followup of RCTs performed in United States			
DiGiorgio (2000) Followup of Clinical Trial EO5	See Clinical Trial EO3	See Clinical Trial EO5	See Clinical Trial EO5
Salinski (1996) Followup of Clinical Trial EO3	See Clinical Trial EO3	See Clinical Trial EO3	See Clinical Trial EO3
Case series performed in United States			
Chayasirisobhon (2001)	Refractory response to AED's given alone or in combination ≥ 6 seizures per mo Patients are unsuitable-for epilepsy surgery	Evidence of non-epilpetic seizures Previous left cervical vagotomy	All patients who met inclusion criteria implanted with VNS at study center
Ergene (2001)	Partial onset seizures Persistant, frequent seizues despite appropriate medical management Not candidates for surgical treatment	Not reported	Not reported
Hosain (2000)	Patients with Lennox Gestaut syndrome Severe medication resistant mixed seizures Static encephalopathy Generalized slow spike-and-wave discharges seen on EEG Undergone video-EEG to confirm diagnosis	Not reported	All patients with Lennox-Gastaut syndrome
Clinical Trial EO4 Labar (1999)	Age >3 years ≥1 seizure per month	Cardiac or progressive neurologic disease	All patients with generalized seizures who met inclusion criteria of study EO4[b]

[b] This report contains a subgroup of patients with generalized seizures who entered Clinical Study EO4. Data from whole study population is not available

Evidence Table 216. Study characteristics: patient selection criteria in studies of vagal nerve stimulation (continued)

Reference	Inclusion Critiera	Excusion Criteira	Patient Sampling Method
Case series performed outside United States			
Aldenkamp (2001)	Multiple seizure types consistent with Lennox-Gastaut syndrome Mental retardation or developmental delay Seizures unacceptable-to patients or parent because of impact on daily life functions and development due to frequency or severity Resistance to existing pharmacological treatments and ineligibility for surgical alternatives (resective surgery, callosotomy) Written and signed informed consent	Progressive neurological disease Bad physical condition that would not allow the surgical implantation procedure Any risk for complications due to the implanataion procedure (cardiac disease, restrictive pulmonary disease, stomach ulcers)	All patients with Lennox-Gastaut syndrome
Hoppe (2001)	Patients with pharmacoresistant complex-partial seizures Patients able to participate in neuropsychological assessment.	Not reported	Consecutive
Ben-Menachem (1999)	Refractory to available AED's Patients deemed unsuitable-for epilepsy surgery or had received unsuccessful surgery	Not reported	Not reported
Boon (1999)	Patients with partial seizures refractory to available AED's who had undergone extensive pre-surgical evaluation but were consequently deemed unsutiable candidates for surgery	Not reported	All patients with >6 mos followup.
Parker (1999)	Mixed generilized seizures refractory to treatment with AED's Age ≤18 yrs	Not reported	All children receiving VNS device at study center who met inclusion criteria
Lundgren (1998)	Not reported	Not reported	Unclear

Evidence Table 217. Study characteristics: settings in studies of vagal nerve stimulation

All studies used the NeuroCybernetic Prosthesis Generator

Reference	Study Arm	Output Current (mA)	Ramp Up Period	Frequency (Hz)	Pulse Width (ms)	On Time (sscs)	Off Time (min)	Manual Activation Mode
RCTs performed in United States								
Clinical Study EO5 Handforth (1999)	High	0.25 to 3.5 (maximum tolerable)	2 weeks	30	500	30	5	Enabled
	Low	0.25 to 3.5 (minimum level consistent sensation of stimulation)	2 weeks	1.0	130	30	180	Disabled
Clinical Trial EO3 The VNS Group (1995)	High	1.5 (range: 0.25 to 3.0 (max tolerable)	NR	30 (range: 20 to 50)	500	30 (range: 30 to 90)	5 (range: 5 to 10)	Enabled
	Low	1.25 (range: 0.25 to 2.75) (minimum level consistent a sensation stimulation)	NR	1 (range: 1 to 2)	130	30	90 (range: 60 to 180)	Disabled
Long-term followup of RCTs performed in United States								
DiGiorgio (2000) Followup of Clinical Trial EO5	High	0.25 to 3.5 (maximum tolerable)	2 weeks	20 to 30	500 to 750	7 to 60	1.1 to 180	Enabled
Salinski (1996) Followup of Clinical Trial EO3	High	1.5 (range: 0.25 to 3.0 (maximum tolerable)	NR	30 (range: 20 to 50)	500	30 (range: 30 to 90)	5 (range: 5 to 10)	Enabled
Case series performed in United States								
Chayasirisobhon (2001)	NA	1.75 to 3.5 (maximum tolerable)	6 weeks	30	500	30	5	Enabled
Ergene (2001)	NA	1.0 to 2.5 (maximum tolerable)	2 to 3months	30	500	30	5	NR
Hosain (2000)	NA	0.50 to 1.75 (maximum tolerable)	2 weeks to 2 months	30	500	30	5	Enabled
Clinical Trial EO4 Labar (1999)	NA	0.25 to 3.5 (maximum tolerable)	3 months	30	500	30	5	Enabled

Evidence Table 217. Study characteristics: settings in studies of vagal nerve stimulation (continud)

Reference	Study Arm	Output Current (mA)	Ramp Up Period	Frequency (Hz)	Pulse Width (ms)	On Time (seconds)	Off Time (minutes)	Manual Activation Mode
Case series performed outside United States								
Aldenkamp (2001)	NA	1.5 to 2.0 (maximum tolerable)	3 months	30	500	30 (or 7 if patient did not respond)	5 (or 18 secs if patient did not respond)	NR
Hoppe (2001)	NA	0.5 to 2.0 (maximum tolerable)	8 weeks	30	500	30 (or 7 if patient did not respond	5 (or 30 secs if patient did not respond)	NR
Ben-Menachem (1999)	NA	1.0 to 1.5 (maximum tolerable)	NR	30	500	30 (or 7 if patient did not respond)	5 (or 20 secs if patient did not respond)	NR
Boon (1999)	NA	1.0 to 2.7 (maximum tolerable)	NR	30	500	30	5 to 10	Enabled
Parker (1999)	NA	1.25 to 2.0 (maximum tolerable)	NR	NR	NR	30	5	NR
Lundgren (1998)	NA	1.25 to 2.0 (maximum tolerable)	2 to 12 weeks	30	500	30 (or 7 if patient did not respond)	5 (or 12 to 30 secs if patient did not respond)	Yes

[a] Information on VNS device settings extracted from Labar (1999)
NA Not applicable
NR Not reported

Evidence Table 218. Patient characteristics: baseline demographics in studies of vagal nerve stimulation

Reference	Presented Baseline Demographic Data For All Patients Who Entered Study	Study Arm	% Male	Mean Age at Implantation in Years (SD)	Age Range in Years	Mean Duration of Disease in Years (SD)	Range of Disease Duration
RCTs performed in United States							
Clinical Study EO5 Handforth (1999)	Yes	High	51.6	32.1 (10.8)	13 to 54	22.1 (11.5)	2 to 48
		Low	42.7	34.2 (10.1)	15 to 60	23.7 (10.8)	2 to 52
Clinical Trial EO3 The VNS Group (1995)	No	High	61	33.1 (NR)	NR	23.1 (NR)	NR
		Low	63.9	33.5 (NR)	NR	20.0 (NR)	NR
Long-term followup of RCTs performed in United States							
DiGiorgio (2000) Followup of Clinical Trial EO5	Yes	NA	46.7	34 (NR)	NR	Median: 22	NR
Salinski (1996) Followup of Clinical Trial EO3	Yes	NA	NR	33 (NR)	13 to 52	NR	NR
Case series performed in United States							
Chayasirisobhon (2001)	Yes	NA	58.3	27.1 (17.2)	6 to 70	20.1 (14.1)	1 to 43
Ergene (2001)	Yes	NA	64.7	33.8 (NR)	11 to 55	NR	NR
Hosain (2000)	Yes	NA	76.9	18.9 (10.8)	4 to 44	NR	NR
Clinical Trial EO4 Labar (1999)	No	NA	54.2	NR (NR)	4 to 40	NR (NR)	4 to 35

Evidence Table 218. Patient characteristics: baseline demographics in studies of vagal nerve stimulation (continued)

Reference	Presented Baseline Demographic Data For All Patients Who Entered Study	Study Arm	% Male	Mean Age at Implantation in Years (SD)	Age Range in Years	Mean Duration of Disease in Years (SD)	Range of Disease Duration
Case series performed outside United States							
Aldenkamp (2001)	Yes	NA	81.3	11.1 (NR)	6 to 17	8.5 (NR)	NR
Hoppe (2001)	Yes	NA	NR	33.6 (9.8)	NR	NR	NR
Ben-Menachem (1999)	No	NA	NR	NR	NR	NR	NR
Boon (1999)	Yes	NA	40.0	30.2 (9.0)	12 to 45	17.0 (8.0)	5 to 35
Parker (1999)	Yes[a]	NA	NR	11.3 (3.1)	5 to 17	10.0 (3.4)	3 to 16
Lundgren (1998)	Yes	NA	62.5	11.0 (4.5)	4 to 19	8.1 (4.3)	3.5 to 18.6

Evidence Table 218. Patient characteristics: baseline demographics in studies of vagal nerve stimulation (continued)

Reference	Mean Age at Onset (SD)	Range of Age at Onset	Postsurgical Patients (%)	AED's Taken by Each Patient	Patients With IQ <70 (%)
RCTs performed in United States					
Clinical Study EO5 Handforth (1999)	NR	NR	0 (0.0)	1 to 3	NR
	NR	NR	0 (0.0)	1 to 3	NR
Clinical Trial EO3 The VNS Group (1995)	NR	NR	0 (0.0)	Mean: 2.09	NR
	NR	NR	0 (0.0)	Mean: 2.08	NR
Long-term followup of RCTs performed in United States					
DiGiorgio (2000) Followup of Clinical Trial EO5	Median: 9 years	NR	0 (0.0)	1 to 3	NR
Salinski (1996) Followup of Clinical Trial EO3	NR	NR	0 (0.0)	1 to 3	NR
Case series performed in United States					
Chayasirisobhon (2001)	7.0 (8.9) years	1 day to 31 years	NR	1 to 3	11 (45.8)
Ergene (2001)	NR	NR	0 (0.0)	2 or 3	NR
Hosain (2000)	NR	NR	3 (23.1)	Median: 6 (range: 4 to 12	NR
Clinical Trial EO4 Labar (1999)	NR (NR)	0 to 14 yrs	NR	1 to 5	NR
Case series performed outside United States					
Aldenkamp (2001)	2.6 (NR)	0 to 8 yrs	0	NR	NR
Hoppe (2001)	NR	NR	NR	NR	0 (0.0)
Ben-Menachem (1999)	NR	NR	NR	1 to 4	NR
Boon (1999)	13.3 (7.8) years	2 to 29 years	0 (0.0)	NR	NR
Parker (1999)	1.3 (1.6) years	1 mo to 3 years	0	NR	NR
Lundgren (1998)	2.9 (2.7) years	1 mos to 9 years	6 (37.5)	1 to 3	14 (87.5)

[a] Demographic data presented for the 15 of 16 patients in whom device was who initiated. Data from one patient who had device removed because of infection prior to device initiation was not presented.
NA = Not applicable
NR = Not reported

Evidence Table 219. Patient characteristics: seizure types and etiology in studies of vagal nerve stimulation

Reference	Treatment Arm	Number of Patients With Each Seizure Type (%)								
		Primary Partial	Primary Generalized	Complex Partial	Simple Partial	Secondary Generalized	Generalized Tonic, Clonic, or Tonic-Clonic	Generalized Absence	Lennox-Gastaut Syndrome	Generalized Atonic
RCTs performed in United States										
Clinical Study EO5 Handforth (1999)	High	95 (100.0)	NR	NR	NR	NR	NR	NR	NR	NR
	Low	103 (100.0)	NR	NR	NR	NR	NR	NR	NR	NR
Clinical Trial EO3 The VNS Group (1995)	High	54 (100.0)	NR	50 (92.6)	24 (44.4)	38 (70.4)	NR	NR	NR	NR
	Low	60 (100.0)	NR	58 (96.7)	25 (41.7)	33 (55.0)	NR	NR	NR	NR
Long-term followup of RCTs performed in United States										
DiGiorgio (2000) Followup of Clinical Trial EO5	NA	195 (100.0)	NR	191 (98.0)	NR	NR	96 (49.2)	NR	NR	NR
Salinski (1996) Followup of Clinical Trial EO3	NA	114 (100.0)	NR	NR	NR	NR	NR	NR	NR	NR
Case series performed in United States										
Chayasirisobhon (2001)	NA	14 (58.3)	?	10 (41.7)	12 (50.0)	?	21 (87.5)	8 (33.3)	6 (25.0)	7 (29.2)
Ergene (2001)	NA	17 (100.0)	0 (0.0%)	NR	NR	NR	NR	NR	NR	NR
Hosain (2000)	NA	13 (100.0)	4 (30.8)	4 (30.8)	0 (0.0)	3 (23.1)	9 (69.2)	12 (92.3)	13 (100.0)	4 (30.8)
Clinical Trial EO4 Labar (1999)	NA	0 (0.0)	24 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (88.0)	12 (48.0)	NR	NR

Evidence Table 219. Patient characteristics: seizure types and etiology in studies of vagal nerve stimulation (continued)

Reference	Treatment Arm	Number of Patients With Each Seizure Type (%)								
		Primary Partial	Primary Generalized	Complex Partial	Simple Partial	Secondary Generalized	Generalized Tonic, Clonic, or Tonic-Clonic	Generalized Absence	Lennox-Gastaut Syndrome	Generalized Atonic
Case series performed outside United States										
Aldenkamp (2001)	NA	NR	NR	5 (31.3)	0 (0.0)	1 (6.3)	10 (62.5)[a] 9 (56.3)[b]	10 (62.5)	12 (75.0) (+4 patients (25.0%) with LG like syndromes)	3 (18.8)
Hoppe (2001)	NA	36 (100.0)	0 (0.0)	36 (100.0)	0 (0.0)	NR	NR	NR	NR	NR
Ben-Menachem (1999)	NA	47 (73.4)	17 (26.6)	47 (73.4)	NR	NR	9 (14.1)	NR	8 (12.5)	NR
Boon (1999)	NA	0 (0.0)	20 (100)	4 (20.0)	18 (90.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Parker (1999)	NA	0 (0.0)	16 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (62.5)	0 (0.0)
Lundgren (1998)	NA	8 (50.0)	8 (50.0)	NR	NR	2 (12.5)	4 (25.0)	0 (0.0)	4 (25.0)	0 (0.0)

[a] Generalized tonic seizures
[b] Generalized tonic-clonic seizures
NA Not applicable
NR Not reported

Evidence Table 219. Patient characteristics: seizure types and etiology in studies of vagal nerve stimulation (continued)

Reference	Treatment Arm	Etiology / Syndrome / History	
RCTs performed in United States			
Clinical Study EO5 Handforth (1999)	High	NR	
	Low	NR	
Clinical Trial EO3 The VNS Group (1995)	High	NR	
	Low	NR	
Long-term followup of RCTs performed in United States			
DiGiorgio (2000) Followup of Clinical Trial EO5	NA	NR	
Salinski (1996) Followup of Clinical Trial EO3	NA	NR	
Case series performed in United States			
Chayasirisobhon (2001)	NA	Lennox-Gestaut syndrome (n = 6) Tuberous sclerosis (n = 3) Encephalitis (n = 2) Head injury (n = 2) Oligodendrioma (n = 1) Meningoencephalitis (n = 1)	Epidermoid tumor (n = 1) Caernous angioma (n = 1) Porencephalopathy (n = 1) Prenatal encephalopathy (n = 1) Unknown (n = 5)
Ergene (2001)	NA	Cerebral palsy/ perinatal brain injury (n = 5 (29.4%) Mesial temporal sclerosis (n = 3 (17.7%) Head injury (n = 2 (11.8%)	Subarachnoid hemorrhage (n = 2 (11.8%) History of meningitis (n = 1 (5.9%) Unknown (n = 4 (23.5%)
Hosain (2000)	NA	Lennox Gestaut syndrome (n = 13)	
Clinical Trial EO4 Labar (1999)	NA	Cryptogenic (n = 10) Postinfectious (n = 4)	Congenital brain injury (n = 3) Unknown (n = 7)

Evidence Table 219. Patient characteristics: seizure types and etiology in studies of vagal nerve stimulation (continued)

Reference	Treatment Arm	Etiology / Syndrome / History	
Case series performed outside United States			
Aldenkamp (2001)	NA	Lennox-Gestaut syndrome (n = 12) Doose syndrome (n = 3)	Myoclonic absence epilepsy (n = 1)
Hoppe (2001)	NA	NR	
Ben-Menachem (1999)	NA	Lennox-Gestaut syndrome (n = 8) NR (n = 56)	
Boon (1999)	NA	History of head injury (n = 5) History of encephalitis (n = 2) History of premature birth (n = 1) History of meningitis (n = 5)	History of forceps delivery (n =1) History of fibrile seizures (n = 6) History of ventricular atrial drainage (n = 1) No history (n = 4)
Parker (1999)	NA	Lennox-Gestaut (n = 10) Juvenile myoclonic epilepsy (n = 6)	
Lundgren (1998)	NA	Lennox-Gestaut (n = 4) NR (n = 12)	

Evidence Table 220. Subpopulations of patients with treatment-resistant epilepsy in whom vagal nerve stimulation was assessed

Reference	Patients Recruited Because of Seizure Type	Patients Recruited Because of Syndrome	Seizure Type or Syndrome (if Applicable)	Patients Chosen Because They Were Children	Patients Chosen Because They Were Adults
RCTs performed in United States					
Clinical Study EO5 Handforth (1999)	✓		Partial seizures		
Clinical Trial EO3 The VNS Group (1995)	✓		Partial seizures		
Followup studies of RCTs					
DiGiorgio 2000) Followup of Clinical Trial EO5	✓		Partial seizures		
Salinski (1996) Followup of Clinical Trial EO3	✓		Partial seizures		
Case series performed in United States					
Chayasiriobhon (2001)			Mixed		
Ergene (2001)	✓		Partial seizures		
Hosain (2000)		✓	Lennox-Gestaut Syndrome		
Clinical Trial EO4 Labar (1999)	✓		Generalized seizures		
Case series performed outside of the United States					
Aldenkamp (2001)		✓	Lennox-Gestaut Syndrome	✓	
Hoppe (2001)	✓		Complex-partial seizures		
Ben-Menachem (1999)			Mixed		
Boon (1999)	✓		Partial seizures		
Parker (1999)	✓		Primary or secondary generlaized seizures	✓	
Lundgren (1998)			Mixed	✓	

Evidence Table 221. Individual patient data extracted from Boon (1999)

Patient	Sex	Age	Seizure Type	Age at Onset of Disease (Years)[a]	Duration of Disease (Years)	History
1	M	36	CPS, SG	14	22	Febrile seizures, head trauma
2	F	34	CPS, SG, SPS	29	5	Head trauma
3	M	39	CPS, SG	26	13	Head trauma
4	F	32	CPS, SG	14	18	Encephalitis
5	M	30	CPS, SG, SPS	12	18	Premature birth, callosotomy
6	M	21	CPC, SG	3	18	Febrile seizures
7	M	29	CPS, SG	7	22	Head trauma
8	F	23	CPS, SG, SPS	5	18	Febrile seizures, head trauma
9	F	32	CPS, SG	23	9	Febrile seizuers
10	F	25	CPS, SG	2	23	Febrile seizures, encephailitis
11	F	39	CPS, SG	8	31	Forceps birth
12	F	44	CPS, SG	9	35	Meningitis, ventricular atrial drainage
13	F	17	CPS, SG, SPS	6	11	None
14	F	25	CPS, SG (atonic)	12	13	None
15	M	20	CPS	14	6	Meningitis, head trauma
16	M	38	CPS, SG	18	20	None
17	F	12	CPS, SG	7	5	None
18	F	37	CPS, SG	23	14	Meningitis
19	M	26	CPS	12	14	Meningitis
20	F	45	CPS, SG	21	24	Meningitis, febrile seizures

[a] Calculated from available data by ECRI
CPS Complex partial seizure
SG Secondary generalized
SPS Simple partial seizure

Evidence Table 221. Individual patient data extracted from Boon (1999) (continued)

Patient	VNS Output Current (mA)	Baseline Mean Seizure Frequency (Seizures Per Month)	Followup Time (Months)	Post VNS Mean Seizure Frequency (Seizures Per Month)	% Reduction In Mean Seizure Rate[a]
1	2.25	8	50	0	100
2	1.75	3	50	0	100
3	1.5	4	45	0	100
4	2.75	40	43	25	37.5
5	2.5	4	38	3	25.0
6	2.5	4	38	1	75.0
7	2.0	30	37	20	33.3
8	1.5	4	31	0	100
9	1.75	16	28	4	25.0
10	3.0	35	26	30	14.3
11	2.75	8	23	2	25.0
12	1.75	2	20	0	100
13	1.5	200	20	0	100
14	1	30	19	30	0.0
15	2.75	4	15	1	25.0
16	2	30	12	30	0.0
17	2	12	10	9	25.0
18	2	3	9	0.5	83.3
19	2.25	20	8	12	40.0
20	1	10	6	6	40.0

[a] Calculated from available data by ECRI

Evidence Table 222. Individual patient data extracted from Chayasirisobhon (2001)

Patient	Sex	Age at Device Implantation (Years)	Age at Onset of Epilepsy	Etiology/Syndrome	Type of Seizures
1	F	43	8 years	Encephalitis	PS, PCS, GS
2 [a]	M	24	6 months	Lennox-Gastaut syndrome	AB, AS, GS, MS, TS
3 [a]	M	11	2 months	Lennox-Gastaut syndrome	AB, AS, GS, MS, TS
4	M	22	2 years	Oligodendroglioma	PS, PCS, GS
5	M	54	12 years	Unknown	PS, PCS, GS
6	M	18	12 years	Head injury	PS, PCS, GS
7	F	45	5 years	Unknown	PS, PCS
8 [a]	M	16	2 months	Meningoencephalitis	PS, GS
9	F	70	17 years	Unknown	AB, AS, GS, MS, TS
10 [a]	M	9	8 years	Encephalitis	PS, GS
11 [a]	F	10	2 years	Tuberous sclerosis	AB, AS, GS, MS, TS
12	F	23	18 years	Head injury	PS, PCS, S
13 [a]	F	12	1 day	Tuberous sclerosis	AB, AS, GS, MS, TS
14	M	41	7 years	Unknown	AB, GS
15	F	45	31 years	Epidermoid tumor	PS, PCS
16	M	32	15 years	Cavernous angioma	PS, PCS, GS
17 [a]	M	13	11 months	Lennox-Gastaut syndrome	AB, AS, GS, MS, TS
18 [a]	M	27	3 months	Lennox-Gastaut syndrome	AB, AS, GS, TS
19	F	46	27 years	Unknown	PCS, GS
20 [a]	M	14	11 months	Lennox-Gastaut syndrome	TS, GS
21	M	43	1 day	Porenephaly	PS, GS
22 [a]	M	6	2 years	Lennox-Gastaut syndrome	AB, AS, GS, MS, TS
23	F	15	6 months	Prenatal encephalopathy	PS, GS
24 [a]	F	12	2 months	Tuberous sclerosis	AB, GS

[a] Mentally retarded

AB Absence seizure
AS Atonic seizure
GS Generalized tonic-clonic seizure
MS Myoclonic seizure
PS Partial seizure
PCS Partial complex seizure
TS Tonic seizure

Evidence Table 222. Individual patient data extracted from Chayasirisobhon (2001) (continued)

Patient	Medications	Current Settings (mA)	Type and Baseline Seizure Rate	Type and Baseline Seizure Rate at Followup	% Decrease in Seizure Frequency
1	CBZ, PRM	2.75	PCS 127	PCS 122	3.9
2	CBZ, VPA	2.25	GS 24 / TS 12	GS 12 / TS 2	50.0 / 83.3
3	VPA	2.50	AS 241 / GS 74	AS 4 / GS 7	98.3 / 90.5
4	CBZ, PRM	2.00	PS 34 / GS 6	PS 3 / GS 1	91.2 / 83.3
5	CBZ, PRM	2.50	PCS 18 / PS 10	PCS 7 / PS 5	61.1 / 50.0
6	CBZ, TGB	3.00	PCS 6	PCS 4	33.3
7	CBZ, TPM	1.75	PCS 31	PCS 12	61.3
8	CBZ, VPA	2.75	PS/GS 63	PS/GS 4	93.7
9	PHT, TGB	2.75	PCS 6	PCS 4	33.3
10	VPA	3.5	PS/GS 30	PS/GS 25	16.7
11	PHT, VPA	2.5	AS 1072 /GS 231	AS 78 / GS41	92.7 / 82.3
12	ETT, LTG	2.0	CPS 10 / GS 2	PCS 4 / GS 0	60.0 / 100.0
13	PRM, TPM, TGB	3.25	AS 1204 / GS 56	AS 84 / GS 4	93.0 / 89.3
14	VPA	2.35	AB 136 / GS 14	AB 66 / GS 0	51.5 / 100.0
15	CBZ	2.0	PS 11 / PCS 8	PS 1 / PCS 0	90.9 / 100.0
16	CBZ, TPM	3.25	PCS 28	PCS 25	10.7
17	CBZ, VPA	3.25	MS 60 / GS 74	MS 56 / GS 60	6.7 / 19.0
18	PB, VPA	3.5	AB 30 / GS 12	AB 15 / GS 11	50.0 / 8.3
19	CNZ, GBP	2.75	PCS 84	PCS 15	82.1
20	VPA, TPM	3.0	TS 126	TS 98	22.2
21	PRM, LTG, TGB	3.0	PS 75 / GS 43	PS 95 / GS 57	-32.6 / -26.7
22	LEV	2.5	TS 168	TS 32	81.0
23	PHT, TPM, LEV	3.25	PCS 5 / GS 6	PCS 2 / GS 2	60.0 / 66.7
24	CBZ, VPA	3.25	AB 71	AB 5	93.0

CBZ	Carbamazepine	PB	Phenobarbital
CNZ	Clonzapam	PHT	Phenytoin
ETT	Ethotoin	PRM	Primodome
GBP	Gabapentin	TGB	Tiagabine
LEV	Levetiracetam	TPM	Topiramate
LTG	Lamotrigine	VPA	Valproate

Evidence Table 223. Individual patient data extracted from Hosain (2000)

Patient	Age at Implant	Sex	Etiology	Seizure Types	Neuroimaging	Baseline Seizure Frequency	% Reduction in Seizures at 6 Months
1	10	M	Cryptogenic	GTC, MY	Atrophy	22	84
2	14	F	Cryptogenic	GTC, MY, ATA	Diffuse atrophy	>100	0
3	14	M	Hypoxic-ischemic encephalopathy	AT, T, ATA, CP, CP/2nd gen	Difuse atrophy	22	54
4	13	M	CNS infection	ATA, MY, CP, GTC	Diffuse atrophy, calcifications	77	77
5	9	M	Tuberous sclerosis	ATA, AT, GTC, CP/2nd gen	Cortical tubers	96	93
6	16	M	Cryptogenic	CP, CP/2nd gen, ATA, MY	Atrophy CC section	123	40
7	15	M	Cryptogenic	ATA, MY, GTC	CC section	19	47
8	4	M	Tuberous sclerosis	ATA, AT, GTC, MY	Cortical tubers	21	37
9	23	M	Immunization-induced encephalopathy	GTC, ATA, T	CC section	118	78
10	26	M	Cryptogenic	ATA	Normal	29	52
11	29	F	Cryptogenic	ATA	Normal	75	43
12	29	F	Encephalitis	ATA, GTC	Atrophy	94	42
13	44	M	Trauma	ATA, AT	Atrophy	54	89

ATA Atypical absence seizure
AT Atonic seizure
GTC Generalized tonic-clonic seizure
MY Myoclonic seizure
CP Partial complex seizure
T Tonic seizure
CP/2nd generation Partial complex seizure with secondary generalization

Evidence Table 224. Individual patient data extracted from Parker (1999)

Patient	Diagnosis	Age at Onset	Age at Implant	Seizure Types	Concurrent Treatment	Seizure Rate (Per Month)	% Change From Baseline at 6 months	% Change From Baseline at 12 months
1	LGS	1 month	13 years 6 months	CPS, secondary generalized, NCS	Carbamazepine, Sodium Valproate	68	-15.0	-34.0
2	LGS	3 months	10 years 9 months	CPS, Atonic	Carbamazepine, Clobazam, Gabapentin	43	-32.0	-17.0
3	LGS	6 months	11 years 11 months	Atonic, CPS	Carbamazepine, Clobazam	72	-19.0	+7.0
4	LGS	1 months	11 years 2 months	GTCS, NCS	Carbamazepine, Vigabatrin, Lamotrigine	6	-41.0	-50.0
5	LGS	3 months	6 years 11 months	Myoclonic, GTCS	Carbamazepine, Clobazam, Lamotrigine	166	-63.0	-80.0
6	LGS	8 months	13 years 9 months	CPS, secondary generalized, atonic, atypical, absence	Carbamazepine, Phenytoin, Clobazam	26	-8.0	+27.0
7	LGS	6 months	16 years 6 months	Myoclonic, atonic, GTCS, NCS	Carbamazepine, Phenytoin, Gabapentin	288	-54.0	-46.0
8	De Novo LGS	3 years	6 years 3 months	CPS	Lamotrigine, Sodium Valproate	4	-25.0	-100.0
9	De Novo LGS	3 years	10 years 7 months	Atonic, atypical, absence, GTCS	Lamotrigine, Sodium Valproate	Device removed after implant		
10	De Novo LGS	2 years	9 years 7 months	GTCS, atonic	Carbamazepine, Clonazepam, Gabapentin	5	+100.0	+40.0

Evidence Table 224. Individual patient data extracted from Parker (1999) (continued)

Patient	Diagnosis	Age at Onset	Age atImplant	Seizure Types	Concurrent Treatment	Seizure Rate (Per Month)	% Change From Baseline at 6 months	% Change From Baseline at 12 months
11	SME	7 months	14 years 11 months	Secondary generalized, CPS, atypical, absences	Lamotrigine, Sodium Valproate, Primidone	26	+165.0	+62.0
12	SME	2 months	11 years 3 months	CPS, secondary generalized	Carbamazepine, Lamotrigine, Phenytoin, Heminevrin	23	+17.0	+65.0
13	SME	12 months	11 years 4 months	GTCS, NCS	Carbamazepine, Vigabatrin, Diazepam	9	-23.0	-23.0
14	SME	3 months	5 years 1 months	Secondary generalized	Phenytoin, Clobazam, Lamotrigine, Vigabatrin	20	0.0	0.00
15	MAE	2 years	12 years 6 months	Atypical, absences, secondary generalized	Sodium Valproate, Lamotrigine, Nitrazepam	7	+14.0	0.00
16	MAE	11 months	14 years 2 months	CPS, secondary generalized	Lamotrigine, Sodium Valproate, Vigabatrin	85	-40.0	-67.0

CPS Complex partial seizures
GTCS Generalized tonic clonic seizures
LGS Lennox-Gastaut Syndrome
MAE Myoclonic astatic epilepsy
NCS Non-convulsive status eplilepticus
SME Severe myoclonic epilepsy

Evidence Table 225. Individual patient data extracted from Lundgren (1998)

Patient	Sex	Age at Onset	Cause	Type of Epilepsy	Seizure Type	Pevious Surgery Type	Mentally Retarded (IQ <70)?	Age at Implant (years)
1	M	3 months	Cryptogenic	JME	TA, MYO, ABS	Anterior callosotomy	Yes	10
2	F	2 years 6 months	Cryptogenic	Partial	SPS	None	No	11
3	M	1 years 8 months	Malformation	Partial	TA, GTCS	Anterior callosotomy	Yes	14
4	F	1 month	Cryptogenic	Partial	CPS	None	Yes	8
5	M	3 years 3 months	Unknown granulomatous tumor	Partial	CPS	Frontal and temporal lobe resection	Yes	7
6	M	5 months	Malformation	LGS	TA, MYO, CPS	Frontal and occipital lobe resection	Yes	4
7	F	5 months	Malformation	LGS	GTCS, ATO	Subtotal hemispherectomy, Anterior callosotomy	Yes	19
8	M	4 years 3 months	Malformation	Partial	CPS	Temproal and frontal lobe resection	Yes	15
9	M	6 months	Cryptogenic	Generalized	ABS, MYO, GTCS	None	Yes	6
10	M	9 years	Malformation	Partial	CPS	None	Yes	15
11	M	4 months	Malformation	LGS	TA, CPS	None	Yes	9
12	F	2 years	Malformation	Partial	CPS	None	Yes	6
13	M	6 years	Idiopathic	Generalized	TA, GTCS	Anterior callosotomy		16
14	F	7 years 6 months	Unknown WM disease	Generalized	TA	None	Yes	11
15	F	4 years	Malformation	Partial	SPS, CPS, TA	None	Yes	17
16	M	4 years	Idiopathic	Generalized	GTCS	None	Yes	8

ABS Absence seizures
CPS Complex partial seizures
GTCS Generalized tonic clonic seizures
PGS Primary generalized seizures
LGS Lennox Gastaut syndrome
MYO Myoclonic seizures
SME Severe myoclonic epilepsy of infancy
SCS Simple partial seizures
TA Tonic-axial seizures
WM White matter

Evidence Table 225. Individual patient data extracted from Lundgren (1998) (continued)

Patient	Number of Seizures Per Month					Quality of Life (Nonvalidated Visual Analog Instrument)				
	Baseline	4 to 6 Months	10 to 12 Months	20 to 18 Months	22 to 24 Months	Baseline	4 to 6 Months	10 to 12 Months	20 to 18 Months	22 to 24 Months
1	26	10	16	14	27	70	75	65	65	70
2	46	0	0	3	15	100	99	99	99	50
3	45	57	68	59		20	15	10	10	
4	24	43	50	75		0	0	0	0	
5	203	300	56	135		60	65	0	0	
6	1195	210	135	160		50	50	50	50	
7	25	23	8	16		30	50	55	55	
8	11	14	14			10	10			
9	>100	>100	>100	>100		0	0	0	0	
10	11	4	4	5		75	75	75	75	
11	25	18	18			10	10			
12	29	7	7	8		0	25	25	25	
13	40	35	35	30		0	0	0	0	
14	30	30	30			0	0			
15	100	80	80			25	30			
16	115	60	70			25	25			

Evidence Table 226. Percentage reduction in seizure frequency from baseline in studies of vagal nerve stimulation

Reference	How Determined	Study Arm	N	Mean Pretreatment Absolute Seizure Frequency (SD)	Evidence of Selection Bias	Followup Time	Used Intent-to-Treat
RCTs performed in United States							
Clinical Study EO5 Handforth (1999)	Patient or caregiver maintained seizure diary	High	95	1.59 (3.26) per day Median: 0.51 (NR) per day	No	3 months	Yes
		Low	103	0.97 (1.13) per day Median: 0.49 (NR) per day			
Clinical Trial EO3 The VNS Group (1995)	Patient or caregiver maintained seizure diary	High	54	Median: 1.49 (Range: NR) per day	No	14 wks	NA
		Low	60	Median: 1.71 (Range: NR) per day			
Long-term followup of RCTs performed in United States							
DiGiorgio (2000) Followup of Clinical Trial EO5	Patient or caregiver maintained seizure diary		195	Median: 0.54 per day		3 months	Yes
						6 months	Yes
Salinski (1996) Followup of Clinical Trial EO3	Patient or caregiver maintained seizure diary		114	Median: 0.79 (Range: NR)		3 months	
						6 months	
						9 months	
						12 months	
Case series performed in United States							
Chayasirisobhon (2001)	Patient or caregiver maintained seizure diary		24	175.3 (348.6) per month Median: 52.5 (Range: 6 to 1303)		6 months	
Hosain (2000)	Unclear		13	65.4 (39.4) per month Median: 75 (Range: 19 to 123)		6 months	NA
Clinical Trial EO4 Labar (1999)	Patient or caregiver maintained seizure diary		24	Median: 48 (2 to 1650) per month		3 months	NA

Evidence Table 226. Percentage reduction in seizure frequency from baseline in studies of vagal nerve stimulation (continued)

Reference	How Determined	Study Arm	N	Mean Pretreatment Absolute Seizure Frequency (SD)	Evidence of Selection Bias	Followup Time	Used Intent-to-Treat
Case series performed outside United States							
Aldenkamp (2001)	NR		16	3906 (NR)		6 months	
Hoppe (2001)	Patient or caregiver maintained seizure diary		36	42.0 (95.0) per month		6 months	NA
Boon (1999)	Patient or caregiver maintained seizure diary		20	23.4 (43.4) per month Median: 9.0 (Range: 2 to 200)		Mean: 26.4 (SD: 14.4)	
Parker (1999)	Patient or caregiver maintained seizure diary		15	72.5 (93.7) per month		6 months	NA
Lundgren (1998)	Patient or caregiver maintained seizure diary		16	Median: 35.5 (Range: 11 to 1195)		4 to 6 months	
						10 to 12 months	
						12 months	NA

Evidence Table 226. Percentage reduction in seizure frequency from baseline in studies of vagal nerve stimulation (continued)

Reference	Study Arm	N	Mean % Change From Baseline (SD)	Reported P = (Within Groups)	Reported P = (Between Groups)	Within Groups[a]			Between Groups[b]		
						% Change From Reduction (CI)	P =	Minimum Detectable Change (Power = 0.8; P = 0.05)	% Reduction From Baseline Differnece (CI)	P =	Minimum Detectable Difference (Power = 0.8; P = 0.05)
RCTs performed in United States											
Clinical Study EO5 Handforth (1999)	High	54	-27.9 (34.3)	<0.0001	0.04	27.9 (18.5 to 37.65)	0.00000	NA	12.70 (2.35 to 23.1)	0.017	NA
	Low	102	-15.2 (39.2)	<0.0001		15.2 (7.6 to 22.80)	0.00090	NA			
Clinical Trial EO3 The VNS Group (1995)	High	54	-24.5 (CI: –14.1 to -34.9)	<0.01	0.01	24.5 (9.79 to 39.21)	0.001094	NA	18.4 (4.5 to 32.3)	0.009	NA
	Low	60	-6.1 (CI: 3.6 to -15.8)	=0.21		6.1 (-3.6 to 15.8)	0.21780	NA			
Long-term followup of RCTs performed in United States											
DiGiorgio (2000) Followup of Clinical Trial EO5		195	Median: -34.0	<0.0001		NC	NC	NA			
		195	Median: -45	<0.0001		NC	NC	NA			
Salinski (1996) Followup of Clinical Trial EO3		114	Median: -20.2	<0.01		NC	NC	NA			
			Median: -24.7	<0.01		NC	NC	NA			
			Median: -25.7	<0.01		NC	NC	NA			

			Median: -31.9	<0.01		NC	NC	NA			

Evidence Table 226. Percentage reduction in seizure frequency from baseline in studies of vagal nerve stimulation (continued)

Reference	Study Arm	N	Mean % Change From Baseline (SD)	Reported P = (Within Groups)	Reported P = (Between Groups)	Within Groups[a]			Between Groups[b]		
						% Change From Reduction (CI)	P =	Minimum Detectable Change (Power = 0.8; P = 0.05)	% Reduction From Baseline Differnece (CI)	P =	Minimum Detectable Difference (Power = 0.8; P = 0.05)
Case series performed in United States											
Chayasirisobhon (2001)		24	-55.1 (35.5) Median: -61.2 (-96.5 to +28.8)			55.1 (30.5 to 79.70)	0.000011	NA			
Hosain (2000)		13	-56.6 (26.4) Median: -52 (0 to 93)	0.04		56.6 (36.30 to 76.90)	0.00000	NA			
Clinical Trial EO4 Labar (1999)		24	Median: -46 (-100 to + 350%)	0.004		NC	NC	NA			
Case series performed outside United States											
Aldenkamp (2001)		16	-26.9 (NR)	0.005		NC	NC	NA			
Hoppe (2001)		36	Median: -20%	NR		NC	NC	NC			
Boon (1999)		20	-52.4 (37.5) Median: -38.75 (0 to -100)	NR		52.4 (28.55 to 76.25)	0.000017	NA			
Parker (1999)		15	-19 (NR)	0.083		NC	NC				
Lundgren (1998)		16	-19.9 (50.2)	NR		19.9 (-4.7 to 44.5)	0.11282				
		16	-26.3 (55.4)	NR		26.3 (-12.90 to 64.69)	0.179357				
		15	-17 (NR)	0.264		NC	NC				

[a] Only applicable if individual patient data available

[b] Only applicable for studies that included ≥2 treatment arms

Evidence Table 227. Percentage change from baseline data in studies of vagal nerve stimulation (results of fixed effects meta-analysis of single treatment arm data)

Reference	N	Percentage Change From Baseline (CI)	P-Value	Standardized Residual	Outlier by Standardized Residual	Outlier by Q
Data from treatment arm of RCT						
Clinical Study EO5 Handforth (1999)	95	27.9 (18.5 to 37.65)	<0.000001	-1.82	Yes	No
Clinical Trial EO3 The VNS Group (1995)	54	24.5 (9.79 to 39.21)	0.001094	-1.49	No	No
Data from case series						
Chayasirisobhon (2001)	16	55.1 (30.5 to 79.7))	0.000011	1.72	Yes	No
Hosain (2000)	13	56.6 (36.3 to 76.9)	<0.000001	2.27	Yes	Yes
Boon (1999)	19	52.4 (28.55 to 76.25)	0.000017	1.54	No	No
Lundgren (1998)	16	26.3 (-12.90 to 64.69)	0.179357	-0.42	No	No
Test of Homogeneity of Fixed Effects Model [b]		**Q = 13.12**	**0.022256**			
Fixed Effects Summary Effect Size		Not applicable due to statistically signficiant test for homogeneity				
Random Effects Summary Effect Size [c]		**39.27 (26.58 to 51.97)**	**<0.000001**			

[a] By convention a positive effect size indicates treatment benefit.
[b] Critical Q (df = 5) = 11.07
[c] The random effects summary effect size is provided as an alternative when the fixed effects model has statistically significant heterogeneity.

Evidence Table 228. Univariate meta-regression analyses of percentage change from baseline data in studies of vagal nerve stimulation

Covariate	Intercept (CI)	P Value for Intercept	Coefficient (CI)	P Value for Coefficient	Q_e =	P (Q_e) =
Study RCT or not?	26.86 (18.73 to 34.99)	<0.000001	25.07 (10.25 to 39.89)	0.000911	2.124000	0.712965
Attrion rate	40.55 (31.07 to 50.02)	<0.000001	-5.06 (-10.50 to 0.38)	0.068322	9.800000	0.043935
Followup time[a]	37.91 (30.18 to 45.63)	<0.000001	1.07 (-0.05 to 2.19)	0.061703	9.630000	0.047143
Age at surgery[a]	40.12 (31.52 to 48.72)	<0.000001	-1.35 (-2.59 to –0.11)	0.033487	8.602000	0.071855
Proportion male	12.21 (-29.62 to 54.03)	0.567343	0.39 (-0.34 to 1.13)	0.290400	12.01100	0.017270
Partial seizures only	54.64 (33.28 to 75.99)	0.000001	-0.23 (-0.46 to 0.00)	0.050799	9.288000	0.054290
Lennox-Gastaut only	30.61 (23.25 to 37.97)	<0.000001	0.29 (0.07 to 0.50)	0.008567	6.187000	0.185611

[a] Mean centered

Evidence Table 229. Difference in absolute seizure frequency in studies of vagal nerve stimulation

Reference	How Determined	Study Arm	N	Mean Pretreatment Seizure Frequency (SD)	Followup Time	Mean Posttreatment Seizure Frequency (SD)	Reported P = (Within Groups)	Reported P = (Between Groups)
Aldenkamp (2001)	NR		16	3906 (NR)	6 months	3172 (NR)	0.005	
Chayasirisobhon (2001)	Patient or caregiver maintained seizure diary		24	1.78 (0.61) log per month[b] [Median: 52.5 (Range: 6 to 1303)]	6 months	1.24 (0.62) log per month[b] [Median: 14.5 (Range: 1 to 152)]	<0.001[c] [<0.001[d]]	
Hoppe (2001)	Patient maintained seizure diary		36	42.0 (95.0) per month	Mean: 8.0 (SD: 2.8)	33.0 (86.3) per month	0.09	
Boon (1999)	Patient or caregiver maintained seizure diary		19[f]	14.0 (12.7) per month [Median: 8.0 (Range: 2 to 40)] per month[f]	Mean: 26.4 (SD: 14.4)	9.1 (11.6) per month [Median: 3.0 (Range: 0 to 30)] per month[g]	0.0003	
Lundgren (1998)	Patient or caregiver maintained seizure diary		16	1.69 (0.51) log per month[c] [Median: 35.5 (Range: 11 to 1195)]	4 to 6 months	1.54 (0.53) log per month[b] [Median: 33.0 (0 to 300)]	0.073[c] [0.140[d]]	
Clinical Trial EO3 The VNS Group (1995)	Patient or caregiver maintained seizure diary	High	54	Median: 0.73 (Range: NR) per day	12 weeks	Median: 0.42 (Range: NR) per day	<0.01	0.02
		Low	60	Median: 0.82 (Range: NR) per day		Median: 0.80 (Range: NR) per day	0.19	
					10 to 12 month	1.48 (0.46) log per month[b] [Median: 33. (0 to 135)]	0.030[c] [0.041[d]]	

Evidence Table 229. Difference in absolute seizure frequency in studies of vagal nerve stimulation (continued)

Reference	How Determined	Study Arm	N	Minimum Detecatble Change (Power = 0.8, P = 0.05)	Minimum Detectable Difference (Power = 0.8, P = 0.05)	Pre-Post Within Groups Summary Effect Size (Hedges' d)[a]	Post-Treatment Between Groups Summary Effect Size (Hedges'd)	Individual Patient Data Availabale
Aldenkamp (2001)	NR		16	NA		NC		No
Chayasirisobhon (2001)	Patient or caregiver maintained seizure diary		24	NA		0.88 (0.48 to 1.27)[e]		Yes
Hoppe (2001)	Patient maintained seizure diary		36	NC		NC		No
Boon (1999)	Patient or caregiver maintained seizure diary		19 [f]	NA		0.39 (0.21 to 0.58)[e]		Yes
Lundgren (1998)	Patient or caregiver maintained seizure diary		16			0.27 (-0.02 to 0.56)[e]		Yes
Clinical Trial EO3 The VNS Group (1995)	Patient or caregiver maintained seizure diary	High	54	NA	NA	NC	NC	No
		Low	60	NC		NC		
				NA		0.41 (0.05 to 0.77)[e]		

[a] Only calculated if individual patient data presented
[b] Calculated from raw data. Data are log transformed because pre-treatment data were non-normally distributed (Kolmogorov-Smirnov test)
[c] Based on a paired t-test of log transformed seizure frequency data
[d] Based on Wilcoxon Rank-Paired Test
[e] Calculated from raw data using method of Dunlap (1996)
[f] Does not include patient 13 who was excluded from analysis because her seizures only occurred in clusters
[g] Calculated from individual patient data presented by Boon (199)
NC = Not calculated. Data not sufficient to calculate an effect size (missing dispersion data, OR, data were presented as median and range, OR, individual patients data not presented)

Evidence Table 230. Proportion of patients seizure-free in studies of vagal nerve stimulation.

Reference	How Determined	N	Seizure Frequency at Baseline (SD)	Followup Time	Number of Patients Seizure Free Posttreatment (%)	Used an Intent-to-Treat Doctrine	Reported P = (Within Groups)	Pre-Post Effect Size (Cohen's h (CI))	Minimum Detectable Change (Power = 0.8; P = 0.05)
Case series performed outside United States									
Boon (1999)	Patient or caregiver maintained seizure diary	20	23.4 (43.4) per month [Median: 9.0 (Range: 2 to 200)]	Mean: 26.4 (SD: 14.4) months	6 (30.0)	Yes	NR	1.16 (0.54 to 1.78)	NA

NA Not applicable
NR Not reported

Evidence Table 231. Proportion of patients with >50% reduction in seizure frequency in studies of vagal nerve stimulation

Reference	How Determined	Study Arm	N	Mean Pretreatment Absolute Seizure Frequency (SD)	Evidence of Selection Bias	Followup Time	Used Intent-To-Treat Doctrine
RCTs performed in United States							
Clinical Study EO5 Handforth (1999)	Patient or caregiver maintained seizure diary	High	95	1.29 (3.26) per day	No	3 months	No[d,e]
		Low	103	0.97 (1.13) per day			
Clinical Trial EO3 The VNS Group (1995)	Patient or caregiver maintained seizure diary	High	54	Median: 0.73 (Range: NR) per day	No	12 weeks	Yes
		Low	60	Median: 0.82 (Range: NR) per day			
Long-term followup of RCTs performed in United States							
DiGiorgio (2000) Followup of Clinical Trial EO5	Patient or caregiver maintained seizure diary		195	Median: 0.54 per day		3 months	Yes
						6 months	
Salinski (1996) Followup of Clinical Trial EO3	Patient or caregiver maintained seizure diary		114	Median 0.79 per day		3 months	Yes
						6 months	
						9 months	
						12 months	
Case series performed in United States							
Chayasirisobhon (2001)	Patient or caregiver maintained seizure diary		24	[Median: 52.5 (Range: 6 to 1303) per months]		6 months	Yes
Hosain (2000)	Unclear		13	65.4 (39.4) per month [Median: 75 (Range: 19 to 123) per months]		6 months	NA[e]
Clinical Trial EO4 Labar (1999)	Patient or caregiver maintained seizure diary		25	[Median: 48 (Range: 2 to 1650) per months]		3 months	Yes

Evidence Table 231. Proportion of patients with >50% reduction in seizure frequency in studies of vagal nerve stimulation (continued)

Reference	How Determined	Study Arm	N	Mean Pretreatment Absolute Seizure Frequency (SD)	Evidence of Selection Bias	Followup Time	Used Intent-To-Treat Doctrine
Case series performed outside United States							
Aldenkamp (2001)	NR		16	3906 (NR)		6 months	Yes
Hoppe (2001)	Patient maintained seizure diary		36	42.0 (95.0) per month		Mean: 8.0 (SD: 2.8)	Yes
Ben-Menachem (1999)	Patient or caregiver maintained seizure diary (n = 57) Unknown (n = 7)		64	NR		Mean: 20 (Range: 3 to 64 months)	Yes
Boon (1999)	Patient or caregiver maintained seizure diary		20	23.4 (43.4) per month [Median: 9.0 (Range: 2 to 200)]		Mean: 26.4 (SD: 14.4)	Yes
Parker (1999)	Patient or caregiver maintained seizure diary		16	[Median:26.0 (Range: 4 to 288)]			Yes
Lundgren (1998)	Patient or caregiver maintained seizure diary		16	[Median: 35.5 (Range: 11 to 1195)]		4 to 6 months 10 to 12 months	Yes Yes

Evidence Table 231. Proportion of patients with >50% reduction in seizure frequency in studies of vagal nerve stimulation (continued)

Reference	Study Arm	N	Number of Patients With >50% Reduction in Seizure Frequency (%)	Reported P = (Within Groups)	Reported P = (Between Groups)	Calculated by ECRI [a]			
						Minimum Detectable Change (Power = 0.8; P = 0.05)	Within Groups Summary Effect Size, Cohens' h (CI)	Minimum Detectable Difference (Power = 0.8; P = 0.05)	Between Groups Summary Effect Size, Cohens'h (CI)
RCTs performed in United States									
Clinical Study EO5 Handforth (1999)	High	95	22 (23.1)	NR	0.172 [f]	NC	1.00 (0.72 to 1.29)		0.19 (-0.09 to 0.47)
	Low	103	16 (15.5)	NR			0.81 (0.54 to 1.08)		
Clinical Trial EO3 The VNS Group (1995)	High	54	17 (31.5)	NR	0.02 [g]	NC	0.91 (0.81 to 1.57)	NA	0.44 (0.08 to 0.81)
	Low	60	8 (13.3)	NR			0.75 (0.39 to 1.11)		
Long-term followup of RCTs performed in United States									
DiGiorgio (2000) Followup of Clinical Trial EO5		195	66 (33.8)	NR		NA	1.24 (1.04 to 1.44)		
			68 (34.9)	NR		NA	1.26 (1.07 to 1.47)		
Salinski (1996) Followup of Clinical Trial EO3		114	28 (24.6)	NR		NA	1.04 (0.78 to 1.30)		
			24 (21.1)	NR		NA	0.95 (0.69 to 1.22)		
			25 (21.9)	NR		NA	0.98 (0.72 to 1.23)		
			31 (27.2)	NR		NA	1.10 (0.84 to 1.36)		
Case series performed in United States									
Chayasirisobhon (2001)		24	15 (62.5)	NR		NA	1.82 (0.57 to 1.26)		
Hosain (2000)		13	7 (53.9)	NR		NA	1.65 (0.88 to 2.42)		
Clinical Trial EO4 Labar (1999)		24	11 (45.8)	NR		NA	1.45 (0.90 to 2.01)		

Evidence Table 231. Proportion of patients with >50% reduction in seizure frequency in studies of vagal nerve stimulation (continued)

Reference	Study Arm	N	Number of Patients With >50% Reduction in Seizure Frequency (%)	Reported P = (Within Groups)	Reported P = (Between Groups)	Calculated by ECRI [a]			
						Minimum Detectable Change (Power = 0.8; P = 0.05)	Within Groups Summary Effect Size, Cohen's h (CI)	Minimum Detectable Difference (Power = 0.8; P = 0.05)	Between Groups Summary Effect Size, Cohen's h (CI)
Case series performed outside United States									
Aldenkamp (2001)		16	4 (25.0)	NR		NA	1.05 (0.35 to 1.74)		
Hoppe (2001)		36	11 (30.6)	NR		NA	1.17 (0.71 to 1.63)		
Ben-Menachem (1999)		63	29 (46.0)	NR		NA	1.48 (1.13 to 1.82)		
Boon (1999)		20	8 (40.0)	NR		NA	1.37 (0.75 to 1.99)		
Parker (1999)		16	4 (25.0)	NR		NA	1.05 (0.35 to 1.74)		
Lundgren (1998)		16	5 (31.3)	NR		NA	1.19 (0.49 to 1.88)		
		16	6 (37.5)	NR		NA	1.32 (0.63 to 2.01)		

[a] All calculations performed using intent-to-treat doctrine
[b] 1-tailed 2-sample arcsine binomial power analysis
[c] Between groups if a controlled trial. If case series based on comparison with a synthetic control group of equal size where no patients spontaneously had a >50% reduction in seizure frequency from baseline
[d] Does not include one patient who was withdrawn during ramp-up stage due to uninterruptible seizure diary
[e] Does not include one patient who withdrew consent during ramp up stage
[f] Chi-Squared test
[g] Fishers exact test
[h] Not an outcome measure reported by Hosain et al.. Data were extracted from individual patient data presented in Evidence Table
[I] Not applicable because this was a case series with no control group
NA = Not applicable
NC = Not calculated
NR = Not reported

Evidence Table 232. Quality of life in studies of vagal nerve stimulation

Reference	Instrument and Followup Time	Domain	Treatment Arm			Control Arm		
			N	Outcome Mean (SD)		N	Outcome Mean (SD)	
				Pretreatment	Posttreatment		Pretreatment	Posttreatment
Clinical Trial EO5 (Data extracted from Dodrill 2001)	QOLIE-31 6 months	Seizure worry	78	51.9 (26.8)	60.7 (23.7)	82	50.9 (25.2)	
		Overall QoL		67.0 (14.7)	67.9 (13.4)		62.1 (15.3)	
		Emotional well-being		68.3 (17.3)	71.5 (16.3)		65.0 (19.3)	
		Energy/fatigue		57.1 (19.2)	58.6 (18.9)		54.7 (19.7)	
		Cognitive function		53.4 (23.2)	59.5 (21.9)		57.6 (21.9)	
		Medication effects		54.1 (31.2)	58.5 (30.2)		57.9 (29.5)	
		Social functioning		53.2 (24.6)	59.1 (24.0)		54.6 (22.0)	
		Overall score		58.1 (15.0)	62.0 (14.1)		57.8 (14.3)	
	SF-36 6 months	Physical function	78	83.3 (17.1)	89.7 (11.7)	82	83.7 (18.4)	
		Role physical		68.5 (34.3)	76.2 (27.2)		62.2 (33.0)	
		Bodily pain		71.9 (22.4)	72.7 (21.0)		68.41 (25.0)	
		General health		66.2 (19.3)	69.3 (16.3)		61.9 (21.5)	
		Vitality		57.1 (19.2)	58.6 (18.9)		54.7 (19.7)	
		Social function		68.9 (27.2)	75.5 (19.7)		68.0 (21.3)	
		Role emotional		76.1 (27.4)	85.9 (21.5)		72.7 (32.0)	
		Mental health		68.3 (17.3)	71.5 (16.3)		65.0 (19.3)	
		Summary: Physical		48.3 (9.4)	49.9 (6.84)		47.1 (6.8)	
		Summary: Emotional		45.4 (10.1)	48.1 (9.12)		44.3 (10.8)	
Ergene (2001)	QOLIE-10[a] 2 weeks	Overall score	17	32.8 (standard error: 2.0)	26.0 (9.5)			
	6 weeks				25.6 (9.9)			
	12 weeks				25.7 (9.9)			
	24 weeks				24.3 (8.7)			
	48 weeks				24.9 (14.8)			

Evidence Table 232. Quality of life in studies of vagal nerve stimulation (continued)

Reference	Instrument and Followup Time	Domain	Reported P Value		ECRI Calculated Effect Sizes Hedges' d (CI)	
			Within Groups	Posttreatment Between Groups	Pretreatment Between Groups	Posttreatment Between Groups
Clinical Trial EO5 (Data extracted from Dodrill 2001)	QOLIE-31 6 months	Seizure worry	NR	0.261	0.04 (-0.27 to 0.35)	0.15 (-0.16 to 0.46)
		Overall QoL	NR	0.991	0.32 (0.01 to 0.64)	0.26 (-0.05 to 0.57)
		Emotional well-being	NR	0.316	0.18 (-0.13 to 0.49)	0.30 (-0.01 to 0.61)
		Energy/fatigue	NR	0.313	0.12 (-0.19 to 0.43)	0.24 (-0.07 to 0.55)
		Cognitive function	NR	0.279	-0.19 (-0.50 to 0.13)	-0.03 (-0.34 to 0.28)
		Medication effects	NR	0.990	-0.12 (-0.43 to 0.19)	-0.19 (-0.50 to 0.12)
		Social functioning	NR	0.283	-0.06 (-0.37 to 0.25)	0.14 (-0.17 to 0.45)
		Overall score	NR	0.274	0.02 (-0.29 to 0.33)	0.15 (-0.17 to 0.46)
	SF-36 6 months	Physical function	NR	0.105	-0.02 (-0.33 to 0.29)	0.28 (-0.03 to 0.59)
		Role physical	NR	0.037	0.19 (-0.12 to 0.50)	0.40 (0.09 to 0.71)
		Bodily pain	NR	0.376	0.15 (-0.16 to 0.46)	0.27 (-0.04 to 0.58)
		General health	NR	0.457	0.21 (-0.10 to 0.52)	0.28 (-0.04 to 0.59)
		Vitality	NR	0.313	0.12 (-0.19 to 0.43)	0.24 (-0.04 to 0.55)
		Social function	NR	0.473	0.04 (-0.27 to 0.35)	0.23 (-0.08 to 0.54)
		Role emotional	NR	0.026	0.11 (-0.20 to 0.42)	0.42 (0.10 to 0.73)
		Mental health	NR	0.316	0.18 (-0.13 to 0.49)	0.30 (-0.01 to 0.62)
		Summary: Physical	NR	0.127	0.15 (-0.16 to 0.46)	0.34 (0.03 to 0.65)
		Summary: Emotional	NR	0.202	0.10 (-0.21 to 0.41)	0.31 (-0.01 to 0.62)
Ergene (2001)	QOLIE-10[a]	Overall score				
	2 weeks		<0.01			
	6 weeks		<0.01			
	12 weeks		<0.01			
	24 weeks		<0.01			
	48 weeks		<0.01			

[a] This is a short form (10-item) version of QOLIE-31, which is in turn a short-form version of QOLIE-89.

NC Not calculated
QOLIE Quality of Life in Epilepsy
SF-36 Short-Form 36

Evidence Table 233. Adverse events in studies of vagal nerve stimulation

Reference	Adverse Event	Treatment Group		Control Group		Reported P = (Between Groups)	Effect Size Cohen's h (CI)
		N	Patients Affected (%)	N	Patients Affected (%)		
RCTs performed in United States							
Clinical Study EO5 Handforth (1999)	Voice alteration	95	63 (66.3)	103	31 (30.1)	0.001	0.74 (0.46 to 1.02)
	Cough		43 (45.3)		44 (42.7)	ns	0.05 (-0.23 to 0.33)
	Pharyngitis		33 (34.7)		26 (25.2)	ns	0.21 (-0.07 to 0.49)
	Pain		27 (28.4)		31 (30.1)	ns	-0.04 (-0.32 to 0.24)
	Dyspnea		24 (25.3)		11 (10.7)	0.007	0.39 (0.11 to 0.67)
	Headache		23 (24.2)		24 (23.3)	ns	0.02 (-0.26 to 0.30)
	Dyspepsia		17 (17.9)		13 (12.6)	ns	0.15 (-0.13 to 0.43)
	Vomiting		17 (17.9)		14 (13.6)	ns	0.12 (-0.16 to 0.40)
	Paresthesia		17 (17.9)		26 (25.2)	ns	-0.18 (-0.46 to 0.10)
	Nausea		14 (14.7)		21 (20.4)	ns	-0.15 (-0.43 to 0.13)
	Accidental injury		12 (12.6)		13 (12.6)	ns	0.00 (-0.28 to 0.28)
	Fever		11 (11.6)		19 (18.4)	ns	-0.19 (-0.47 to 0.09)
	Infection		11 (11.6)		12 (11.7)	ns	0.00 (-0.28 to 0.28)

Evidence Table 233. Adverse events in studies of vagal nerve stimulation (continued)

Reference	Adverse Event	Treatment Group		Control Group		Reported P = (Between Groups)	Effect Size Cohen's h (CI)
		N	Patients Affected (%)	N	Patients Affected (%)		
Clinical Trial EO3 The VNS Group (1995)	Hoarseness/voice change	54	20 (37.2)	60	8 (13.3)	<0.01	0.56 (0.19 to 0.93)
	Throat pain		6 (11.0)		7 (11.7)	1.00	-0.02 (-0.39 to 0.35)
	Coughing		4 (7.4)		5 (8.3)	1.00	-0.03 (-0.40 to 0.33)
	Dyspnea		3 (5.6)		1 (1.7)	0.34	0.22 (-0.15 to 0.58)
	Paresthesia		3 (5.6)		2 (3.3)	0.67	0.11 (-0.26 to 0.48)
	Muscle pain		3 (5.6)		1 (1.7)	0.34	0.22 (-0.15 to 0.58)
	Headache		1 (1.8)		5 (8.3)	0.21	-0.31 (-0.68 to 0.05)
Long-term followup of RCTs performed in United States							
Salinski (1996) Followup of Clinical Trial EO3	Accidental injury	195	30 (15.4)				
	Cough, increased		29 (14.9)				
	Voice alteration		107 (54.9)				
	Dyspnea		25 (12.8)				
	Pain		30 (15.4)				
	Parasthesia		30 (15.4)				
	Headache		31 (15.9)				
	Pharyngitis		20 (10.3)				
	Depression		10 (5.1)				
	Infection		12 (6.2)				
Salinski (1996) Followup of Clinical Trial EO3	Device malfunction	114	2 (1.8)				
	Myocardial infaction		1 (0.9)				
Case series performed in the United States							
Chayasirisobhon (2001)	Vocal cord paralysis	24	2 (8.3)				
	Hoarseness		12 (50.0)				

Evidence Table 233. Adverse events in studies of vagal nerve stimulation (continued)

Reference	Adverse Event	Treatment Group		Control Group		Reported P = (Between Groups)	Effect Size Cohen's h (CI))
		N	Patients Effected (%)	N	Patients Effected (%)		
Ergene (2001)	Throat irritation	17	4 (23.5)				
	Difficulty breathing		1 (5.9)				
	Difficulty speaking		1 (5.9)				
	Epigastric discomfort		1 (5.9)				
	Increased snoring		1 (5.9)				
Hosain (2000)	Hoarseness	13	3 (23.1)				
	Excessive coughing		3 (23.1)				
	Infection		1 (7.7)				
Clinical Trial EO4 Labar (1999)	Incisional parasthesias	24	2 (8.3)				
	Incisional pain		2 (8.3)				
	Cough		6 (25.0)				
	Abdominal pain		2 (8.3)				
	Anorexia		1 (4.2)				
	Hiccups		1 (4.2)				
	Dysphagia		1 (4.2)				
	Emesis		1 (4.2)				
	Fatigue		1 (4.2)				
Case series performed outside United States							
Ben-Menachem (1999)	Hoarseness	64	11 (17.2)				
	Dyspnea		1 (1.6)				
	Cord paresis		1 (1.6)				
	Throat pain		3 (4.7)				
	Generator placement problem		1 (1.6)				
Boon (1999)	Throat parestaesias	20	1 (5.0)				
	Hoarseness or voice change		4 (20.0)				
	Exercise dyspnea		1 (5.0)				

Evidence Table 233. Adverse events in studies of vagal nerve stimulation (continued)

Reference	Adverse Event	Treatment Group		Control Group		Reported P = (Between Groups)	Effect Size Cohen's h (CI)
		N	Patients Affected (%)	N	Patients Affected (%)		
Lundgren (1998)	Aspiration	16	2 (12.5)				
	Hoarseness		6 (37.5)				
	Throat pain		1 (6.3)				
	Increased salivation		2 (12.5)				
	Tiredness		2 (12.5)				
	Electrical line fracture		1 (6.3)				
	Premature current failure		5 (31.3)				

Evidence Table 234. Mortality in studies of vagal nerve stimulation

Reference	Treatment Group			Control Group		
	N	Number of Deaths (%)	Cause of Death	N	Number of Deaths (%)	Cause of Death
RCTs performed in United States						
Clinical Study EO5 Handforth (1999)	95	0 (0.0)	NA	103	0 (0.0)	
Clinical Trial EO3 The VNS Group (1995)	54	0 (0.0)	NA	60	0 (0.0)	
Followup studies of RCT's performed in the United States (case-series)						
DiGiorgio (2000) Followup of Clinical Trial EO5	195	2 (1.0)	1 patient: Pneumonia, sepsis and respiratory failure related to untreated infection. Authors state that death was a direct result of VNS implantation and/or use. 1 patient: Suden unexpected death			
Salinski (1996) Followup of Clinical Trial EO3	114	2 (1.8)	1 patient: Thrombotic thrombocytopenic purpura 1 patient: Drowning. Authors state that deaths were unlikely to be related to VNS.			
Case series performed in the United States						
Chayasirisobhon (2001)	24	0 (0.0)				
Ergene (2001)	17	0 (0.0)				
Hosain (2000)	13	0 (0.0)				
Clinical Trial EO4 Labar (1999)	24	0 (0.0)				
Case series performed outside of the United States						
Aldenkamp (2001)	16	0 (0.0)				
Hoppe (2001)	36	0 (0.0)				
Ben-Menachem (1999)	64	4 (6.3)	3 patients: Status epilepticus 1 patient: Sudden unexpected death			
Boon (1999)	20	0 (0.0)				
Parker (1999)	16	0 (0.0)				
Lundgren (1998)	16	0 (0.0)				

Evidence Table 235. Articles addressing the ketogenic diet excluded for quality reasons

Study	Reason for Exclusion
Pulsifier (2001)	The aim of this study was to evaluate effects of ketogenic diet on behavior and cognitive function. Study only evaluated patients who had successfully completed 1 year of treatment. According to the authors 40% of patients who started ketogenic diet had discontinued it by 1 year due to treatment disatisfaction. This study provides a highly biased estimate of the effects of ketogenic diet on behavior and cognitive function because it is based entirely on data from patients who are satisfied with the treatment.
Mak (1998)	Although authors state that outcome data were recorded at 1 month followup, they refer to a table that states that seizure frequency data was recorded at least three months after discontinuation of the ketogenic diet in 10 of the 13 patients included in study. This flaw precludes determining whetehr there was a causal relationship between diet and outcome.
Edelstein (1996)	Efficacy and adverse event outcome data were poorly described. Changes in seizure frequency were only subjectively described (e.g. “deminished seizure activity occurred in 16 patients.” No empirical data presented).
Schwartz (1988)	59 patients allocated to one of three ketogenic diets (Classical 4:1, MCT, modified MCT). If seizure control was unsatifactory or if major diet problems were encountered, patients were offered the option to change to alternative diet. If patient opted to try another diet, the child was readmitted, existing diet discontinued and new diet commenced. Four patients withdrew. Eight patients opted to try a new diet and data from both diets in the same patient were included in analysis resulting in an assessment of efficacy of treatment based on 63 studies originating from 55 patients. Data for three separate diets were not analyzed seperately but instead were combined leading to double counting of data from some patients. Double counting of data from a single patient is a fatal flaw.

Question 6

Which social, psychological or psychiatric services for treatment-resistant epilepsy lead to, or can be expected to lead to improved patient outcomes?

Evidence Table 236. Excluded studies of nondrug, nonsurgical treatments for treatment-resistant epilepsy

Reference	Intervention	Reason for Exclusion
Uhlmann (2001)	EEG Biofeedback and End-tidal CO_2 biofeedback	Patients were treated with one of two interventions. Outcomes were reported for all patients combined, regardless of treatment group.
Andrews (2000)	Comprehensive multidisciplinary neurobehavioral treatment	Fewer than five studies reported on this intervention.
Reiter (2000)	Comprehensive multidisciplinary neurobehavioral treatment	Patients changed their AED regimen during treatment, making this trial subject to a strong extraneous events bias. Therefore, outcomes cannot be separately associated with either the result of the training or the change in AEDs.
Sidorenko (2000)	Medical Resonance Therapy Music	Fewer than five studies reported on this intervention.
Kotchoubey (1999)	EEG Biofeedback	Fewer than five studies reported on this intervention.
Kotchoubey (1999)	EEG Biofeedback	Fewer than five studies reported on this intervention.
Schmid-Schonbein (1998)	Self-control training	Patients changed their AED regimen during treatment, making this trial subject to a strong extraneous events bias. Therefore, outcomes cannot be separately associated with either the result of the training or the change in AEDs.
Kotchoubey (1996)	EEG Biofeedback	Patients received behavioral therapy during treatment, making this trial subject to a strong extraneous events bias. Therefore, outcomes cannot be separately associated with either the result of the biofeedback or the behavioral therapy.
Panjwani (1996)	Sahaja yoga	Fewer than five studies reported on this intervention.
Deepak (1994)	Meditation	Fewer than five studies reported on this intervention.
Eriksen (1994)	Physical Exercise	Fewer than five studies reported on this intervention.
Becu (1993)	Self-Help Group (Group Therapy)	Fewer than five studies reported on this intervention.
Rockstroh (1993)	EEG Biofeedback	Fewer than five studies reported on this intervention.

Evidence Table 236. Excluded studies of nondrug, nonsurgical treatments for treatment-resistant epilepsy (continued)

Reference	Intervention	Reason for Exclusion
Usiskin (1993)	Counseling	Fewer than five studies reported on this intervention.
Andrews (1992)	Comprehensive multidisciplinary neurobehavioral treatment	Fewer than five studies reported on this intervention.
Puskarich (1992)	Progressive muscle relaxation	Fewer than five studies reported on this intervention.
Fried (1990) and Fried (1993)	End-Tidal CO_2 Biofeedback	Fewer than five studies reported on this intervention.
Gillham (1990)	Comprehensive multidisciplinary neurobehavioral and psychological treatment	Fewer than five studies reported on this intervention.
Nakken (1990)	Physical Exercise	Fewer than five studies reported on this intervention.
Whitman (1990)	Progressive muscle relaxation	Fewer than five studies reported on this intervention.
Denio (1989)	Physical Exercise	Fewer than five studies reported on this intervention.
Lantz (1988)	EEG Biofeedback	Fewer than five studies reported on this intervention.
Dahl (1987)	Contingent relaxation with neurobehavioral training	Fewer than five studies reported on this intervention.
Fraser (1986)	Vocational Services	Fewer than five studies reported on this intervention.
Virudhagirinathan (1986)	Systematic Desensitization	Fewer than five studies reported on this intervention.

Question 7

What characteristics of treatment-resistant epilepsy interfere with ability to obtain and maintain employment, or attend and perform well in school?

Evidence Table 237. Excluded studies of employment and schooling

Reference	Reason for Exclusion
Clemmons (1987)	No data are reported on patient characteristics. The number of patients who are treatment-resistant cannot be determined, and other factors such as the presence of severe neurological disorders are not considered.
Fraser (1986)	This study involved highly specialized patients: those with suspected brain impairment who enrolled in an intensive vocational intervention program. The reported data are unlikely to be generalizable to the greater population of patients with treatment-resistant epilepsy.

Question 8

What is the mortality rate in patients with treatment-resistant epilepsy?

Evidence Table 238. Excluded studies of mortality rate in patients with treatment-resistant epilepsy

Reference	Reason for Exclusion
Dashieff (1991)	Length of followup not reported, therefore person-years of exposure cannot be determined and mortality rate cannot be calculated.
Tudehope (1988)	Article does not provide enough information to determine whether patients had treatment-resistant epilepsy. Also not clear that all patients had epilepsy.
Derby (1996)	Patients with epilepsy identified through AED prescriptions in databases rather than by clinical diagnosis. Since AEDs may be prescribed for conditions other than epilepsy, this increases the likelihood of including patients who were never diagnosed with epilepsy.
Tennis (1995)	Patients with epilepsy identified through AED prescriptions in databases rather than by clinical diagnosis. Since AEDs may be prescribed for conditions other than epilepsy, this increases the likelihood of including patients who were never diagnosed with epilepsy.

Evidence Table 239. Design and conduct of included studies mortality rate in patients with treatment-resistant epilepsy

Reference	Country	N	Epilepsy Diagnosis Determined	Study Design	Standardized Mortality Ratio Reported (or Calculable)	Standardized Mortality Ratio Adjusted For Factors Other Than Age	Compliance Reported
Physician's desk reference Gabapentin trial data (2001)	United States	2203	Clinical diagnosis	Retrospective case series	No	Not applicable	No
Racoosin (2001)	United States	9144	Clinical diagnosis	Retrospective case series[a]	Yes	Gender (only for male vs. female standardized mortality ratio)	No
Wong (2001)	United Kingdom	1050	Clinical diagnosis	Retrospective double cohort	Yes	Gender	Yes
Annegers (2000)	United States	1819	Clinical diagnosis	Retrospective double cohort	Yes	Gender	Not applicable
Hennessy (1999)	United Kingdom	305	Clinical diagnosis	Retrospective double cohort	Yes	None	Not applicable
Sperling (1999)	United States	393	Clinical diagnosis	Prospective double cohort	Yes	Gender	Not applicable
Vickrey (1997)	United States	248	Clinical diagnosis	Retrospective case series	No	Not applicable	Not applicable
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	Clinical diagnosis	Retrospective case series	No	Not applicable	No
Leppik (1995)	United States, Europe, Australia	2600	Clinical diagnosis	Retrospective case series	No	Not applicable	No
Klenerman (1993)	United Kingdom	Reported as person-years	Clinical diagnosis	Retrospective double cohort	Yes	Gender	No

[a] ECRI was able to calculate standardized mortality ratios using a general reference population. For our purposes, this study became a retrospective double cohort study.

Evidence Table 240. Overall mortality rates in studies of treatment-resistant epilepsy patients

Comparison to mortality rates of general population in studies with reported standardized mortality ratios or from which standardized mortality ratios could be calculated

Reference	Country	N	Treatment	Subgroup	Overall Mortality Rate Per 1000 Person-Years (CI)		Standardized Mortality Ratio (CI)
					Study Population	General Reference Population	
Racoosin (2001)	United States	9144	AEDs	All patients	9.11 (7.64-10.85)[c]	2.53[a]	3.60 (2.99-4.29)[d]
				Male	11.3 (9.2-13.9)	3.20[a]	3.6 (2.9-4.4)[d]
				Female	6.1 (4.4-8.5)	1.75[a]	3.5 (2.5-4.8)[d]
				Ages:			
				1-14	4.1 (1.7-9.8)	0.25[a]	16.4 (4.5-41.5)[d]
				15-34	7.2 (5.4-9.5)	1.01[a]	7.1 (5.3-9.6)[d]
				35-54	9.6 (7.2-12.9)	3.23[a]	3.0 (1.4-5.5)[d]
				55-72	32.1 (21.5-47.8)	14.56[a]	2.2 (1.5-3.1)[d]
Wong[f] (2001)	United Kingdom	1050	AEDs	All patients	16.6 (12.1-22.6)[c]	1.59[c]	10.4 (7.1-13.7)
Annegers (2000)	United States	1819	Vagal nerve stimulation	All patients	7.87 (5.34-11.59)[c]	2.18[a]	3.62 (2.34-5.35)
				Male	8.1		2.80 (1.53-4.70)
				Female	7.7		5.79 (2.89-10.37)
				Ages:			
				<25			11.4 (4.9-22.5)
				25-34			6.1 (2.6-11.9)
				≥35			1.8 (0.8-3.5)
Hennessy (1999)	United Kingdom	305	Surgery	All patients	7.33 (4.75-11.29)[c] (includes some patients seizure-free after surgery)	1.62	4.52 (2.76-6.99)[e]
Sperling (1999)	United States	194[b]	Surgery	All patients	13.72 (7.68-24.41)[c]	2.90[a]	4.69 (2.34-8.41)[e]
Klenerman (1993)	United Kingdom	Not reproted	AEDs	All patients	33.31 (27.78-39.90)[c]	17.19[c]	1.94 (1.60-2.34)[e]

[a] Calculated by ECRI from U.S. Census Bureau, Statistical Abstract of the United States, 2000.
[b] This study followed a total of 393 patients after surgery; 199 became seizure free and were not included in the mortality analysis (none of these patients died).
[c] Calculated by ECRI from Mortality Statistics (England and Wales, 1999).
[d] Calculated by ECRI
[e] 95% CI calculated by ECRI
[f] The study by Wong (2001) reported mortality data for groups of patients receiving different AEDs (lamotrigine, gabapentin, and/or vigabatrin). Because many patients received more than one of these drugs, they were included in more than one group. Therefore, we have evaluated only the patients receiving lamotrigine (the largest group, n = 1,050) to avoid double counting.

Evidence Table 241. Sudden unexpected death rates in studies of treatment-resistant epilepsy patients

Reference	Country	N	Treatment	Subgroup	Sudden Unexpected Death Rate Per 1000 Person-Years (CI)	Percentage of Total Deaths Represented by SUDEP
Physician's desk reference (PDR) Gabapentin trial data (2001)	United States	2203	AEDs	All patients	3.80 (1.93-7.49)[a]	Cannot be calculated
Racoosin (2001)	United States	9144	AEDs	All patients Male Female Ages: 1-14 15-34 35-54 55-72	3.82 (2.91-5.00)[a] 4.4 (3.2-6.2) 3.0 (1.8-4.8) 2.4 (0.8-7.6) 3.2 (2.1-4.8) 4.9 (3.3-7.4) 5.3 (2.0-14.2)	41.9%
Wong (2001)	United Kingdom	1050	AEDs	All patients	7.64 (4.84-12.05)[a]	46.1%
Annegers (2000)	United States	1819	Vagal nerve stimulation	All patients	4.09 (2.39-6.99)[a]	52%
Sperling (1999)	United States	194	Surgery	All patients	7.49 (3.44-16.24)[a]	54.5%
Hennessy (1999)	United Kingdom	305	Surgery	All patients	2.20 (1.01-4.79)[a]	30%
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	All patients	3.13 (1.98-4.95)[a]	40%
Leppik (1995)	United States, Europe, Australia	2600	AEDs	All patients	3.87 (1.87 to 7.96)[a]	29.2%
Klenerman (1993)	United Kingdom	NR	AEDs	All patients	2.06 (1.00-4.25)[a]	6.2%

[a] Calculated by ECRI

Evidence Table 242. Drowning rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Drowning Rate Per 1000 Person-Years (All Patients)				
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]	Highest Age-Specific Rate in General Reference Population	Crude Mortality Ratio (CI)[c]
Hennessy (1999)	United Kingdom	305	Surgery	1.10 (0.37-3.23)	0.005[e]	214 (43.07-626.11)	0.0196[e]	56.18 (11.29-165.39)
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	0.35 (0.10- 1.27)	0.013[d]	26.67 (3.00-96.29)	0.0196[e]	17.70 (1.99-63.91)
Vickrey (1997)	United States	248	Surgery or AEDs	0.67 (0.12-3.80)	0.013[d]	51.81 (0.68-259.67)	0.0196[r]	34.48 (0.45-170.14)
Klenerman (1993)	United Kingdom	NR (reported as patient-years)	AEDs	0.59 (0.16- 2.15)	0.005[e]	117.65 (13.21-424.80)	0.0196[e]	30.30 (3.40-109.42)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] Study population rate / highest age-specific rate in general reference population, calculated by ECRI
[d] From U.S. Census Bureau, Statistical Abstract of the United States, 2000
[e] Calculated by ECRI from Mortality Statistics (England and Wales, 1999)

Evidence Table 243. Accident-related mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Accident-Related Mortality Rate Per 1000 Person-Years				
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]	Highest Rate in General Reference Population	Crude Mortality Ratio (CI)[c]
Racoosin (2001)	United States	9144	AEDs	All patients: 1.47 (0.95-2.27)	Age-adjusted: 0.29[d]	5.06 (3.09-7.83)	0.92[d]	1.60 (0.98-2.47)
Hennessy (1999)	United Kingdom	305	Surgery	All patients: 1.47 (0.57-3.76) (includes some patients seizure-free after surgery)	All patients: 0.21[e]	6.98 (1.86-17.88)	0.25[e]	5.87 (1.57-15.02)
Sperling (1999)	United States	194	Surgery	All patients: 1.25 (0.22-7.03)[a]	Age-adjusted: 0.29[d]	4.31 (0.06-23.97)	0.37[d]	3.37 (0.04-18.73)
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	All patients: 0.52 (0.18-1.53)	Age-adjusted: 0.29[d]	1.80 (0.36-5.26)	0.92[d]	0.57 (0.11-1.67)
Leppik (1995)	United States, Europe, Australia	2600	AEDs	All patients: 1.66 (0.56 to 4.86)	Age-adjusted: 0.29[d]	5.71 (1.15-16.70)	0.92[d]	1.80 (0.36-5.26)
Klenerman (1993)	United Kingdom	NR	AEDs	All patients: 0.88 (0.30-2.60)	All patients: 0.21[e]	4.21 (0.85-12.32)	2.57[e]	0.34 (0.07-1.01)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] Study population rate / highest rate in general reference population, calculated by ECRI
[d] From U.S. Census Bureau, Statistical Abstract of the United States, 2000. The standard population for age-adjustment was the U.S. population in 1940.
[e] Calculated by ECRI from Mortality Statistics (England and Wales, 1999).

Evidence Table 244. Automobile accident-related mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Automobile-Accident-Related Mortality Rate Per 1000 Person-Years		
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]
Sperling (1999)	United States	194	Surgery	All patients: 1.25 (0.22-7.03)	Age-adjusted: 0.16[c]	7.81 (0.10-43.47)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] From U.S. Census Bureau, Statistical Abstract of the United States, 2000. The standard population for age-adjustment was the U.S. population in 1940.

Evidence Table 245. Aspiration-related mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Aspiration-Related Mortality Rate Per 1000 Person-Years		
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]
Racoosin (2001)	United States	9144	AEDs	All patients: 0.29 (0.11- 0.76)	Not reported	Cannot be calculated
Hennessy (1999)	United Kingdom	305	Surgery	All patients: 0.73 (0.20-2.67) (includes some patients seizure-free after surgery)	Not reported	Cannot be calculated
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	All patients: 0.17 (0.03-0.99)	Not reported	Cannot be calculated
Klenerman (1993)	United Kingdom	Not reported (reported as patient-years)	AEDs	All patients: 1.77 (0.81- 3.85)	Not reported	Cannot be calculated

[a] Calculated by ECRI
[b] Available studies did not report any deaths from aspiration.

Evidence Table 246. Pneumonia-related mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Pneumonia Mortality Rate Per 1000 Person-Years				
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]	Highest Rate in General Reference Population	Crude Mortality Ratio (CI)[c]
Sperling (1999)	United States	194	Surgery	All patients: 1.25 (0.22- 7.03)	Age-adjusted: 0.13[d]	9.62 (0.13-53.53)[a]	Not applicable[f]	Not applicable[f]
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	All patients: 0.17 (0.03- 0.99)	Age-adjusted: 0.13[d]	1.34 (0.02-7.45)[a]	2.28[e]	0.08 (0.01-0.42)
Klenerman (1993)	United Kingdom	Not reported (reported as patient-years)	AEDs	All patients: 8.25 (5.72- 11.90)	All patients: 0.34[e]	24.28 (16.13-35.10)[a]	34.12[e]	0.24 (0.16-0.35)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] Study population rate / highest rate in general reference population, calculated by ECRI
[d] From U.S. Census Bureau, Statistical Abstract of the United States, 2000.
[e] From Mortality Statistics (England and Wales, 1999).
[f] The highest value for an individual age group was not higher than the value for the overall reference population, so no sensitivity analysis could be performed.

Evidence Table 247. Cardiovascular mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Cardiovascular Mortality Rate Per 1000 Person-Years		
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]
Hennessy (1999)	United Kingdom	305	Surgery	Crude: 0.37 (0.06-2.07)	0.42[c]	0.87 (0.01-4.87)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] Calculated from age-specific rates in Mortality Statistics (England and Wales, 1999).

Evidence Table 248. Cerebrovascular mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Cerebrovascular Mortality Rate Per 1000 Person-Years		
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]
Racoosin (2001)	United States	9144	AEDs	All patients: 0.51 (0.25- 1.06)	Age-adjusted: 0.25[c]	2.06 (0.55- 4.24)
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	All patients: 0.17 (0.03- 0.99)	Age-adjusted: 0.25[c]	0.70 (0.01- 3.87)
Klenerman (1993)	United Kingdom	Not reported (reported as patient-years)	AEDs	All patients: 1.77 (0.81- 3.85)	All patients: 1.01[d]	1.75 (0.64-3.81)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] From U.S. Census Bureau, Statistical Abstract of the United States, 2000. The standard population for age-adjustment was the U.S. population in 1940.
[d] From Mortality Statistics (England and Wales, 1999).

Evidence Table 249. Cancer-related mortality rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Cancer Mortality Rate Per 1000 Person-Years		
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]
Klenerman (1993)	United Kingdom	Not reported (reported as patient-years)	AEDs	All patients: 8.55 (5.96-12.25)[a]	4.28[c]	SMR cancer: 2.0 (1.3-2.9) Lung: 3.3 (1.7-5.9) Pancreas: 6.2 (1.7-15.8) Lymphatic/ Haemopoetic: 3.3 (0.7-9.3) Hepatobiliary: 17.6 (3.6-51.5)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] Calculated by ECRI from age-specific rates in Mortality Statistics (England and Wales, 1999).

Evidence Table 250. Suicide rates among patients with treatment-resistant epilepsy

Reference	Country	N	Treatment	Suicide Rate Per 1000 Person-Years		
				Study Population Rate (CI)[a]	General Reference Population Rate	Crude Mortality Ratio (CI)[b]
Sperling (1999)	United States	194	Surgery	All patients: 1.25 (0.22 to 7.03)	Age-adjusted: 0.10[c]	12.5 (0.16 to 69.53)
Hennessy (1999)	United Kingdom	305	Surgery	All patients: 0.37 (0.06-2.07)	0.11[d]	3.33 (0.37-18.55)
Leestma (1997)	United States, United Kingdom, Europe, Australia, South Africa	4700	AEDs	All patients: 0.17 (0.03 to 0.99)	Age-adjusted: 0.10[c]	1.74 (0.02 to 9.68)

[a] Calculated by ECRI
[b] Study population rate / general reference population rate, calculated by ECRI
[c] From U.S. Census Bureau, Statistical Abstract of the United States, 2000. The standard population for age-adjustment was the U.S. population in 1940.
[d] From Mortality Statistics (England and Wales, 1999).

Question 9

Is there a correlation between the number and/or type of seizure and sudden death?

Evidence Table 251. Design and conduct of included studies of sudden unexpected death from epilepsy (SUDEP)

Reference	Country	N	Epilepsy Diagnosis	Study Reported Criteria For Diagnosis of SUDEP	Proportion (Percent) SUDEP Cases Determined by Autopsy
Walczak (2001)	United States	4578	Clinical diagnosis	Yes	10/20 (50%)
McKee (2000)	United States	180	Clinical diagnosis plus AED treatment	Yes	4/11 (36.4%)
Kloster (1999)	Norway	79	Clinical diagnosis	Yes	42/42 (100%)
Nilsson (1999)	United Kingdom	228	Clinical diagnosis	Yes	52/57 (91.2%)
Sperling (1999)	United States	393	Clinical diagnosis	Yes	Not reported
Nashef (1995)	United Kingdom	601	Clinical diagnosis	No	10/11 (90.9%)
Timmings (1993)	United Kingdom	1820	Clinical diagnosis	No	Not reported
Jick (1992)	United States	3280 (only 31 were relevant to this question)	Anticonvulsant usage and other information on file (based on random review of only 5% of records)	Yes	11/11 (100%)
Birnbach (1991)	United States	108	Clinical diagnosis	No	Not reported

Evidence Table 251. Design and conduct of included studies of sudden unexpected death from epilepsy (continued)

Reference	Study Design	Controls	Controls Matched to Cases	Methods Used to Correlate Seizure Type/Frequency And SUDEP	Study Adjusted For Potential Confounding Variables
Walczak (2001)	Prospective nested case-control	Living patients	Yes (matched by time of enrollment and epilepsy center)	Multiple logistic regression	Yes
McKee (2000)	Retrospective nested case-control	Living patients	No	t-test	No
Kloster (1999)	Retrospectivenested case-control	Deceased	No	Student's t-test or Pearson's χ^2 test	No
Nilsson (1999)	Retrospectivenested case-control	Living patients	Yes (matched for year of birth, gender, and assessment period)	Multiple logistic regression	Yes
Sperling (1999)	Prospective nested case-control	All patients in cohort (living and dead)	No	No statistical comparison (only for overall mortality)	No (only in overall mortality analysis, not for sudden death)
Nashef (1995)	Retrospectivenested case-control	All patients in cohort (living and deceased)	No	No statistical comparison	No
Timmings (1993)	Retrospectivenested case-control	Unclear, but could be all other patients in cohort	No	χ^2 test	No
Jick (1992)	Retrospectivenested case-control	Living patients	Yes (matched on age at index date and gender)	No statistical comparison	No
Birnbach (1991)	Retrospectivenested case-control	Deceased and living patients	No	Student's t-test, χ^2 test	No

Evidence Table 252. Correlation between SUDEP and seizure frequency

Studies adjusted for potential confounding variables

Reference	Country	N	Seizure Frequency	SUDEP (N)	Control (N)	Published Results	Statistically Significant Association	Other Variables Adjusted For in Multiple Regression Analysis
Walczak (2001)	United States	4578 (only 100 were relevant to this question)	Monthly average: 0 ≤1 >1 to ≤15 >15 to ≤50 >50 Unknown Males <1 1-5 >5 Unknown Females <1 1-5 >5 Unknown	 2 3 10 2 3 0 2 3 3 0 2 5 5 0	 23 16 30 5 3 3 17 11 16 0 19 5 9 3	OR[a] (CI) Multiple regression 1.1 (0.3-4.0) 1.0[b] 3.4 (0.5-22) 1.0 (0.1-7.9) 1.0[b] 5.7 (0.6-43.9) 7.4 (1.3-43.0)	No (possibly for females, but the publication did not specifically report that the gender-specific ratios were derived from a multivariate analysis)	Frequency of tonic-clonic seizures, number of AEDs used
Nilsson (1999)	United Kingdom	228	Seizures/year 0-2 3-12 >12 Males 0-2 3-12 13-50 >50 Unknown Females 0-2 3-12 13-50 >50 Unknown	 5 16 24 2 12 7 4 9 3 4 8 5 3	 87 33 39 56 18 12 7 9 31 15 14 6 3	Multiple regression RR[c] (CI) 1.00[b] 4.47 (1.33-15.03) 4.64 (1.22-17.63) Unadjusted RR[c] 1.00[b] 14.8 (3.1-69.7) 15.1 (2.8-81.2) 14.8 (2.3-96.1) 24.1 (4.2-138.6) Unadjusted RR[c] 1.00[b] 2.5 (0.5-12.0) 4.7 (1.1-19.6) 6.5 (1.2-34.3) 7.2 (0.9-56.6)	Yes	Age at epilepsy onset, epilepsy type, number of AEDs, changes in AED dose per year

[a] Odds ratio

[b] Used as a reference value for the other seizure frequencies

[c] Relative risk

Evidence Table 253. Correlation between SUDEP and seizure frequency

Studies did not adjust for potential confounding variables

Reference	Country	N	Seizure Frequency	SUDEP (N)	Control (N)	Published Results	Odds Ratio (CI)[a]	Statistically Significant Association If Not, What W as The Minimum Detectable Difference
McKee (2000)	United States	180	Yearly mean SUDEP: 143 Control: 27	NA	NA	p = 0.07	Cannot be calculated	No Cannot be calculated
Kloster (1999)	Norway	79	Seizures per year ≤1 2-12 >12 No data	 4 3 32 3	 6 1 26 4	p = 0.56	 0.54 (0.14-2.10) 2.77 (0.28-27.85) 1.35 (0.50-3.68) 0.63 (0.13-3.04)	No 6.28
Sperling (1999)	United States	393	Seizures: 0 >0	 0 6	 199 188	None[b]	 0.07 (0.00-1.30) 13.76 (0.77-245.93)	No 15.1
Timmings (1993)	United Kingdom	1820	Seizures per month <1 1-4 5-60 Unknown	 4 5 4 1	NR	p = NS[c]	Cannot be calculated	No Cannot be calculated

[a] Calculated by ECRI
[b] No statistical analysis
[c] Specific p-value not reported
NA Not applicable
NR Not reported
NS Not statistically significant

Evidence Table 253. Correlation between SUDEP and seizure frequency (continued)

Reference	Country	N	Seizure Frequency	SUDEP (N)	Control (N)	Published Results	Odds Ratio (CI)[a]	Statistically Significant Association If Not, What Was The Minimum Detectable Difference
Jick (1992)	United States	3280 (only 31 were relevant to this question)	Seizures per month ≤1 >1 Unknown	 6 3 2	 13 4 3	None[b]	 0.65 (0.14-2.90) 1.50 (0.27-8.38) 1.26 (0.18-8.97)	No 6.36
Birnbach (1991)	United States	48	Mean ±SD generalized seizures per month SUDEP: 1.86 ± 3.47 Non-SUDEP deaths: 1.24 ± 1.52 Living: 0.43 ± 0.80	NA	NA	SUDEP vs. Non-SUDEP deaths: t = 0.70[d] p = 0.255[a] SUDEP vs. Living controls: t = 2.57[a] p = 0.013[a]	Cannot be calculated	No (SUDEP vs. Non-SUDEP deaths) 1.56 Yes (SUDEP vs. Living controls)

[a] Calculated by ECRI
[b] No statistical analysis
[d] Student's t-test
NA Not applicable

Evidence Table 254. Correlation between SUDEP and seizure type

Studies adjusted for potential confounding variables

Reference	Country	N	Seizure Type	SUDEP (N)	Control (N)	Published Results	Statistically Significant Association	Other Variables Adjusted For In Multiple Regression Analysis
Walczak (2001)	United States	4578 (only 100 were relevant to this question)	All patients Tonic-clonic 0 1-3 >3 Unknown Males Tonic-clonic 0 1-3 >3 Unknown Females Tonic-clonic 0 1-3 >3 Unknown	 4 6 9 1 2 2 3 1 2 4 6 0	 54 11 15 0 26 6 12 0 28 5 3 0	Multiple Regression OR (CI) 7.0 (2.0-24.2) OR (CI) 1.0[b] 4.3 (0.5-37.3) 3.3 (0.5-22.1) 1.0[b] 11.2 (1.6-78.4) 28.0 (3.8-205.8)	Yes	Overall seizure frequency, number of AEDs used
Nilsson (1999)	United Kingdom	228	Generalized idiopathic Partial symptomatic Partial cryptogenic Undetermined	7 26 17 7	12 92 45 22	Multiple regression RR (CI) 1.00 1.15 (0.18-7.17) 1.94 (0.27-13.71) 1.17 (0.14-9.78)	No	Seizure frequency during last year, age at epilepsy onset, number of AEDs, changes in AED dose per year

[a] Calculated by ECRI

[b] Used as a reference value for the other seizure frequencies

OR Odds ratio

RR Relative risk

Evidence Table 255. Correlation between SUDEP and seizure type

Studies did not adjust for potential confounding variables

Reference	Country	N	Seizure Type	SUDEP (N)	Control (N)	Published Results	Odds Ratio (CI)[a]	Statistically Significant Association If Not, What Was The Minimum Detectable Difference
Kloster (1999)	Norway	79	Generalized motor seizures Partial seizures	42 0	35 2	p = 0.07 (χ^2 test)	5.99 (0.28-128.8) 0.17 (0.01-3.59)	No 10.27
Sperling (1999)	United States	393	Non-tonic-clonic Tonic-clonic	2 4	297 90	None[b]	0.15 (0.03-0.84) 6.60 (1.19-36.63)	Yes
Nashef (1995)	United Kingdom	601	Partial cryptogenic/ symptomatic Generalized idiopathic Generalized cryptogenic/ symptomatic Undetermined	5 1 3 2	396 75 44 63	None[b]	0.41 (0.12-1.35) 0.69 (0.09-5.44) 4.65 (1.19-18.17) 1.86 (0.39-8.80)	Yes
Timmings (1993)	United Kingdom	1820	Idiopathic generalized tonic clonic Partial seizures (with or without secondary generalization)	10 4	Not reported Not reported	p <0.05 (χ^2 test)	Cannot be calculated	Yes
Jick (1992)	United States	3280 (only 31 were relevant to this question)	Primary generalized Primary partial Unknown	6 2 3	10 5 5	None[b]	1.20 (0.27-5.25) 0.67 (0.11-4.18) 1.13 (0.21-5.97)	No 9.71
Birnbach (1991)	United States	108	Generalized convulsive Other	24 1	Non-SUDEP 22 1	None[b]	1.09 (0.06-18.52) 0.92 (0.05-15.56)	No
			Generalized convulsive Other	24 1	Living 47 13	None[b]	6.64 (0.82-53.81) 0.15 (0.02-1.22)	No 7.34

[a] Calculated by ECRI

[b] No statistical analysis

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