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 Specific 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		
					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	**Domain**	**Measure**	**Patients in Drug Reduction Group**	**Patients in Control Group**					
Rey (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		
					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	**Domain**	**Measure**	**Patients in Drug Reduction Group**	**Patients in Control Group**					
Reference (1990)	Memory and 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		
					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	**Domain** Psychomotor function	**Measure** Tapping Rate: Dominant hand	**Patients in Drug Reduction Group** PHT: 19	**Patients in Control Group** 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		
					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	**Domain**	**Measure**	**Patients in Drug Reduction Group**	**Patients in Control Group**					
Pecknold (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		
					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	Domain	Measure	Patients in Drug Reduction Group	Patients in Control Group					
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)

					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) 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