Table 1. Technologies addressed

Drug Strategies	Surgery	Nondrug, Nonsurgical	Service-related Interventions	Diagnostics
Sequential monotherapy	***Temporal lobe***	***Vagal nerve stimulation (VNS)***	Multidisciplinary neurobehavioral treatments	***Blood prolactin***
Polytherapy	***Hemispherectomy***	Ketogenic diets	EEG biofeedback	Routine-EEG
Drug reduction	***Corpus callosotomy***	Chiropractic	Epilepsy education	Video-EEG
Maximum tolerable dosage	***Multiple subpial transection***	Acupuncture	Vocational services	Ambulatory-EEG
Dose frequency optimization	***Frontal lobe***	Hyperbaric oxygen	Physical exercise	Blood creatine kinase
	Parietal lobe	Herbal medicine and homeopathy	Medical resonance therapy music	Computed tomography
	Occipital lobe	Cranial realignment	Sahaja yoga	Magnetic resonance imaging
		Magnetic therapy	Meditation	Single Photon Emission Computed Tomography
		Electrical brain stimulation	Self-help group (group therapy)	Minnesota Multiphasic Personal Inventory
		Vitamin B_6	Counseling	Provocation techniques
			Progressive muscle relaxation	Tilt table
			End-tidal CO_2 biofeedback	Auditory evoked potentials
			Systematic desensitization	Hypnotic recall
				Tongue biting

Note: Bolded, italicized technologies are those addressed in this report. The remaining technologies were not addressed due to insufficient literature

Table 2. Number of articles in the Evidence Report

Key Question Number	Retrieved	Met Criteria	Included
1	185	185	185
2	470	34	10
3	201	20	20
4	654	57	50
5	804	206	206
6	86	12	0
7	48	5	0
8	61	14	10
9	32	9	9
Totals =	**2541**	**542**	**490**

Note: Articles for Question 1 were also used to address other questions. Because these articles were evaluated twice, each for a different purpose, they are double-counted in the totals shown in the table. The article count in the text does not incorporate this double-counting

Statistical Methods

Meta-Analyses

We performed meta-analyses of data from RCTs and uncontrolled trials. We performed meta-analyses of RCTs to estimate an average effect of treatment. We performed meta-analytic threshold analyses of uncontrolled studies to determine whether an intervention was *plausibly* effective. All meta-analyses, except meta-regressions, were performed with software programs developed by ECRI. This software has been extensively validated using published examples and hand calculations. Meta-regressions were performed using SPSS (version 10.1) Statistical Software (Copyright © SPSS Inc., 1989-2000).

Meta-analyses of Randomized Controlled Trials

Our meta-analyses of RCTs are exclusively comprised of random effects models. These analyses appear only in Question 4, and only in regard to the polytherapy drug strategy. We employed random effects models because of the types of trials that addressed this question. These trials were each of a single AED, and not all trials studied the same drug. Therefore, no assumption is made that these trials were all drawn from a single population.

An important aspect of these meta-analyses is that each of the trials is an *instance* of polytherapy, rather than a study of polytherapy, *per se.* This is because a planned study of polytherapy would investigate more than one drug and means that each trial in each meta-analysis in Question 4 represents only one way polytherapy might be tested. However, combining these trials into a single meta-analysis of polytherapy means that this analysis approximates a single trial that directly studied this strategy of drug administration.

Another important aspect of the RCTs in our meta-analyses is that some of the trials consisted of more than two groups and therefore have more than two effect sizes. These effects

Table 3. Definitions of treatment resistance

Source	Number of Publications Selected for Question	Number of Publications Reporting Definitions	Percentage of Publications Reporting Definitions
Question 2	6	3	50%
Question 3	10	4	40%
Question 4	26	7	27%
Question 5	39	9	23%
Question 6	1	1	100%
Research Articles Total	**82**	**24**	**29%**
Treatment Guidelines	3	1	33%
Review Articles	100	21	21%
Grand Total	**185**	**46**	**25%**

Table 4. Evidence base for determining if patients diagnosed with treatment-resistant epilepsy actually have epilepsy

Reference	Study Design	Country in Which Study Performed	Size (N)	Multicenter	Number of Centers
Zaidi (2000)[38]	Cross-sectional case series	United Kingdom	74	Yes	2[a]
Holmes (1998)[39]	Cross-sectional case series	United States	379	No	1
Henry (1997)[37]	Cross-sectional case series	United States	145	No	1
Arnold (1996)[40]	Cross-sectional case series	United States	45	No	1
Slater (1995)[41]	Cross-sectional case series	United States	101	No	1

[a] Patients enrolled at two centers but diagnostic reassessment was performed at a single study center

Table 5. Articles addressing each diagnostic

Diagnostic	Number of Articles
Blood Prolactin Levels	8
Minnesota Multiphasic Personality Inventory	6
Video-EEG	6
Ambulatory -EEG	5
Provocation techniques	4
Routine EEG	4
Creatinine kinase levels	3
Tilt table	2
Auditory evoked potentials	1
Hypnotic recall	1
Magnetic Resonance Imaging	1
Single Photon Emission Computed Tomography	1
Tongue biting	1
Computed Tomography	0

Table 6. Differential diagnoses of seizures

	Epileptic Seizure Type					Nonepileptic Seizure Type		
Reference	Mixed ES	GTCS	CPS	SPS		Mixed NES	PsyS	SynS
Lusic (1999)[53]			✓		From			✓
Anzola (1993)[45]		✓			From			✓
Zelnik (1991)[56]		✓			From			✓
Mishra (1990)[57]	✓				From			✓
Wroe (1989)[50]	✓	✓	✓	✓	From		✓	
Lusic (1999)[53]	✓				From		✓	

CPS Complex partial seizure
ES Epileptic seizure
FS Febrile seizure
GTCS Generalized tonic-clonic seizure
NES Nonepileptic seizure
PsyS Psychogenic seizure
SPS Simple partial seizure
SynS Syncopal seizure

Table 7. Drugs and doses in studies of sequential monotherapy

Reference	Felbamate	Gabapentin		Lamotrigine	Oxcarbazepine	Primidone	Tiagabine	Topiramate	Valproate
	3600 mg/day	2400 mg/day	3600 mg/day	500 mg/day	2400 mg/day	750 mg/day	36 mg/day	1000 mg/day	150 µg/ml
Sachdeo (2001)[68]					✓				
Beydoun (2000)[86]					✓				
Kanner (2000)[87]						✓			
Schachter (1999)[79]					✓				
Gilliam (1998)[76]				✓					
Bergey (1997)[78]			✓						
Beydoun (1997)[85]									✓
Beydoun (1997)[83]		✓							
Sachdeo (1997)[84]								✓	
Devinsky (1995)[75]	✓								
Schachter (1995)[88]							✓		
Theodore (1995)[89]	✓								
Faught (1993)[77]	✓								
Totals	**3**	**1**	**1**	**1**	**3**	**1**	**1**	**1**	**1**

mg/day Maximum dose in milligrams per day
µg/ml Maximum dose in micrograms per milliliter

Table 8. Outcomes in studies of sequential monotherapy

Reference	Seizure Frequency	Adverse Effects	Quality of Life	Mood	Cognitive Function	Ability to Return to Work	Ability to Return to School	Ability to Hold a Driver's License	Mortality
Sachdeo (2001)[68]	✓	✓							✓
Beydoun (2000)[86]	✓	✓							
Kanner (2000)[87]	✓	✓							
Schachter (1999)[79]	✓	✓							
Gilliam (1998)[76]	✓	✓							
Bergey (1997)[78]	✓	✓							✓
Beydoun (1997)[85]	✓	✓							✓
Beydoun (1997)[83]	✓	✓	✓	✓	✓				✓
Sachdeo (1997)[84]	✓	✓							✓
Devinsky (1995)[75]	✓	✓							
Schachter (1995)[88]	✓	✓	✓	✓	✓				
Theodore (1995)[89]	✓	✓		✓					
Faught (1993)[77]	✓	✓							
Totals	**13**	**13**	**2**	**3**	**2**	**0**	**0**	**0**	**5**

Table 9. Seizure frequency outcomes in studies of sequential monotherapy

Reference	Mean Absolute Seizure Frequency	Median Absolute Seizure Frequency	Median Absolute Difference From Baseline	Median Percent Difference From Baseline	Number of Patients Seizure-free	Number of Patients With ≥ 75 Percent Reduction	Number of Patients With ≥ 50 Percent Reduction	Number of Patients With Any Reduction	Mean Rank of Seizure Frequency	Number of Patients With Doubling of Monthly Seizure Frequency	Number of Patients With Doubling of Highest Consecutive Two-Day Seizure Frequency	Median Time to Exit	Mean Time on Monotherapy	Risk Ratio of Time to Exit
Sachdeo (2001)[68]										✓	✓	✓		
Beydoun (2000)[86]					✓		✓			✓	✓	✓		
Kanner (2000)[87]					✓								✓	
Schachter (1999)[79]		✓			✓									✓
Gilliam (1998)[76]												✓		
Bergey (1997)[78]					✓								✓	
Beydoun (1997)[85]			✓	✓	✓	✓	✓	✓						
Beydoun (1997)[83]										✓	✓	✓	✓	
Sachdeo (1997)[84]					✓	✓	✓			✓	✓			✓
Devinsky (1995)[75]									✓					
Schachter (1995)[88]		✓					✓						✓	
Theodore (1995)[89]	✓													
Faught (1993)[77]										✓	✓			
Totals	**1**	**2**	**1**	**1**	**6**	**2**	**4**	**1**	**1**	**5**	**5**	**4**	**4**	**2**

Table 10. Overview of adverse effects of sequential monotherapy

Reference	Drug	Dose in mg/day	Percent of Patients Who Experienced Any Adverse Effect	Name of Most Commonly Experienced Adverse Effect	Percent of Patients Who Experienced This Adverse Effect
Sachdeo (2001)[68]	Oxcarbazepine	2400	NR	Headache	11% (5/45)
Beydoun (2000)[86]	Oxcarbazepine	2400	NR	Dizziness	46% (19/41)
Kanner (2000)[87]	Primidone	750	53% (16/30)	Irritability	37% (11/30)
Schachter (1999)[79]	Oxcarbazepine	2400	91% (46/51)	Nervous system	45% (23/51)
Gilliam (1998)[76]	Lamotrigine	500	75% (57/76)	Dizziness	20% (15/76)
Bergey (1997)[78]	Gabapentin	3600	73% (29/40)	Ataxia	20% (8/40)
Beydoun (1997)[85]	Valproate	150 µG/mL	NR	Tremor	64% (61/96)
Beydoun (1997)[83]	Gabapentin	2400	88% (80/91)	Dizziness	25% (23/91)
Sachdeo (1997)[84]	Topiramate	1000	NR	Paresthesia	58% (14/24)
Devinsky (1995)[75]	Felbamate	3600	NR	NR	NR
Schachter (1995)[88]	Tiagabine	36	95% (91/96)	Dizziness	35% (34/96)
Theodore (1995)[89]	Felbamate	3600	NR	NR	NR
Faught (1993)[77]	Felbamate	3600	NR	Headache	34% (19/56)

mg/day Milligrams per day
NR Not reported
µG/ml Micrograms per milliliter

Table 11. Drugs and doses in trials of polytherapy

Reference	Drug	Trial Dose(s) [a]	Total Number of Trials That Used This Drug/Dose Combination
Faught (2001)[94]	Zonisamide	400	1
Ben-Menachem (2000)[95]	Levetiracetam	3000	2
Betts (2000)[96]	Levetiracetam	2000, 4000	1, 1
Cereghino (2000)[97]	Levetiracetam	1000, 3000	1, 2
Glauser (2000)[98]	Oxcarbazepine	Tailored to weight	1
Appleton (1999) [99]	Gabapentin	Tailored to weight	1
Biton (1999)[100]	Topiramate	Tailored to weight	3
Duchowny (1999)[30]	Lamotrigine	Tailored to weight	2
Elterman (1999) [101]	Topiramate	Tailored to weight	3
Korean Topiramate Study Group (1999)[102]	Topiramate	600	4
Sachdeo (1999) [103]	Topiramate	Tailored to weight	3
Uthman (1998)[104]	Tiagabine	16, 32, 56	1, 2, 1
Sachdeo (1997) [105]	Tiagabine	32[b], 32[c]	2, 1
Ben-Menachem (1996)[90]	Topiramate	800	2
Chadwick (1996)[106]	Gabapentin	1200	3
Faught (1996)[91]	Topiramate	200, 400, 600	1, 2, 4
Privitera (1996)[107]	Topiramate	600, 800, 1000	4, 2, 1
Sharief (1996)[108]	Topiramate	400	2
Tassinari (1996)[109]	Topiramate	600	4
Willmore (1996) [110]	Valproate	Tailored to weight	1
Anhut (1994)[111]	Gabapentin	900, 1200	2, 3
Messenheimer (1994)[112]	Lamotrigine	400	1
Bourgeois (1993)[113]	Felbamate	3600	1
Felbamate Study Group (1993)[114]	Felbamate	Tailored to weight	1
Matsuo (1993)[115]	Lamotrigine	300, 500	1, 1
McLean (1993)[116]	Topiramate	600, 1200, 1800	4, 1, 1
Schmidt (1993)[117]	Zonisamide	Tailored to weight	1
Sivenius (1991)[118]	Gabapentin	900	2
UK Gabapentin Study Group (1990)[119]	Gabapentin	1200	3
Jawad (1989)[70]	Lamotrigine	Tailored to weight	2

[a] Maximum dose in milligrams per day
[b] Based on 16 milligrams twice per day
[c] Based on 8 milligrams four times a day

Table 12. Outcomes in trials of polytherapy

Reference	Seizure Frequency	Adverse Effects	Quality of Life	Mood	Cognitive Function	Ability to Return to Work	Ability to Return to School	Ability to Hold a Driver's License	Mortality
Faught (2001)[94]	✓	✓							
Ben-Menachem (2000)[95]	✓	✓							
Betts (2000)[96]	✓	✓							
Cereghino (2000)[97]	✓	✓	✓						✓
Glauser (2000)[98]	✓	✓							✓
Appleton (1999)[99]	✓	✓							✓
Biton (1999)[100]	✓	✓							
Duchowny (1999)[30]	✓	✓							
Elterman (1999)[101]	✓	✓							✓
KTSG (1999)[102]	✓	✓							
Sachdeo (1999)[103]	✓	✓							
Uthman (1998)[104]	✓	✓	✓	✓	✓				
Sachdeo (1997)[105]	✓	✓							
Ben-Menachem (1996)[90]	✓	✓							✓
Chadwick (1996)[106]	✓	✓							✓
Faught (1996)[91]	✓	✓							✓
Privitera (1996)[107]	✓	✓							✓
Sharief (1996)[108]	✓	✓							
Tassinari (1996)[109]	✓	✓							
Willmore (1996)[110]	✓	✓							
Anhut (1994)[111]	✓	✓							✓
Messenheimer (1994)[112]	✓	✓							
Bourgeois (1993)[113]	✓	✓							
FSG (1993)[114]	✓	✓							
Matsuo (1993)[115]	✓	✓							
McLean (1993)[116]	✓	✓							
Schmidt (1993)[117]	✓	✓							
Sivenius (1991)[118]	✓	✓							

Table 12. Outcomes in trials of polytherapy (continued)

Reference	Seizure Frequency	Adverse Effects	Quality of Life	Mood	Cognitive Function	Ability to Return to Work	Ability to Return to School	Ability to Hold a Driver's License	Mortality
UKGSG (1990) [119]	✓	✓							
Jawad (1989)[70]	✓	✓							
Totals	**30**	**30**	**2**	**1**	**1**	**0**	**0**	**0**	**9**

Table 13. Seizure frequency outcomes in trials of polytherapy

Reference	Absolute Monthly Seizure Frequency		Absolute Difference From Baseline		Absolute Percent Difference From Baseline		Number of Patients With								Mean Response Ratio [a]	Mean Adjusted Response Ratio [a]
	Mean	Median	Mean	Median	Mean	Median	Seizure-free	³75 Percent Reduction	³50 Percent Reduction	³25 Percent Reduction	Any Reduction	Any Increase	³50 Percent Increase	³75 Percent Increase		
Faught (2001)[94]						✓	✓	✓	✓							
Ben-Menachem (2000)[95]		✓				✓	✓		✓							
Betts (2000)[96]		✓				✓	✓		✓							
Cereghino (2000)[97]						✓	✓	✓	✓							
Glauser (2000)[98]						✓	✓		✓							
Appleton (1999)[99]						✓	✓	✓	✓	✓		✓	✓	✓		✓
Biton (1999)[100]						✓	✓	✓	✓							
Duchowny (1999)[30]		✓				✓			✓	✓						
Elterman (1999)[101]						✓	✓	✓	✓							
KTSG (1999)[102]		✓			✓	✓	✓		✓							
Sachdeo (1999)[103]						✓	✓	✓	✓							
Uthman (1998)[104]		✓		✓		✓			✓			✓				
Sachdeo (1997)[105]		✓		✓					✓							
Ben-Menachem (1996)[90]						✓	✓	✓	✓						✓	✓

Table 13. Seizure frequency outcomes in trials of polytherapy (continued)

Reference	Absolute Monthly Seizure Frequency		Absolute Difference From Baseline		Absolute Percent Difference From Baseline		Number of Patients With								Mean Response Ratio [a]	Mean Adjusted Response Ratio [a]
	Mean	Median	Mean	Median	Mean	Median	Seizure-free	[3] 75 Percent Reduction	[3] 50 Percent Reduction	[3] 25 Percent Reduction	Any Reduction	Any Increase	[3] 50 Percent Increase	[3] 75 Percent Increase		
Chadwick (1996)[106]						✓			✓							
Faught (1996)[91]						✓	✓	✓	✓							
Privitera (1996)[107]						✓		✓	✓							
Sharief (1996)[108]						✓	✓	✓	✓							
Tassinari (1996)[109]		✓				✓	✓	✓	✓							
Willmore (1996)[110]	✓	✓	✓	✓			✓	✓	✓	✓						
Anhut (1994)[111]		✓				✓			✓		✓	✓	✓			
Messenheimer (1994)[112]						✓										
Bourgeois (1993)[113]																
FSG (1993)[114]					✓		✓	✓	✓	✓						
Matsuo (1993)[115]						✓	✓		✓	✓			✓		✓	✓
McLean (1993)[116]						✓		✓	✓	✓	✓	✓				
Schmidt (1993)[117]						✓	✓	✓	✓		✓					
Sivenius (1991)[118]		✓						✓	✓	✓	✓	✓				✓

Table 13. Seizure frequency outcomes in trials of polytherapy (continued)

Reference	Absolute Monthly Seizure Frequency		Absolute Difference From Baseline		Absolute Percent Difference From Baseline		Number of Patients With								Mean Response Ratio [a]	Mean Adjusted Response Ratio [a]
	Mean	Median	Mean	Median	Mean	Median	Seizure-free	³ 75 Percent Reduction	³ 50 Percent Reduction	³ 25 Percent Reduction	Any Reduction	Any Increase	³ 50 Percent Increase	³ 75 Percent Increase		
UKGSG (1990)[119]						✓		✓	✓	✓	✓	✓	✓	✓		
Jawad (1989)[70]	✓	✓														
Totals [b]	**2**	**11**	**1**	**3**	**2**	**24**	**18**	**17**	**27**	**8**	**5**	**6**	**4**	**2**	**2**	**4**

[a] The response ratio is the ratio (T-B)/(T+B) where T is the number of seizures a month during treatment and B is the number of seizures a month during baseline. Some authors adjusted the response ratio in order to account for differences between centers in multi-center trials (using ANOVA).

Table 14. Overview of adverse effects of polytherapy

Reference	Drug and Dose (mg/day)	Percent of Patients Who Experienced Any Adverse Event	Name of Most Commonly Experienced Adverse Event	Percent of Patients Who Experienced This Adverse Event
Faught (2001)[94]	Zonisamide 400	NR	Somnolence	15% (18/118)
Ben-Menachem (2000)[95]	Levetiracetam 3000	55% (100/181)	Asthenia	13.8% (25/181)
Betts (2000)[96]	Levetiracetam 2000	83% (35/42)	Asthenia	31% (13/42)
Betts (2000)[96]	Levetiracetam 4000	84% (32/38)	Somnolence	45% (17/38)
Cereghino (2000)[97]	Levetiracetam 1000	89% (87/98)	Infection	28% (27/98)
Cereghino (2000)[97]	Levetiracetam 3000	89% (90/101)	Infection	27% (27/101)
Glauser (2000)[98]	Oxcarbazepine 1800	91% (125/138)	Vomiting	36% (50/138)
Appleton (1999)[99]	Gabapentin 1800	NR	Viral infection	11% (13/119)
Biton (1999)[100]	Topiramate 400	NR	Upper respiratory tract infection	41% (16/39)
Duchowny (1999)[30]	Lamotrigine 750	94% (92/98)	Somnolence	24% (24/98)
Elterman (1999)[101]	Topiramate 400	NR	Upper respiratory tract infection	41% (17/41)
KTSG (1999)[102]	Topiramate 600	81% (74/91)	Anorexia	21% (19/91)
Sachdeo (1999)[103]	Topiramate 600	NR	Somnolence	42% (20/48)
Uthman (1998)[104]	Tiagabine 16	NR	Nervous system	69% (42/61)
Uthman (1998)[104]	Tiagabine 32	NR	Nervous system	70% (62/88)
Uthman (1998)[104]	Tiagabine 56	NR	Nervous system	77% (44/57)
Sachdeo (1997)[105]	Tiagabine 32	NR	Nervousness	10.5% (11/105)
Ben-Menachem (1996)[90]	Topiramate 800	NR	Fatigue	79% (22/28)
Chadwick (1996)[106]	Gabapentin 1200	67% (39/58)	Somnolence	12% (7/58)
Faught (1996)[91]	Topiramate 200	NR	Dizziness	36% (16/45)
Faught (1996)[91]	Topiramate 400	NR	Dizziness	33% (15/45)
Faught (1996)[91]	Topiramate 600	NR	Dizziness	35% (16/46)
Privitera (1996)[107]	Topiramate 600	NR	Fatigue	38% (18/48)
Privitera (1996)[107]	Topiramate 800	NR	Abnormal thinking	44% (21/48)
Privitera (1996)[107]	Topiramate 1000	NR	Dizziness	38% (18/47)
Sharief (1996)[108]	Topiramate 400	NR	Somnolence	35% (8/23)
Tassinari (1996)[109]	Topiramate 600	NR	Headache	27% (8/30)
Willmore (1996)[110]	Valproate 90 mg/kg	NR	Nausea	48% (37/77)

Table 14. Overview of adverse effects of polytherapy (continued)

Reference	Drug and Dose (mg/day)	Percent of Patients Who Experienced Any Adverse Event	Name of Most Commonly Experienced Adverse Event	Percent of Patients Who Experienced This Adverse Event
Anhut (1994)[111]	Gabapentin 900	63% (33/52)	Somnolence	22% (24/111)
Anhut (1994)[111]	Gabapentin 1200	68% (76/111)	Somnolence	13% (7/52)
Messenheimer (1994)[112]	Lamotrigine 400	NR	Rash	7% (3/44)
Bourgeois (1993)[113]	Felbamate 3600	NR	Headache	40% (12/30)
FSG (1993)[114]	Felbamate 3600	NR	Anorexia	49% (18/37)
Matsuo (1993)[115]	Lamotrigine 300	NR	Headache	32% (23/71)
Matsuo (1993)[115]	Lamotrigine 500	NR	Dizziness	54% (39/72)
McLean (1993)[116]	Gabapentin 600	88% (89/101)	Dizziness	25% (13/53)
McLean (1993)[116]	Gabapentin 1200	91% (49/54)	Somnolence	36% (36/101)
McLean (1993)[116]	Gabapentin 1800	87% (46/53)	Somnolence	20% (11/54)
Schmidt (1993)[117]	Zonisamide 20 mg/kg	59% (42/71)	Fatigue	23% (16/71)
Sivenius (1991)[118]	Gabapentin 900	NR	Drowsiness	25% (4/16)
UKGSG (1990)[119]	Gabapentin 1200	62% (38/61)	Somnolence	14.8% (9/61)
Jawad (1989)[70]	Lamotrigine 400	NR	NR	NR

mg/day Milligrams per day
NR Not reported
mg/kg Milligrams per kilogram

Table 15. Outcomes in studies of drug reduction

Reference	Reported Seizure Outcomes					Reported Nonseizure Outcomes			
	Difference in Absolute Seizure Frequency	Percent Change in Seizure Frequency	Percent Patients Seizure-free	Percent of Patients With >50 Percent Reduction in Seizure Rate	Percent of Patients With an Increase in Seizure Frequency	Mood	Cognitive Function	Adverse Events	Mortality
Controlled trials performed outside of the United States									
May (1992)[121]	✓[a]						✓		✓
Duncan (1990)[122]	✓					✓[b]	✓[c]	✓[d]	✓
Thompson (1982)[126]	✓					✓	✓		✓
Case series performed in the United States									
Mirza (1993)[120]			✓	✓				✓	✓
Case series performed outside of the United States									
Specht (1989)[123]	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]			✓	✓
Callaghan (1984)[124]			✓	?	✓			✓	✓
Schmidt (1983)[125]	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]			✓	✓
Number of articles addressing outcome	**4[f]**	**2**	**4**	**4**	**3**	**2**	**3**	**5**	**7**

[a] May, Bulmahn, Wolhlhuter et al.[121] reported that no statistically significant between groups differences in seizure frequency were seen but did not present any data
[b] Mood data abstracted from Kendrick, Duncan, and Trimble[136]
[c] Cognitive function data abstracted from Duncan, Shorvon, and Trimble[137]
[d] Adverse events data abstracted from Duncan, Shorvon, and Trimble[138]
[e] Data calculated by ECRI from individual patient data
[f] Does not include May, Bulmahn, Wolhlhuter et al.[121] (see footnote a above).

Table 16. Possible decisions based on hypothesis test

True Difference $X_{DRS} - X_c$	Testing H_0: $X_c = X_{DRS}$		Testing H_0': $X_{DRS} \geq X_c + d$	
	Fail to Reject (good for DRS)	Reject (bad for DRS)	Reject (good for DRS)	Fail to Reject (bad for DRS)
$X_{DRS} - X_c = 0$ (good for DRS)	Correct Decision	Type I error	Correct Decision	Type II error
$X_{DRS} - X_c = \delta$ (bad for DRS)	Type II error	Correct Decision	Type I error	Correct Decision

Adapted from Blackwelder[128]
DRS Drug reduction study
H_0 Null hypothesis (standard)
H_0' Null hypothesis (therapeutic equivalence studies)
X_c Mean seizure frequency in control group
X_{DRS} Mean seizure frequency in drug reduction therapy group
δ Predefined difference in mean seizure frequency above which use of drug reduction study is unacceptable

Table 17. Epilepsy surgery studies

Intervention	Total Number of Studies [a]
Temporal Lobe Surgery	105
Corpus Callosotomy	26
Frontal Lobe Surgery	18
Hemispherectomy	11
Multiple Subpial Transection	10
Parietal Lobe Surgery	2
Occipital Lobe Surgery	2
Surgical Controls	12

[a] Seven studies reported on more than one surgery category and are therefore double counted in this table

Table 18. Temporal lobe surgery: seizure-free outcome reporting

Reference	Undefined	No Auras	With Auras	Engel Class I	Reference	Undefined	No Auras	With Auras	Engel Class I
Bouilleret (2002)[165]		✓		✓	Son (1999)[166]				✓
Alsaadi (2001)[167]				✓	Maher (1998)[168]		✓		✓
Boling (2001)[169]				✓	Radhakrishnan (1998) [170]			✓	
Hennessy (2001) [171]			✓		Szabo (1998)[172]		✓		✓
Hennessy (2001) [148]			✓		Bizzi (1997) [173]				✓
Jan (2001)[174]			✓		Cappabianca (1997) [175]	✓			
Kanemoto (2001)[176]				✓	Casazza (1997)[177]		✓		✓
Schramm (2001)[178]				✓	Ho (1997) [179]			✓	
Sotero de Menezes (2001)[180]			✓	✓	Keene (1997)[181]				✓
Verma (2001) [182]			✓		Kilpatrick (1997) [183]			✓	✓
Wilson (2001) [184]		✓	✓		McLachlan (1997) [185]		✓		
Dupont (2000)[186]		✓		✓	Schwartz (1997) [187]		✓	✓	
Eberhardt (2000)[188]		✓	✓	✓	Silander (1997) [189]	✓			
Foldvary (2000) [190]				✓	Sisodiya (1997)[191]		✓	✓	✓
Holmes (2000) [192]		✓			Adam (1996) [193]		✓	✓	✓
Iannelli (2000)[194]				✓	Goldstein (1996) [195]	✓			
Markand (2000) [151]		✓	✓	✓	Holmes (1996)[196]		✓		
Rao (2000)[197]		✓			Sirven (1996)[198]	✓			
Robinson (2000)[199]				✓	Acciarri (1995)[200]	✓			
Assaf (1999) [201]			✓		Berkovic (1995)[202]				✓
Eriksson (1999) [203]			✓		Davies (1995)[163]				✓
Henry (1999)[204]	✓				Jooma (1995) [205]				✓
Holmes (1999) [206]		✓			Jooma (1995) [207]				✓
Mathern (1999)[208]	✓				Liu (1995)[209]			✓	
Mitchell (1999)[210]			✓		Renowden (1995) [211]		✓		
Rossi (1999) [212]		✓			Thadani (1995) [213]				✓
Salanova (1999)[214]				✓	Vossler (1995)[215]			✓	

Table 18. Temporal lobe surgery: seizure-free outcome reporting (continued)

Reference	Undefined	No Auras	With Auras	Engel Class I
Blume (1994)[146]			✓	✓
Guldvog (1994)[160]	✓			
Guldvog (1994)[161]	✓			
Berkovic (1991)[216]				✓
Hopkins (1991)[217]	✓			
Rasmussen (1991)[218]	✓			
Wieser (1991)[219]				✓
Bidzinski (1990)[162]	✓			
Mizrahi (1990)[152]	✓			
Walczak (1990)[164]			✓	
Yeh (1990)[220]			✓	
Sperling (1989)[221]				✓
Estes (1988)[222]			✓	
Bladin (1987)[223]	✓			
Cutfield (1987)[147]	✓			
Drake (1987)[224]	✓			
Lieb (1986)[225]				✓
Meyer (1986)[226]		✓	✓	
Delgado-Escueta (1985)[153]		✓	✓	✓

Table 19. Temporal lobe surgery: seizure-free outcome reporting in "control" patients

Reference	Seizure-Free Outcome Measurements			
	Undefined	No Auras	With Auras	Engel Class I
Bauer (2001)[227]	✓			
Kumlien (2001)[228]	✓			
Wiebe (2001)[145]		✓	✓	
Markand (2000) [151]		✓		
Holmes (1998) [229]	✓			
Wolf (1998) [230]		✓	✓	✓
McLachlan (1997) [185]	✓			
Hermanns (1996)[231]	✓			
Vickrey (1995)[232]		✓	✓	
Guldvog (1991)[233]	Reported changes in seizure frequency only			
Huttenlocher (1990)[234]	✓			
Harbord (1987)[235]	✓			

Table 20. Temporal lobe surgery: study designs

Study designs for studies of temporal lobe surgery reporting seizure-free outcomes

Prospective Nested Case-controlled Studies[a]	Retrospective Nested Case-controlled Studies	Prospective Case Series Studies	Retrospective Case Series Studies
5	30	5	33

[a] Nested case-controlled studies are defined as any study reporting patient characteristics (age at treatment, age at seizure onset, duration of epilepsy prior to treatment, etc.) separately for patients with good outcomes (seizure-free, Engel Class I, etc.) and patients with poor outcomes. Nested case-controlled studies are also considered case series studies because all patients received the same treatment.

Table 21. Temporal lobe surgery: individual patient data

Studies of temporal lobe surgery reporting individual patient data for patients with successful and nonsuccessful surgery

Reference	Age at Treatment	Age at Seizure Onset	Duration of Epilepsy Prior to Treatment	Gender	Side of Surgery	Simple Partial Seizures	Secondarily Generalized Seizures
Bouilleret (2002)[165]	✓	✓	✓	✓	✓	✓	
Hennessy (2001)[148]				✓	✓	✓	✓
Hennessy (2001)[171]							✓
Sotero de Menezes (2001)[180]	✓				✓		
Verma (2001)[182]	✓	✓	✓	✓	✓		
Eberhardt (2000)[188]	✓			✓	✓		
Holmes (1999)[206]	✓			✓	✓		
Szabo (1998)[172]	✓	✓	✓	✓	✓		
Kilpatrick (1997)[183]	✓			✓	✓		
Schwartz (1997)[187]	✓			✓	✓		
Sisodiya (1997)[191]	✓			✓	✓		
Adam (1996)[193]		✓			✓		
Goldstein (1996)[195]					✓		
Jooma (1995)[205]	✓	✓	✓				
Liu (1995)[209]	✓	✓	✓	✓	✓		✓
Vossler (1995)[215]	✓	✓	✓	✓	✓		
Blume (1994)[146]	✓						
Berkovic (1991)[216]	✓	✓	✓	✓	✓	✓	✓
Hopkins (1991)[217]	✓	✓	✓				
Mizrahi (1990)[152]	✓	✓	✓		✓		
Yeh (1990)[220]	✓	✓	✓	✓	✓	✓	✓
Estes (1988)[222]					✓		
Drake (1987)[224]	✓	✓	✓	✓		✓	✓
Delgado-Escueta (1985)[153]	✓	✓	✓	✓	✓	✓	✓

Table 22. Temporal lobe surgery: employment studies

Reference	Number of Patients	Country	Years Study Conducted	Mean Age at Surgery	Youngest Patient	Oldest Patient
Boling (2001)[169]	18	Canada	1981-1999	54	50	64
Reeves (1997) [154]	134	United States	1988-1991	31		
Sperling (1995)[236]	73	United States	1986-1990	33.2		
Mizrahi (1990)[152]	22	United States	1980-1986	21	7	36
Delgado-Escueta (1985)[153]	15	United States	1972-1983	26.5	12	39

Table 23. Temporal lobe surgery: new cases of depression after surgery

Reference	Number of Patients	Country	Years Study Conducted	Number of Cases
Kanemoto (2001)[176]	52	Japan	1987-1999	2
Kohler (2001)[237]	58	United States	1986-1999	6
Nees (2001)[238]	50	England	1992-1994	14
Wiebe (2001)[145]	36	Canada	1996-2000	7
Anhoury (2000)[239]	109	England	1988-1997	26
Derry (2000) [240]	39	Canada	1996-1998	4
Altshuler (1999) [156]	49	United States	1974-1990	5
Ring (1998)[241]	60	England	1995-1996	7
Naylor (1994)[242]	37	Denmark	1987-1991	2
Bladin (1992)[243]	107	Australia	1975-1991	5

Table 24. Temporal lobe surgery: new cases of psychosis after surgery

Reference	Number of Patients	Country	Years Study Conducted	Number of Cases
Kanemoto (2001)[176]	52	Japan	1987-1999	7
Wiebe (2001)[145]	36	Canada	1996-2000	1
Anhoury (2000) [239]	109	England	1988-1997	3
Blumer (1998) [244]	44	United States	1994-1995	2
Naylor (1994)[242]	37	Denmark	1987-1991	0
Bladin (1992) [243]	107	Australia	1975-1991	3

Table 25. Temporal lobe surgery: changes in IQ

Studies of temporal lobe surgery reporting both the number of patients with IQ changes after surgery and the pretreatment and posttreatment mean IQ.

Reference	Number of Patients	Country	Years Study Conducted	Number of Decreases	Number of Increases	Mean Age at Surgery	Youngest Patient	Oldest Patient
Miranda (2001) [245]	50	Canada	1976-1998	7	7	13.3	6.4	18.3
Robinson (2000)[199]	21	United States	1993-1998	1	4	15.4	9.4	21.7
Westerveld (2000)[246]	82	United States		8	7	14.4	6	17
Chelune (1993)[158]	96	United States	1990-1991	8	8	29.4		
Ivnik (1988)[247]	141	United States	1972-1987	13	27	28		
Powell (1985)[248]	59	England	1973-1984	10	8	25.5	15	

Table 26. Temporal lobe surgery: changes in memory

Studies of temporal lobe surgery reporting individual changes in patient memory after surgery

Reference	Number of Patients	Country	Years Study Conducted	Number of Decreases	Number of Increases	Mean Age at Surgery	Youngest Patient	Oldest Patient
Canizares (2000)[249]	33	Spain	1998-1999	3	10	30.9		
Chelune (1993)[158]	96	United States	1990-1991	28	1	29.4		
Ivnik (1988)[247]	141	United States	1972-1987	48	48	28		
Ojemann (1985)[250]	13	United States	1983-1983	8	3	28.9	17	49
Powell (1985)[248]	59	England	1973-1984	8	13	25.5	15	

Table 27. Temporal lobe surgery: complications due to surgery

Reference	N	Years Study Conducted	Country	Permenant Complications	Reference	N	Years Study Conducted	Country	Permenant Complications
Boling (2001)[169]	18	1981-1999	Canada	0	Acciarri (1995)[200]	10	1975-1992	Italy	0
Schramm (2001)[178]	61	1993-1999	Germany	0	Davies (1995)[163]	12	1969-1988	England	1
Sotero de Menezes(2001)[180]	15	1978-1993	United States	1	Jooma (1995)[205]	30	1985-1992	United States	2
Wiebe (2001)[145]	36	1996-2000	Canada	2	Liu (1995)[209]	22	1983-1990	United States	2
Iannelli (2000)[194]	37	1981-1997	Italy	1	Wyler (1995)[142]	70	1990-1992	United States	3
Rao (2000)[197]	164	1995-1998	India	1	Blume (1994)[146]	125	1974-1989	Canada	1
Robinson (2000)[199]	21	1993-1998	United States	0	Guldvog (1994)[160]	64	1952-1988	Norway	0
Wurm (2000)[251]	16	1997-1998	Austria	1	Guldvog (1994)[161]	35	1949-1988	Norway	6
Altshuler (1999)[156]	49	1974-1990	United States	5	Hopkins (1991)[217]	11	1978-1988	Australia	0
Leung (1999)[252]	11	1994-1998	Hong Kong	1	Bidzinski (1990)[162]	320	1957-1988	Poland	2
Parrent (1999)[253]	19	1994-1997	Canada	0	Mackenzie (1990)[254]	30	1983-1989	Australia	0
Salanova (1999)[214]	145	1984-1995	United States	2	Mizrahi (1990)[152]	22	1980-1986	United States	0
Son (1999)[166]	71	1994-1999	South Korea	2	Walczak (1990)[164]	100	1964-1985	United States	1
Visudhiphan (1999)[255]	14	1993-1998	Thailand	0	So (1989)[256]	48	1973-1987	Canada	0
Radhakrishnan (1998)[170]	175	1988-1991	United States	2	Cutfield (1987)[147]	26	1961-1980	New Zealand	0
Wyllie (1998)[257]	72	1990-1996	United States	0	Drake (1987)[224]	16	1974-1986	Canada	0
Bizzi (1997)[173]	14	1990-1994	United States	1	King (1986)[258]	23	1981-1983	United States	0
Blume (1997)[259]	14	1977-1994	Canada	0	Meyer (1986)[226]	50	1970-1983	United States	0
Kilpatrick (1997)[183]	36	1993-1995	Australia	0	Carey (1985)[260]	24	1975-1984	Ireland	0
Adam (1996)[193]	30	1991-1994	France	2	Delgado-Escueta(1985)[153]	15	1972-1983	United States	1

Table 28. Temporal lobe surgery: surgery-related mortality

Reference	N	Years Study Conducted	Country	Deaths
Boling (2001)[169]	18	1981-1999	Canada	0
Schramm (2001)[178]	61	1993-1999	Germany	0
Wiebe (2001)[145]	36	1996-2000	Canada	0
Iannelli (2000)[194]	37	1981-1997	Italy	0
Rao (2000)[197]	164	1995-1998	India	1
Robinson (2000)[199]	22	1993-1998	United States	0
Wurm (2000)[251]	16	1997-1998	Austria	0
Altshuler (1999)[156]	49	1974-1990	United States	0
Leung (1999)[252]	11	1994-1998	Hong Kong	0
Parrent (1999)[253]	19	1994-1997	Canada	0
Salanova (1999)[214]	145	1984-1995	United States	0
Son (1999)[166]	71	1994-1999	South Korea	0
Visudhiphan (1999)[255]	14	1993-1998	Thailand	0
Wyllie (1998)[257]	72	1990-1996	United States	1
Bizzi (1997)[173]	14	1990-1994	United States	0
Blume (1997)[259]	14	1977-1994	Canada	0
Kilpatrick (1997)[183]	36	1993-1995	Australia	0
Adam (1996)[193]	30	1991-1994	France	0
Acciarri (1995)[200]	10	1975-1992	Italy	0
Berkovic (1995)[202]	135	1986-1991	Australia	0
Davies (1995)[163]	12	1969-1988	England	0
Liu (1995)[209]	22	1983-1990	United States	0
Wyler (1995)[142]	70	1990-1992	United States	0
Blume (1994)[146]	125	1974-1989	Canada	0
Guldvog (1994)[160]	64	1952-1988	Norway	0
Guldvog (1994)[161]	35	1949-1988	Norway	0
Bladin (1992)[243]	107	1975-1991	Australia	0
Elwes (1991)[261]	108	1976-1987	England	1
Hopkins (1991)[217]	11	1978-1988	Australia	0
Bidzinski (1990)[162]	320	1957-1988	Poland	2
Mizrahi (1990)[152]	22	1980-1986	United States	0
Yeh (1990)[220]	12	1982-1986	Japan	0
So (1989)[256]	48	1973-1987	Canada	0
Cutfield (1987)[147]	26	1961-1980	New Zealand	0
Drake (1987)[224]	16	1974-1986	Canada	0
Meyer (1986)[226]	50	1970-1983	United States	0
Carey (1985)[260]	24	1975-1984	Ireland	0

Table 29. Corpus callosotomy and seizure frequency outcomes

Method of reporting effect of surgery on seizure frequency

Reference	Types of Seizures Evaluated	Percent Reduction in Seizure Frequency	Actual Change in Mean Seizure Frequency	Seizure-free
Kwan (2001)[270]	All seizure types	✓		
Maehara (2001)[271]	Disabling generalized seizures	✓		
Matsuzaka (1999)[272]	Most disabling seizures	✓		✓
McInerney (1999)[273]	Most disabling seizures	✓		✓
Sakas (1996)[268]	Drop attacks and generalized tonic-clonic seizures	✓		✓
Claverie (1995)[274]	All seizure types	✓		
Reutens (1993)[275]	All seizure types	✓		
Marino (1990)[276]	All seizure types	✓		✓
Murro (1988)[277]	All seizure types	✓	✓	✓
Purves (1988)[278]	All seizure types	✓		
Spencer (1988)[267]	All seizure types	✓	✓	✓
Gates (1987)[265]	All seizure types	✓	✓	✓

Table 30. Corpus callosotomy: individual patient data

Studies of corpus callosotomy reporting individual patient data for patients with successful and nonsuccessful surgery

Reference	Age at Treatment	Age at Seizure Onset	Duration of Epilepsy Prior to Treatment
Sakas (1996)[268]	✓	✓	
Claverie (1995)[274]	✓		
Nordgren (1991)[279]	✓	✓	✓
Marino (1990)[276]	✓	✓	✓
Murro (1988)[277]	✓	✓	✓
Purves (1988)[278]	✓	✓	✓
Spencer (1988)[267]	✓	✓	✓

Table 31. Corpus callosotomy and specific seizure types

Studies reported patients who were free of specific seizure types after surgery

Reference	Specified Most Disabling Seizure	Patients with Generalized Tonic-Clonic Seizures	Patients with Atonic Seizures
Kwan (2001)[270]		✓	✓
Maehara (2001)[271]		✓	✓
Matsuzaka (1999)[272]	✓		
McInerney (1999)[273]	✓	✓	✓
Sakas (1996)[268]	✓	✓	✓
Marino (1990)[276]	✓	✓	✓
Murro (1988)[277]	✓	✓	
Spencer (1988)[267]	✓	✓	
Gates (1987)[265]	✓	✓	✓

Table 32. Corpus callosotomy and complications due to surgery

Reference	Number of Patients	Country	Years Study Conducted	Number of Permanent Complications
Hodaie (2001)[280]	17	Canada	1992-1999	0
Maehara (2001)[271]	52	Japan	1991-1998	0
Fandino-Franky (2000)[281]	97	Colombia	1989-1997	0
Pinard (1999)[282]	17	France	1989-1995	2
Carmant (1998)[283]	28	United States	1989-1993	0
Sorenson (1997)[284]	23	United States	1991-1994	1
Andersen (1996)[285]	20	Denmark	1988-1994	7
Rossi (1996)[286]	20	Italy	1988-1995	1
Sakas (1996)[268]	20	Ireland	1984-1993	0
Reutens (1993)[275]	64	Australia	1973-1991	4
Fuiks (1991)[287]	80	United States	1985-1990	0
Nordgren (1991)[279]	18	United States	1972-1987	1
Oguni (1991)[288]	43	Canada	1981-1989	0
Marino (1990)[276]	28	Brazil	1978-1985	1
Provinciali (1990)[289]	15	Italy	1987-1988	0
Sass (1990)[290]	32	United States	1985-1987	4
Murro (1988)[277]	25	United States	1980-1986	0
Purves (1988)[278]	24	Canada	1977-1987	0
Garcia-Flores (1987)[291]	14	Mexico	1980-1986	0
Gates (1987)[265]	24	United States	1979-1985	3

Table 33. Corpus callosotomy and surgery-related mortality

Reference	Number of Patients	Country	Years Study Conducted	Number of Deaths
Hodaie (2001)[280]	17	Canada	1992-1999	0
Maehara (2001)[271]	52	Japan	1991-1998	0
Fandino-Franky (2000)[281]	97	Colombia	1989-1997	0
McInerney (1999)[273]	47	United States	1972-1999	0
Carmant (1998)[283]	28	United States	1989-1993	0
Sorenson (1997)[284]	23	United States	1991-1994	0
Andersen (1996)[285]	20	Denmark	1988-1994	1
Sakas (1996)[268]	20	Ireland	1984-1993	0
Reutens (1993)[275]	64	Australia	1973-1991	0
Fuiks (1991)[287]	80	United States	1985-1990	2
Nordgren (1991)[279]	18	United States	1972-1987	1
Oguni (1991)[288]	43	Canada	1981-1989	0
Provinciali (1990)[289]	15	Italy	1987-1988	0
Sass (1990)[290]	32	United States	1985-1987	0
Murro (1988)[277]	25	United States	1980-1986	2
Purves (1988)[278]	24	Canada	1977-1987	0
Garcia-Flores (1987)[291]	14	Mexico	1980-1986	0
Gates (1987)[265]	24	United States	1979-1985	0

Table 34. Frontal lobe surgery: seizure-free outcome reporting

Reference	Seizure-Free Outcome Measurement			
	Undefined	No Auras	With Auras	Engel Class I
Ferrier (2001)[296]	✓			
Siegel (2001)[297]				✓
Hong (2000)[298]				✓
Eriksson (1999)[203]			✓	
Wennberg (1999)[299]				✓
Swartz (1998)[292]		✓		
Cappabianca (1997)[175]	✓			
Smith (1997)[293]	✓			
Acciarri (1995)[200]	✓			
Adler (1991)[300]		✓		
Garcia Sola (1991)[301]	✓			
Palmini (1991)[302]			✓	
Rasmussen (1991)[303]	✓			

Table 35. Frontal lobe surgery and complications due to surgery

Reference	Number of Patients	Country	Years Study Conducted	Number of Perrnanent Complications	Number of Surgery-related Deaths
Kral (2001)[295]	32	Germany	1989-2000	0	0
Mosewich (2000)[304]	68	United States	1987-1994	0	Not reported
Chassoux (1999)[294]	120	France	1964-1995	27	Not reported
Ferrier (1999)[305]	42	England	1975-1996	0	Not reported
Helmstaedter (1998)[306]	33	Germany	1995-1996	0	Not reported
Swartz (1998)[292]	19	United States	1986-1995	0	Not reported
Smith (1997)[293]	53	United States		4	1
Acciarri (1995)[200]	13	Italy	1975-1992	0	0

Table 36. Hemispherectomy: seizure-free outcome reporting

Reference	Number of Patients	Seizure-free with No Auras	Seizure-free Undefined	Engel Class I
Di Rocco (2000)[311]	15	✓		✓
Tinuper (1988)[309]	14		✓	
Lindsay (1987)[310]	15		✓	✓

Table 37. Hemispherectomy and complications and/or surgery-related mortality

Reference	Number of Patients	Country	Years Study Conducted	Number of Permanent Complications	Number of Surgery-related Deaths
Carreno (2001) [312]	13	United States	1992-1999	0	0
Schramm (2001)[313]	20	Germany	1991-1999	0	1
Di Rocco (2000)[311]	15	Italy	1985-1996	0	0
Shimizu (2000) [314]	34	Japan	1993-1999	1	0
Battaglia (1999)[315]	10	Italy	1987-1998	0	0
Wyllie (1998)[257]	16	United States	1990-1996	0	0
Vining (1997)[307]	58	United States	1968-1996	1	3
Peacock (1996)[316]	58	United States	1986-1995	0	2
Schramm (1995)[317]	13	Germany	1992-1994	0	0
Tinuper (1988)[309]	14	Canada	1974-1987	0	0
Lindsay (1987)[310]	17	England	1948-1986	1	1

Table 38. Multiple subpial transection: seizure outcomes

Reference	Number of Patients	Seizure-Free With Auras	Seizure-Free Undefined	Engel Class I	90 Percent Reduction in Seizure Frequency	No Change or an Increase in Seizure Frequency
Mulligan (2001)[321]	12		✓		✓	✓
Orbach (2001)[320]	54	✓		✓	✓	
Shimizu (2000)[323]	25			✓		
Smith (1998)[324]	84			✓		
Hufnagel (1997)[325]	22	✓			✓	✓
Pacia (1997)[326]	21	✓		✓	✓	✓
Patil (1997)[327]	19		✓			✓
Morrell (1995)[328]	14		✓			
Sawhney (1995)[322]	21		✓			

Table 39. Multiple subpial transection: individual patient data

Studies of multiple subpial transection reporting individual patient data for patients with successful and nonsuccessful surgery

Reference	Number of Patients	Age at Surgery	Gender
Hufnagel (1997)[325]	22	✓	✓
Pacia (1997)[326]	21	✓	✓
Patil (1997)[327]	19	✓	✓
Morrell (1995)[328]	14	✓	✓
Sawhney (1995)[322]	21	✓	✓

Table 40. Multiple subpial transection and complications and/or surgery-related mortality

Reference	Number of Patients	Country	Years Conducted	Number of Permanent Complications	Number of Deaths
Mulligan (2001)[321]	12	United States	1990-1999	0	0
Shimizu (2000)[323]	31	Japan	1983-1998	0	0
Smith (1998)[324]	84	United States		7	0
Hufnagel (1997)[325]	22	Germany	1993-1996	4	0
Pacia (1997)[326]	21	United States	1992-1994	1	0
Patil (1997)[327]	19	United States	1991-1995	0	0
Morrell (1995)[328]	14	United States	1987-1994	0	0
Sawhney (1995)[322]	21	England	1989-1993	2	0
Shimizu (1991)[329]	12	Japan	1989-1990	0	0

Table 41. Articles addressing nondrug, nonsurgery interventions

Intervention	Total Number of Studies	Intervention	Total Number of Studies
Vagal Nerve Stimulation	15	Magnetic Therapy	0
Ketogenic Diet	8	Vitamin B6 Therapy	0
Herbal Medicine	4	Chiropractic Therapy	0
Electrical Brain Stimulation	4	Cranial Realignment	0
Acupuncture	2	Hyperbaric Oxygen Therapy	0

Table 42. Vagal nerve stimulation: included articles

Reference	Number of Patients	Study Design	Country	Multicenter?	Number of Centers	Industry Funded?
Aldenkamp (2001)[337]	16	Case Series	Holland	No	1	Not reported
Chayasirisobhon (2001)[346]	24	Case Series	United States	No	1	Yes
Ergene (2001)[335]	17	Case Series	United States	No	1	Not reported
Hoppe(2001)[339]	36	Case Series	Germany	No	1	Yes
DiGiorgio (2000)[333] Followup of Clinical Trial EO5	199	Case Series	United States	Yes	20	Yes
Hosain (2000)[336]	13	Case Series	United States	No	1	Not reported
Ben-Menachem (1999)[343]	64	Case Series	Sweden	No	1	No
Boon (1999)[338]	25	Case Series	Belgium	No	1	No
Clinical Trial EO4 Labar (1999)[334]	25	Case Series	United States	Yes	Not reported	Yes
Parker (1999)[340]	16	Case Series	United Kingdom	No	1	No
Clinicial Study EO5 Handforth (1998)[332]	199	Randomized Controlled Trial	United States	Yes	20	Yes
Lundgren (1998)[341]	16	Case Series	Sweden	No	1	Not reported
Salinski (1996)[31] Followup of Clinical Trial EO3	114	Case Series	Multinational[a]	Yes	17	Yes
Clinical Trial EO3 The VNS Group (1995)[331]	114	Randomized Controlled Trial	Multinational[a]	Yes	17	Yes

[a] United States / Germany / Sweden / Canada / Holland
NA Not applicable

Table 43. Outcome reporting in studies of vagal nerve stimulation

Reference	Reported Seizure Outcomes			
	Percent of Patients with >50 percent Reduction in Seizure Rate	Percent of Patients Sezure -free	Difference in Absolute Seizure Frequency	Percent Reduction in Seizure Frequency[a]
RCTs performed in United States				
Clinical Study EO5 (1998)[332]	✓[b]			✓[c]
Clinical Trial EO3 (1995)[331]	✓		✓	✓
Long-term followup of RCTs performed in United States				
DiGiorgio (2000)[333] Followup of Clinical Trial EO5	✓			✓
Salinski (1996)[31] Followup of Clinical Trial EO3	✓			✓
Case series performed in United States				
Chayasirisobhon (2001)[346]	✓		✓	✓
Ergene (2001)[335]				
Hosain (2000)[336]	✓			✓
Clinical Trial EO4 Labar (1999)[334]	✓			✓
Case series performed outside United States				
Aldenkamp (2001)[337]	✓		✓	✓
Hoppe (2001)[339]	✓		✓	✓
Ben-Menachem (1999)[343]	✓			
Boon (1999)[338]	✓	✓	✓	✓
Parker (1999)[340]	✓			✓
Lundgren (1998)[341]	✓		✓	✓
Totals	**13**	**1**	**6**	**12**

[a] Reduction from baseline unless otherwise indicated
[b] This data comes from article by Handforth, DeGiorgio, Schachter, et al.[332]
[c] This data comes from article by Dodrill and Morris[347]

Table 43. Outcome reporting in studies of vagal nerve stimulation (continued)

Reference	Reported Non-Seizure Outcomes							
	Quality of Life	Mood	Cognition	Ability to Return, Obtain, or Remain at Work	Ability to Return, Obtain, or Remain in School	Ability to Hold Driver's Licence	Adverse Event	Mortality
RCTs performed in United States								
Clinical Study EO5 (1998)[332]	✓[c]						✓[b]	✓[b]
Clinical Trial EO3 (1995)[331]							✓	✓
Long-term followup of RCTs performed in United States								
DiGiorgio (2000)[333] Followup of Clinical Trial EO5							✓	✓
Salinski (1996)[31] Followup of Clinical Trial EO3							✓	✓
Case series performed in United States								
Chayasirisobhon (2001)[346]	✓[d]						✓	✓
Ergene (2001)[335]	✓						✓	✓
Hosain (2000)[336]							✓	✓
Clinical Trial EO4 Labar. (1999)[334]							✓	✓
Case series performed outside United States								
Aldenkamp (2001)[337]	✓[e]							✓
Hoppe (2001)[339]								✓
Ben-Menachem (1999)[343]							✓	✓
Boon (1999)[338]							✓	✓
Parker (1999)[340]	✓[g]							✓
Lundgren (1998)[341]	✓[f]						✓	✓
Totals	**2[h]**	**0**	**0**	**0**	**0**	**0**	**11**	**14**

[b] This data comes from article by Handforth, DeGiorgio, Schachter, et al.[332]
[c] This data comes from article by Dodrill and Morris[347]

Footnotes continue on the next page.

[d] Authors reported that they measured quality of life and discuss findings in conclusions section. However, they do not present any data

[e] Authors stated that they measured quality of life but did not use a validated quality of life instrument. Instead they used four instruments that measured four domains that the authors claim provide a estimate of quality of life. We were unable to confirm that these four domains are related to overall quality of life and thus do not consider this data further

[f] Authors used a nonvalidated quality of life instrument. These data are not considered further

[g] Authors used a validated instrument (Welcome Quality of Life Assessment). However, they only report p-values and did not present data that could be validated

[f] Excludes quality of life data from four articles (see footnotes d and g)

association between the observed outcomes and the treatment. This left four studies remaining. Because fewer than five included studies examined this intervention, we did not proceed with a further analysis.

EEG Biofeedback

EEG biofeedback uses auditory or visual signals to train patients to control their EEG. By altering their EEG patterns to increase waveforms thought to discourage seizures and decrease waveforms believed to promote seizures, patients may be able to reduce or eliminate seizures. The precise waveforms promoted or repressed may vary somewhat among studies depending on the theoretical underpinnings of the treatment.

Evidence base

Six studies of EEG biofeedback, describing 143 patients, met the inclusion criteria for this question (Evidence Table 236).

Excluded studies

Two studies of EEG biofeedback were excluded for reasons of quality.[348,349] In one study, patients received behavioral therapy in addition to EEG biofeedback, and therefore neither therapy could be associated with the studies outcomes. In the other, some patients received EEG biofeedback while others received end-tidal CO_2 biofeedback. Outcomes for the two groups were not individually reported, again preventing any interpretation of the effect of EEG biofeedback. This left four studies remaining. Because fewer than five included studies reported on this intervention, we did not proceed with further analyses. A complete list of studies, and the reason for their exclusion, is presented in Evidence Table 236.

Table 44. Interventions for nonmedical treatments

Intervention	Number of Studies Reporting
Multidisciplinary Neurobehavioral Treatments	6
EEG Biofeedback	6[a]
Medical Resonance Therapy Music	1
Sahaja Yoga	1
Meditation	1
Physical Exercise	3
Self-Help Group (Group Therapy)	1
Counseling	1
Progressive Muscle Relaxation	2
End-Tidal CO_2 Biofeedback	2[a]
Vocational Services	1
Systematic Desensitization	1
Epilepsy Education	0

[a] One study reported on both of these interventions.

Table 45. External validity of studies of mortality rate

Reference	Country	Number of Patients (Person-Years of Followup)	Type of Study	Treatment	Mean Age (Range)	Mean Age at Death (Range)
Physician's desk reference Gabapentin trial data (2001)[358]	United States	2203 (2103)	Clinical trial	AEDs	Not reported	Not reported
Racoosin (2001)[357]	United States	9144 (13617)	Clinical trial	AEDs	(1-72)	Not reported
Wong (2001)[353]	United Kingdom	1050 (2294)	Epidemiologic	AEDs	31 (7-77)	Not reported
Annegers (2000)[356]	United States	1819 (3176)	Epidemiologic with some clinical trial patients	VNS	Not reported	(6-52)
Hennessy (1999)[362]	United Kingdom	305 (2729)	Clinical trial	Surgery	Not reported	34 (19-54)
Sperling (1999)[360]	United States	194 (801.5)	Clinical trial	Surgery	33.4	34.6 (22.5-42)
Vickrey (1997)[361]	United States	248 (1488)	Clinical trial	Surgery or nonsurgical treatment (not described)	Not reported	Not reported
Leestma (1997)[355]	United States, United Kingdom, Europe, Australia, South Africa	4700 (5747)	Epidemiologic with some clinical trial patients	AEDs	Not reported	36 (0.5-74)
Leppik (1995)[359]	United States, Europe, Australia	2600 (1810)	Clinical trial	AEDs	(12-77)	Not reported
Klenerman (1993)[354]	United Kingdom	Not reported (3392)	Epidemiologic	AEDs	52 (18-91)	64 (23-91)

Table 45. External validity of studies of mortality rate (continued)

Reference	Percent Female Patients (all patients)	Percent Female Patients (Deaths)	Patients Recruited Because of Seizure Type	Seizure Types in Study Group
Physician's desk reference, Gabapentin trial data (2001)[358]	Not reported	Not reported	Not reported	Not reported
Racoosin (2001)[357]	45	Not reported	No	Partial, generalized tonic-clonic, Lennox-Gastaut syndrome
Wong (2001)[353]	50.4	Not reported	No	Partial, generalized
Annegers (2000)[356]	Not reported	44	No	Not reported
Hennessy (1999)[362]	Not reported	60	No	Not reported
Sperling (1999)[360]	48.1	45.5	No	Tonic-clonic, simple partial, complex partial, others not reported
Vickrey (1997)[361]	Not reported	Not reported	No	Not reported
Leestma (1997)[355]	Not reported	37.8	Yes	Partial, partial with secondary generalization, generalized
Leppik (1995)[359]	Not reported	Not reported	No	Partial, other uncontrolled seizures (not described)
Klenerman (1993)[354]	33.3	Not reported	No	Not reported

Table 46. Types of reported mortality

Reference	Overall Mortality	Sudden Unexpected Death (SUDEP)	Epilepsy-Related Mortality	Aspiration	Drowning	Accident	Suicide	Pneumonia	Cardiovascular Disease	Cerebrovascular Disease	Cancer	Treatment Complication
Physician's desk reference, Gabapentin trial data (2001)[358]		✓										
Racoosin (2001)[357]	✓	✓		✓		✓			✓	✓	✓	
Wong (2001)[353]	✓	✓										
Annegers (2000)[370]	✓	✓										
Hennessy (1999)[362]	✓	✓	✓	✓	✓	✓			✓	✓	✓	✓
Sperling (1999)[360]	✓	✓				✓	✓	✓			✓	
Leestma (1997)[355]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Vickrey (1997)[361]	✓											✓
Leppik (1995)[359]	✓	✓				✓					✓	
Klenerman (1993)[354]	✓	✓	✓	✓	✓	✓		✓		✓	✓	

Table 47. External validity in studies of mortality related to seizure type and frequency

Reference	Country	Number of Patients	Mean Age (Range)	Percent Female	Seizure Types in Study Group	Treatment
Studies conducted in the United States						
Walczak (2001)[369]	United States	4578	Not reported (but contained children and adults up to age 80+)	SUDEP: 60 Controls: 45	Generalized tonic-clonic, others not described	AEDs
McKee (2000)[377]	United States	180	20.3	46	Not reported	AEDs
Sperling (1999)[360]	United States	393	32.7	48.1	Tonic-clonic, complex partial	Surgery
Jick (1992)[378]	United States	3280 (only 31 were relevant to this question)	(15-49)	SUDEP: 36 Controls: 45	Primary generalized, primary partial, unknown	AEDs
Birnbach (1991)[379]	United States	108	SUDEP: 31.6 Non-SUDEP: 28.7 Living: 29.4	SUDEP: 24 Non-SUDEP: 34.8 Living: 29.4	Generalized convulsive, others not described	Not reported
Studies conducted in the United Kingdom						
Nilsson (1999)[374]	United Kingdom	228	SUDEP: 44 Non-SUDEP: 44.7	SUDEP: 40.4 Non-SUDEP: 40.4	Generalized idiopathic, partial symptomatic, partial cryptogenic, undetermined	AEDs
Nashef (1995)[376]	United Kingdom	601	32.5 (10-80)	Not reported	Partial cryptogenic/ symptomatic, generalized idiopathic, generalized cryptogenic/ symptomatic, undetermined	Not reported

Table 47. External validity in studies of mortality related to seizure type and frequency (continued)

Reference	Country	Number of Patients	Mean Age (Range)	Percent Female	Seizure Types in Study Group	Treatment
Timmings (1993)[375]	United Kingdom	1820	SUDEP: 35 (20-69)	SUDEP: 35.7 Controls: 53	Idiopathic generalized tonic clonic, partial seizures (with or without secondary generalization)	AEDs
Studies conducted in other countries						
Kloster (1999)[380]	Norway	79	SUDEP: 27.9 Non-SUDEP: 32.6	SUDEP: 38 Non-SUDEP: 49	Generalized motor seizures, partial seizures	AEDs

Table 48. Reporting of seizure type and seizure frequency in studies of mortality

Reference	Seizure Type	Seizure Frequency
Walczak (2001)[369]	✓	✓
McKee (2000)[377]		✓
Kloster (1999)[380]	✓	✓
Nilsson (1999)[374]	✓	✓
Sperling (1999)[360]	✓	✓
Nashef (1995)[376]	✓	
Timmings (1993)[375]	✓	✓
Jick (1992)[378]	✓	✓
Birnbach (1991)[379]	✓	✓

Table 49. Potential biases for Question 2A

Reference	Potential Biases		
	Sampling Bias	Reference Standard Bias	Diagnostic Yield Bias
Studies performed in the United States			
Holmes (1998)[39]	No	Yes	Yes
Henry (1998)[37]	No	Yes	No
Arnold (1996)[40]	No	Yes	Yes
Slater (1995)[41]	No	Yes	No
Studies performed outside of the United States			
Zaidi (2000)[38]	No	Yes	No

Table 50. Internal validity of blood prolactin studies (Question 2B)

Reference	Potential bias								
	Imperfect Reference Standard Bias	Differential Reference Standard Bias	Prevelance Bias	Spectrum Bias	Interpretation Bias	Experimenter Bias	Patient Bias	Diagnostic Yield Bias	Verification Bias
Lusic (1999)[53]	Yes	?	Yes	Yes	?	No	No	No	No
Anzola (1993)[45]	Yes	Yes	Yes	Yes	?	Yes	No	No	No
Zelnik (1991)[56]	Yes	Yes	Yes	Yes	?	No	No	No	No
Mishra (1990)[57]	Yes	?	Yes	Yes	?	No	No	No	No
Wroe (1989)[50]	Yes	No	No	?	?	No	No	No	No

Table 51. Internal validity of trials of sequential monotherapy

Reference	Potential Biases							
	Sampling Bias	Sample Specification	Selection Bias	Regression Bias	Investigator Bias	Patient Bias	Measurement Bias	Extraneous Event Bias
Sachdeo (2001)[68]	No	Yes	NA	Yes	No	No	Yes	Yes
Beydoun (2000)[86]	No	Yes	NA	Yes	No	No	Yes	Yes
Kanner (2000)[87]	No	No	NA	Yes	Yes	Yes	Yes	Yes
Schachter (1999)[79]	No	Yes	NA	Yes	No	No	No	Yes
Gilliam (1998)[76]	No	Yes	NA	Yes	No	No	Yes	Yes
Bergey (1997)[78]	No	Yes	NA	Yes	No	No	?	Yes
Beydoun (1997a)[85]	No	Yes	NA	Yes	No	No	Yes	Yes
Beydoun (1997b)[83]	No	Yes	NA	Yes	No	No	Yes	Yes
Sachdeo (1997a)[84]	No	Yes	NA	Yes	No	No	Yes	Yes
Devinsky (1995)[75]	No	Yes	NA	Yes	No	No	Yes	Yes
Schachter (1995)[88]	No	Yes	NA	Yes	No	No	Yes	Yes
Theodore (1995)[89]	No	Yes	NA	Yes	No	No	?	Yes
Faught (1993)[77]	No	Yes	NA	Yes	No	No	Yes	Yes

NA Not applicable

Table 52. Internal validity of trials of polytherapy

Reference	Potential Bias							
	Sampling Bias	Sample Specification Bias	Selection Bias	Regression Bias	Investigator Bias	Patient Bias	Measurement Bias	Extraneous Event Bias
Faught (2001)[94]	No	Yes	Yes	No	No	No	Yes	No
Ben-Menachem (2000)[95]	No	Yes	No	No	No	No	Yes	No
Betts (2000)[96]	No	Yes	No	No	No	No	Yes	No
Cereghino (2000)[97]	No	Yes	No	No	No	No	Yes	No
Glauser (2000)[98]	No	Yes	No	No	No	No	Yes	No
Appleton (1999)[99]	No	Yes	No	No	No	No	Yes	No
Biton (1999)[100]	No	Yes	No	No	No	No	Yes	No
Duchowny (1999)[30]	No	Yes	No	No	No	No	Yes	No
Elterman (1999)[101]	No	Yes	No	No	No	No	Yes	No
KTSG (1999)[102]	No	No	No	No	No	No	Yes	No
Sachdeo (1999)[103]	No	Yes	No	No	No	No	Yes	No
Uthman (1998)[104]	No	Yes	No	No	No	No	Yes	No
Sachdeo (1997b)[105]	No	Yes	No	No	No	No	Yes	No
Ben-Menachem (1996)[90]	No	Yes	No	No	No	No	Yes	No
Chadwick (1996)[106]	No	Yes	No	No	No	No	Yes	No
Faught (1996)[91]	No	No	No	No	No	No	Yes	No
Privitera (1996)[107]	No	Yes	No	No	No	No	Yes	No
Sharief (1996)[108]	No	Yes	No	No	No	No	Yes	No
Tassinari (1996)[109]	No	Yes	No	No	No	No	Yes	No
Willmore (1996)[110]	No	Yes	No	No	No	No	Yes	No
Anhut (1994)[111]	No	No	No	No	No	No	Yes	No
Messenheimer (1994)[112]	No	Yes	No	No	No	No	Yes	No
Bourgeois (1993)[113]	No	Yes	No	No	No	No	Yes	No
FSG (1993)[114]	No	Yes	No	No	No	No	Yes	No
Matsuo (1993)[115]	No	Yes	Yes	No	No	No	Yes	No
McLean (1993)[116]	No	Yes	No	No	No	No	Yes	No
Schmidt (1993)[117]	No	Yes	No	No	No	No	Yes	No
Sivenius (1991)[118]	No	Yes	No	No	No	No	Yes	No

Table 52. Internal validity of trials of polytherapy (continued)

Reference	Potential Bias							
	Sampling Bias	Sample Specification Bias	Selection Bias	Regression Bias	Investigator Bias	Patient Bias	Measurement Bias	Extraneous Event Bias
UKGSG (1990)[119]	No	Yes	No	No	No	No	Yes	No
Jawad (1989)[70]	No	Yes	No	No	No	No	Yes	No

Table 53. Potential biases in studies of drug reduction strategies

Reference	Potential Bias								
	Sampling Bias	Selection Bias	Investigator Bias	Patient Reporting Bias	Attrition Bias	Measurement Bias	Regression To Mean	Extraneous Event Bias	Sample Specification Bias
Controlled trials performed outside of the United States									
May (1992)[121]	?	Yes	?	Yes	No	Yes	Yes	Yes	Yes
Duncan (1990)[122]	?	Yes	No	No	No	Yes	Yes	Yes	Yes
Thompson (1982)[126]	?	Yes	?	Yes	No	Yes	Yes	Yes	Yes
Case series performed in the United States									
Mirza (1993)[120]	?	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Case series performed outside of the United States									
Specht (1989)[123]	No	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Callaghan (1984)[124]	?	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Schmidt (1983b)[125]	?	NA	Yes	Yes	No	Yes	Yes	Yes	Yes

NA Not applicable

Table 54. Potential biases in studies of vagal nerve stimulation

Reference	Potential Biases									
	Sampling Bias	Sample Specification Bias	Selection Bias	Investigator Bias	Patient Reporting Bias	Attrition Bias	Measurement Bias	Regression to Mean	Extraneous Event Bias	Maturation Bias
RCT's performed in the United States										
Clinicial Study EO5 Handforth (1998)[332]	No	Yes	No	No	Yes	Yes	Yes	No	No	NA[a]
Clinical Trial EO3 The VNS Group (1995)[331]	No	Yes	No	No	Yes	No	Yes	No	No	NA[a]
Followup studies of RCT's performed in the United States										
De Giorgio (2000)[333] Followup of Clinical Study EO5	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Salinski (1996)[31] Followup of Clinical Trial EO3	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Case series performed in the United States										
Chayasirisobhon (2001)[346]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	NA[a]
Ergene (2001)[335]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Hosain (2000)[336]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	NA[a]
Clinical Trial EO4, Labar (1999)[334]	?	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	NA[a]
Case series performed outside of the United States										
Aldenkamp (2001)[337]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	NA[a]
Hoppe (2001)[339]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Ben-Menachem (1999)[343]	?	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Boon (1999)[338]	No	Yes	NA	Yes	Yes	No	Yes	Yes	Yes	Yes
Parker (1999)[340]	?	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lundgren (1998)[341]	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Sampling bias. All of the retrospective studies (9/10 studies) were vulnerable to sampling bias (for a definition of this bias, see Methodology section of this document). Patient selection in the one prospective study appeared to preclude this bias.[360]

Sample specification bias. Because none of the included studies specified that patients described as "refractory" or "treatment-resistant" had received at least one AED at the maximum tolerated dosage, all of the studies were potentially affected by sample specification bias (see Methodology section for more detailed description of this bias).

Table 55. Internal validity of studies of mortality rate

Reference	Country	Potential bias			
		Mortality Ratio Bias (Overall Mortality)	Mortality Ratio Bias (Cause-Specific Mortality)	Sampling Bias	Sample Specification Bias
Physician's desk reference, Gabapentin trial data (2001)[358]	United States	No	Yes	Yes	Yes
Racoosin (2001)[357]	United States	No	Yes	Yes	Yes
Wong (2001)[353]	United Kingdom	No	Yes	Yes	Yes
Annegers (2000)[356]	United States	No	Yes	Yes	Yes
Hennessy (1999)[362]	United Kingdom	No	Yes	Yes	Yes
Sperling (1999)[360]	United States	No	Yes	No	Yes
Vickrey (1997)[361]	United States	Yes	Yes	Yes	Yes
Leestma (1997)[355]	United States, United Kingdom, Europe, Australia, South Africa	Yes	Yes	Yes	Yes
Leppik (1995)[359]	United States, Europe, Australia	Yes	Yes	Yes	Yes
Klenerman (1993)[354]	United Kingdom	No	Yes for some causes, no for others	Yes	Yes

Table 56. Internal validity in studies of mortality related to seizure type and frequency

Reference	Country	Potential Bias			
		Cause Validation Bias	Sampling Bias	Statistical Control Bias	Possible Confounding Variables Unaccounted For
Walczak (2001)[369]	United States	Yes	No	No	Yes
McKee (2000)[377]	United States	Yes	Yes	Yes	Yes
Kloster (1999)[380]	Norway	No	Yes	Yes	Yes
Nilsson (1999)[374]	United Kingdom	Yes	Yes	No	Yes
Sperling (1999)[360]	United States	?	No	Yes	Yes
Nashef (1995)[376]	United Kingdom	Yes	Yes	Yes	Yes
Timmings (1993)[375]	United Kingdom	?	Yes	Yes	Yes
Jick (1992)[378]	United States	No	Yes	Yes	Yes
Birnbach (1991)[379]	United States	?	Yes	Yes	Yes