

Evidence Extractions

Question: How effective and cost-effective are anti-epileptic drugs for focal seizures with/without secondary generalisation

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Anhut H;Ashman P;Feuerstein TJ;Sauermaun W;Saunders M;Schmidt B;

Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. The International Gabapentin Study Group

Ref ID 4753

1994

Study Type	Randomised Controlled Trial	Funding	Parke Davis
Number of participant	272 patients total; 109 placebo; 111 Gabapentin (GBP) 900 mg/day; 52 Gabapentin 1200 mg/day		
Inclusion/Exclusion Criteria	Inclusion: Stable AED dose during the 3 months before screening with four partial seizures per month despite medication; males and females greater than or equal to 12 years with body weight of 40-110 kg and women of children potential using adequate contraception. Excluded: Patients with progressive structural lesions in CNS, severe hepatic or renal disease, low WBC, or neutropenia or chronic drug or alcohol abuse.		
Patient Characteristics	There were 56% men and 44% women with a mean age of 32 years (range (12-67) and median baseline seizure frequency of 10.2 (range 0.5-634.3). Most patients were receiving one (24%) or two (68%) concurrent AEDs, most frequently CBZ (75%), VPA (31%) and PHT (28%).The only significant difference between groups was body mass with 900 mg/day group smaller (P=0.015)		
Recruitment	Unknown		
Setting	24 centres: Europe, Canada, South Africa and Austr		
Interventions/ Test/ Factor being investigated	GBP as an add on therapy in patients with refractory partial seizures in doses of 900 mg/day and 1200 mg/day to evaluate safety, efficacy and dose response.		
Comparisons	Comparisons are between treatments (2) and placebo		
Length of Study/ Follow-up	12 week open label extension phase.		
Outcome measures studied	Primary: Percentage of change in the frequency of partial seizures relative baseline; responder rate and response ratio. Secondary: Response ratio for all seizures and global evaluations of patients overall ability to perform ADLs		
Results	The ITT analysis (2 patients missing) and the analysis for the evaluable population (32 patients missing) were in close agreement. In the ITT analysis the responder rate was 22% for the 900 mg/day group and 10.1% for the placebo group (p=0.026) ; rate ration was -0.138 for the 900 mg/day group and -0.017 for the placebo group (p=0.0002). For the 1200 mg/day group, responder rate was 27% and the rate ratio was -0.184. GBP produced a dose related reduction in seizure frequency in all types of partial seizures.		
Safety and adverse effects	Adverse events occurred in 69% of patients in the 900 mg/day group and 64% in the 1200 mg/day group compared with 52% in placebo group. The most frequent events among those on GBP were somnolence, dizziness and fatigue. There were no clinically important effects.		
Does the study answer the question?	GBP appears to be safe and effective in treating some patients with refractory partial seizures.		
Effect due to factor in study?	Yes.		
Consistency of results with other studies?			

Directly applicable to guideline population? Direct.

Internal Validity Multi centre

Appleton R;Fichtner K;LaMoreaux L;Alexander J;Halsall G;Murray G;Garofalo E;

Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. Gabapentin Paediatric Study Group

Ref ID 4604

1999

Study Type Randomised Controlled Trial **Funding** Parke Davis

Number of participant Total: 247; placebo: 128; Gabapentin: 119

Inclusion/Exclusion Criteria Inclusion: Patients with history of medically uncontrolled seizures classified as simple partial, complex partial, or partial becoming generalized, aged 12 years or younger, weigh 17-72 kg at screening and were to be receiving one to three AEDs. Exclusion: Patients with absence seizures or seizures related to drugs, alcohol or acute medical illness; patients with structural CNS lesions or encephalopathies, diagnosed as progressive within 2 years before screening; children with benign epilepsy syndromes

Patient Characteristics	Total (n=247)
Gender, n(%)	
male	134 (54.3%)
female	113 (45.7%)
Age (yr)	
Mean +/- SD	8.4 +/-2.6
Race	
White	226 (91.5%)
Other	21 (8.5%)

Recruitment Not described

Setting 54 centres in Europe, Sough Africa and the US from

Interventions/ Test/ Factor being investigated Gagapentin vs. placebo

Comparisons Treatment vs. placebo

Length of Study/ Follow-up 6 week baseline phase followed by a 12 week double blind treatment phase

Outcome measures studied Primary: Seizure frequency as a Response Ratio; Secondary: responder rate, percentage change (PCH) in the frequency of all partial seizures from baseline to treatment phase, PCH and RRatio for individual types of partial seizures.

Results RRatio for all partial seizures was significantly lower (better) for GBP treated patients: p=0.0407. Responder rate favoured GBP but the difference between treatment groups was not statistically significant. Median PCH for all partial seizures for the GBP treatment group (-17.0%) was better than that for the placebo group (-6.5%). Median PCH for specific seizure types showed GBP to be most effective in controlling complex partial seizures (-35%) and secondarily generalized seizures (-28%) when compared with placebo (112% and +13%) respectively).

Safety and adverse effects The most frequently reported treatment related adverse events were somnolence, hostility, nausea and/or vomiting, fatigue, headache, convulsions, hyperkinesia and emotional liability.

Does the study answer the question? GBP was effective and well tolerated as an add on therapy for partial seizures in paediatric patients with previously drug resistant seizures.

Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Multicentre trial in Europe, US and South Africa

Arroyo S;Anhut H;Kugler AR;Lee CM;Knapp LE;Garofalo EA;Messmer S;International Study Group;

Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures

Ref ID 4409

2004

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=288(n=99 on 150mg/d, n=92 on 600mg/d and n=97 on placebo)

Inclusion/Exclusion Criteria Men or women aged 18 years or older, weighing 50– 135 kg, with partial seizures were allowed to enter. They were required to have unsuccessfully tried at least one AED at the maximum tolerated dose, to have had at least three partial seizures in the month before screening, and were receiving one to three AEDs. Patients were required to have at least six partial seizures during the 8-week period before randomization and not to have been free of seizures for any 4-week period during this time.
Exclusion criteria: patients with absence seizures, Lennox–Gastaut syndrome, status epilepticus in the past year, clinically relevant medical illness or electrocardiogram (ECG) abnormalities or a significant psychiatric disorder.

Patient Characteristics	Pregabalin		
	Pregabalin mg/day	Placebo	Pregabalin 150 mg/day
Number of patients	96	99	92
Age (yr)			
Mean (SD)	38.1 (12.4)	36.5 (11.3)	36.4
(10.5)			
Gender, N (%)			
Men	54 (56.3)	44 (44.4)	47
(51.1)			
Race, N (%)			
White	89 (92.7)	93 (93.9)	84
(91.3)			
Black	1 (1.0)	2 (2.0)	2
(2.2)			
Hispanic	2 (2.1)	2 (2.0)	1
(1.1)			
Weight (kg)			
Mean (SD)	73.00 (14.49)	75.12 (18.39)	71.22
(16.21)			
Creatinine clearance at baseline			
Mean (ml/min)	105.7	114.3	
110.7			
Years with epilepsy			
Mean (SD)	22.78 (13.58)	24.8 (12.65)	25.06
(11.63)			
Baseline 28-day seizure rate			
Mean (SD)	23.5 (41.1)	26.2 (40.8)	19.3
(24.4)			
Seizure history at screening, N (%)			
Simple partial	47 (49.0)	40 (40.4)	37

(40.2)			
Complex partial (95.7)	88 (91.7)	89 (89.9)	88
Partial secondarily generalized (75.0)	72 (75.0)	65 (65.7)	69
Generalized (6.5)	3 (3.1)	9 (9.1)	6
Concurrent AED, N (%)			
1 AED (17.4)	23 (24.0)	14 (14.1)	16
2 AEDs (55.4)	42 (43.8)	54 (54.5)	51
3 AEDs (26.1)	30 (31.3)	31 (31.3)	24

Recruitment	Unknown.
Setting	45 centres worldwide.
Interventions/ Test/ Factor being investigated	Pregabalin (PGB) 150mg/day (50mg three times a day) and PGB 600mg/day (200mg three times a day).
Comparisons	Comparisons are made between two doses of PGB and placebo as adjunctive therapy to currently used AEDs.
Length of Study/ Follow-up	20 weeks: 8 week baseline period and 12 week treatment period.
Outcome measures studied	The primary efficacy criterion was seizure-frequency change from baseline expressed as RRatio. Secondary outcomes: responder rate, % free of seizures, change in seizure freq.
Results	<p>Primary outcome</p> <p>The reduction in seizures point was significantly greater in the 150-mg/day PGB and 600-mg/day PGB groups compared with placebo. The 150-mg/day and 600-mg/day PGB dosages were both significantly more effective than placebo in reducing the RRatio [-11.5 ($p = 0.0007$) and -31.4 ($p \leq 0.0001$), respectively, vs. 0.9]. These Rratio values correspond to seizure-frequency reductions from baseline of 20.6, and 47.8% for 150 mg/day, and 600mg/day, respectively, and a seizure-frequency increase of 1.8% with placebo. Difference in the treatment means [95% confidence interval (CI)] compared with the placebo group was -12.4 (-20.5; -4.3) in the 150-mg/day PGB group and -32.3 (-40.6; -24.0) in the 600-mg/day PGB group. The 600-mg/day PGB group was statistically superior to the 150-mg/day PGB group ($p \leq 0.0001$).</p> <p>Secondary outcomes</p> <p>Responder rate The responder rate was significantly greater in the 600-mg/day PGB group (43.5%) than in the placebo group (6.2%) ($p \leq 0.001$). In the 150-mg/day PGB group, the difference from placebo approached significance (14.1%; $p=0.087$). Responder rate for the 600-mg/day PGB group was statistically superior to the 150-mg/day PGB group ($p \leq 0.001$).</p> <p>Median percentage reduction A median percentage reduction was seen in all partial seizures of 16.5% in the 150-mg/day PGB group and 42.6% in the 600-mg/day PGB group, and an increase of 1.3% in the placebo group.</p> <p>Seizure free During the last 28 days of treatment, 12% of patients in the 600-mg/day PGB group were free of seizures, as were 7% in the 150-mg/day PGB group and just 1% in the placebo group ($p = 0.002$ and $p = 0.065$ vs. placebo, respectively).</p> <p>Subgroup analysis The analysis of median percentage change in seizure frequency according to seizure type was consistent with the analysis of all partial seizures combined.</p>

Adverse events	Pregabalin		
	Placebo	150 mg/day	600 mg/day
Number of patients	97	99	92
Any adverse event	61 (63.5)	75 (75.8)	80 (87.0)
Discontinued with adverse event	6 (6.2)	10 (10.1)	17 (18.5)
Adverse events occurring in ≥10% of patients			
Somnolence	7 (7.3)	6 (6.1)	27 (29.3)
Dizziness	8 (8.3)	19 (19.2)	24 (26.1)
Ataxia	3 (3.1)	2 (2.0)	16 (17.4)
Asthenia	11 (11.5)	13 (13.1)	13 (14.1)
Diplopia	5 (5.2)	6 (6.1)	13 (14.1)
Weight gain	2 (2.1)	7 (7.1)	13 (14.1)
Headache	15 (15.6)	6 (6.1)	11 (12.0)
Tremor	3 (3.1)	3 (3.0)	10 (10.9)
Blurred vision	3 (3.1)	7 (7.1)	9 (9.8)

Safety and adverse effects Frequency of serious treatment-emergent adverse events were higher in the PGB treatment groups.

Does the study answer the question? Yes. PGB, 150mg/day and 600mg/day is effective as add-on therapy in patients with partial seizures.

Effect due to factor in study? Yes. The study was well conducted and the sample size was derived from a power calculation which was based on results from other trials.

Consistency of results with other studies?

Directly applicable to guideline population? The study comprised subjects who suffered from partial seizures.

Internal Validity

Barcs G;Walker EB;Elger CE;Scaramelli A;Stefan H;Sturm Y;Moore A;Flesch G;Kramer L;D'Souza J;

Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy

Ref ID 4701

2000

Study Type Randomised Controlled Trial **Funding** Novartis

Number of participant Total 694 enrolled, 173 placebo, in OXC: 169 for 600mg/day, 178 for 1200mg/day, 174 for 2400 mg/day

Inclusion/Exclusion Criteria
 Inclusion:
 Partial seizures classified as simple, complex, or partial seizures evolving to secondarily generalised seizures (ILEA 1981 and 1989)
 Men or women aged 15-65 years
 A average of ≥4 partial seizures per month during the 8 week baseline period while maintained on 1-2 concomitant AEDs

Exclusion criteria:
 Women who were nursing/pregnant or trying to conceived
 History of generalised status epilepticus in 2 years preceding trial
 Seizures of metabolic, neoplastic, or infectious origin
 Non-compliance
 A cardiovascular, respiratory, hepatic, renal, gastrointestinal, haematologic, oncologic, psychiatric or progressive neurologic disorder
 Attempted suicide, substance abuse, hypersensitivity to CBZ
 Clinically significant laboratory abnormalities
 History of OXC treatment
 History of MAOI treatment within a 15 day period before inclusion
 Concomitant treatment by ethosuximide and Felbamate, or oestrogen therapy, or other hormonal contraceptive therapy

Patient Characteristics	placebo	OXC 600mg/day	OXC 200mg/day	OXC 2400mg/day																																					
	Male (%):		51.2	45.2	56.3	44.5																																			
Mean age, yr (range):		34.6(15-65)	33.8(16-64)	35.2(15-66)	34.3(15-65)																																				
Mean weight kg (range):		73.1(44-139)	70.5(45-135)	70.9(44-131)	70.2(35-120)																																				
Median 28 days baseline Seizure frequency:		9.6	9.8	10.0	8.6																																				
Median 28 days baseline secondary generalised Seizure frequency:		3.5 (n=51)	2.0(n=68)	2.4(n=60)																																					
Recruitment	International, multi-centre study.																																								
Setting	International, multi-centre study.																																								
Interventions/ Test/ Factor being investigated	OXC 600mg/d 1200mg/day, 2400mg/day or placebo																																								
Comparisons	Adjunctive therapy: Adding OXC 600mg/d 1200mg/day, 2400mg/day or placebo																																								
Length of Study/ Follow-up	Total 38 weeks: 8 weeks baseline, 2 weeks titration, 24 weeks maintenance, 2 weeks of tapering off. Patients had the option to join an open label study																																								
Outcome measures studied	Primary: % reduction in seizure frequency/28 days during the double blind treatment phase relative to the baseline phase Secondary: 50% or greater reduction in seizure frequency in the double blind treatment phase relative to the baseline phase																																								
Results	<p>Proportion of seizure free participants</p> <p>OXC 600mg/day: 5/168 (3%)</p> <p>OXC 1200mg/day: 18/177 (10%)</p> <p>OXC 2400mg/day: 38/174 (22%)</p> <p>Placebo: 1/173 (0.6%)</p> <p>P value: all statistically significant vs placebo</p> <p>Proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders)</p> <p>OXC 600mg/day: 20/168(26.8%)</p> <p>OXC 1200mg/day: 64/177(41.2%)</p> <p>OXC 2400mg/day: 116/174(50.0%)</p> <p>Placebo: 15/173(12.7%)</p> <p>P value: all statistically significant vs placebo</p> <p>The proportion of participants having treatment withdrawn due to unsatisfactory treatment effect</p> <p>OXC 600mg/day: 1/168 (0.6%)</p> <p>OXC 1200mg/day: not reported</p> <p>OXC 2400mg/day: not reported</p> <p>Placebo: 22/173(12.7%)</p> <p>The proportion of participants having treatment withdrawn due to adverse events</p> <p>OXC 600mg/day: 20/168 (11.9%)</p> <p>OXC 1200mg/day: 64/177 (36.2%)</p> <p>OXC 2400mg/day: 116/174 (66.7%)</p> <p>Placebo: 15/173 (8.7%)</p> <p>P value:</p> <p>Incidence of adverse events >10%</p> <table border="1"> <thead> <tr> <th></th> <th>OXC 600mg/day N=168</th> <th>OXC 1200mg/day n=177</th> <th>OXC 2400mg/day n=174</th> <th>OXC Total n=519</th> <th>Placebo n=173</th> </tr> </thead> <tbody> <tr> <td>Dizziness</td> <td>42[25.0]</td> <td>56[31.6]</td> <td>74[42.5]</td> <td>172[33.1]</td> <td>22[12.7]</td> </tr> <tr> <td>Headache</td> <td>54[32.1]</td> <td>48[27.1]</td> <td>40[23.0]</td> <td>142[27.4]</td> <td>41[23.7]</td> </tr> <tr> <td>Somnolence</td> <td>33[19.6]</td> <td>48[27.1]</td> <td>56[32.2]</td> <td>137[26.4]</td> <td>20[11.6]</td> </tr> <tr> <td>Ataxia</td> <td>16[9.5]</td> <td>31[17.5]</td> <td>56[32.2]</td> <td>103[19.8]</td> <td>9[5.2]</td> </tr> <tr> <td>Nystagmus</td> <td>11[6.5]</td> <td>36[20.3]</td> <td>41[23.6]</td> <td>88[17.0]</td> <td>7[4.0]</td> </tr> </tbody> </table>						OXC 600mg/day N=168	OXC 1200mg/day n=177	OXC 2400mg/day n=174	OXC Total n=519	Placebo n=173	Dizziness	42[25.0]	56[31.6]	74[42.5]	172[33.1]	22[12.7]	Headache	54[32.1]	48[27.1]	40[23.0]	142[27.4]	41[23.7]	Somnolence	33[19.6]	48[27.1]	56[32.2]	137[26.4]	20[11.6]	Ataxia	16[9.5]	31[17.5]	56[32.2]	103[19.8]	9[5.2]	Nystagmus	11[6.5]	36[20.3]	41[23.6]	88[17.0]	7[4.0]
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Abnormal gait	9[5.4]	17[9.6]	26[14.9]	52[10.0]	2[1.2]
Tremor	6[3.6]	14[7.9]	25[14.4]	45[8.7]	7[4.0]
Vomiting	22[13.1]	44[24.9]	58[33.3]	124[23.9]	8[4.6]
Nausea	25[14.9]	43[24.3]	49[28.2]	117[22.5]	14[8.1]
Abdominal pain	16[9.5]	22[12.4]	14[8.0]	52[10.0]	8[4.6]
Diplopia	23[13.7]	54[30.5]	68[39.1]	145[27.9]	8[4.6]
Abnormal vision	11[6.5]	24[13.6]	30[17.2]	65[12.5]	7[4.0]
Vertigo	11[6.5]	20[11.3]	24[13.8]	55[10.6]	4[2.3]
Fatigue	25[14.9]	21[11.9]	26[14.9]	72[13.9]	12[6.9]
Viral Infection	20[11.9]	17[9.6]	10[5.7]	47[9.1]	4[13.9]

Safety and adverse effects

A large number of patients withdrawn due to adverse events. Protocol amendment was made to allow reduction to 1800mg in the 1400mg/day group

Does the study answer the question?

OXC is safe and effective as adjunctive therapy in patients with uncontrolled partial seizures. 600mg/day is the minimum effective dose, effectiveness increases with dose.

The fixed and rapid titration to high doses is associated with increased risk of adverse events.

Effect due to factor in study?

There was an overall 295/694(42.5%) dropout rate. The dropout rate for the 2400mg arm was 128/174(73.6%)

Consistency of results with other studies?

Directly applicable to guideline population?

None noted

Internal Validity

Ben-Menachem E;Biton V;Jatuzis D;bou-Khalil B;Doty P;Rudd GD;

Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures

Ref ID 1615

2007

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=421 (n=97 in placebo group, n=107 in lacosamide 200mg per day group, n=108 in lacosamide 400mg per day, n=106 in lacosamide 600mg per day)

Inclusion/Exclusion Criteria
 Inclusion criteria:partial-onset seizures for at least the last 2 years despite prior therapy with at least 2 AEDs. During the 8-week baseline period, patients must have had at least 4 partial onset seizures per 28 days on average, with no seizure-free period longer than 21 days. In the 4 weeks before enrollment and during the baseline period, patients must have been on a stable dosage regimen of 1 or 2 AEDs.
 Exclusion criteria:Female patients if pregnant, breast-feeding, or of childbearing potential; received lacosamide in a previous trial or had participated in any other investigational drug or experimental device trial within the last 2 months; history of chronic alcohol or drug abuse within the previous 2 years; any medical or psychiatric condition that might jeopardize the patient's health or compromise the patient's ability to participate in this trial.

Patient Characteristics Demographic and baseline characteristics of patients analyzed for safety

	Placebo	LCM 200 mg/day	LCM 400 mg/day	LCM 600 mg/day
Characteristic	(n = 97)	(n = 107)	(n = 108)	(n = 106)
Age, year				
Mean ± SD	38.9 ± 11.11	39.9 ± 11.71	41.2 ± 11.61	39.4 ± 10.53
Range	19 – 66	18 – 65	18 – 68	18 – 64
Sex, n (%)				
Male	47 (48)	46 (43)	53 (49)	45 (42)

Female (58)	50 (52)	61 (57)	55 (51)	61
Race, n (%)				
Caucasian (95)	88 (91)	98 (92)	100 (93)	101
Black (2)	6 (6)	4 (4)	5 (5)	2
Asian (0)	0 (0)	2 (2)	0 (0)	0
Other (3)	3 (3)	3 (3)	3 (3)	3
Weight, Kg (mean ± SD)	79.5 ± 20.90	74.5 ± 17.16	77.5 ± 18.63	75.7 ± 19.40
Mean time since diagnosis (year)	24.6 ± 11.77	25.1 ± 12.89	24.7 ± 13.08	23.6 ± 12.74
Seizure type at baseline, n (%)				
Simple partial-onset seizures (50 (47))	33 (34)	48 (45)	41 (38)	
Complex partial-onset seizures (96 (91))	83 (86)	101 (94)	94 (87)	
Partial-onset seizures with secondary generalization (70 (66))	73 (75)	79 (74)	77 (71)	

Recruitment

Not reported

Setting

68 centres in Europe and the USA inc. the UK.

Interventions/ Test/ Factor being investigated

Four different doses of lacosamide (200, 400 or 600mg per day) as adjunctive therapy with currently used AEDs.

Comparisons

The comparison is between lacosamide in four doses and placebo as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up

26 weeks: 8 weeks baseline period, 6 week titration and 12 week maintenance period.

Outcome measures studied

Primary outcome: change in seizure frequency (1) reduction in seizure frequency (2) responder rate. Secondary outcomes: seizure freq, seizure free days, CGI, QOLIE-31

Results

Primary outcomes

Median percent reduction in seizure frequency from baseline to maintenance
The median % reduction in seizure frequency from baseline to maintenance was 10% in the placebo, 26% in the lacosamide 200 mg/day, 39% in the 400 mg/day, and 40% in the 600 mg/day treatment groups. Statistically significant reductions in seizure frequency over placebo were observed in the lacosamide 400 mg/day (28.4%; $p = 0.0023$) and 600 mg/day (21.3%; $p = 0.0084$) treatment groups. For the lacosamide 200 mg/day treatment group, the reduction in seizure frequency over placebo was 14.6% ($p = 0.1010$), indicating a difference that did not reach statistical significance.

Response rates

The proportion of patients with at least a 50% reduction in seizure frequency during maintenance for lacosamide 400 mg/day (41.1%; $p = 0.0038$) and 600 mg/day (38.1% $p = 0.0141$) was statistically significant when compared to placebo (21.9%). For the lacosamide 200 mg/day treatment group, the 50% responder rate was 32.7% ($p = 0.0899$), indicating a difference that did not reach statistical significance.

Secondary outcomes

Seizure free rates

Seven patients were seizure-free throughout the 12-week maintenance period, all were randomized to lacosamide; 1 patient in the lacosamide 200 mg/day group, 5 in the 400 mg/day group, and 1 in the 600 mg/day group. At the end of the maintenance period, the median change from baseline in the percentage of seizure-free days was 3% for patients randomized to placebo, 6% for patients randomized to lacosamide 200 mg/day, 12% for 400 mg/day, and 12% for 600 mg/day. Statistically significant differences in the percentage of seizure-free days over placebo were observed in the

lacosamide 400 mg/day (p=0.0036) and 600 mg/day (p = 0.0004) groups.

Quality of life

Patients in the lacosamide 400 mg/day group experienced more improvement in quality of life than patients in the other treatment groups, as assessed by median changes in QOLIE-31 overall score from baseline, with an improvement of 2.7 points compared to an overall score of -1.3 points in the placebo group.

Clinical Global Impression of Change (CGIC)

The CGIC analysis showed an improvement (“very much improved” or “much improved”) from baseline to maintenance in a greater percentage of patients in the lacosamide 200mg/day (35%), 400 mg/day (40%), and 600 mg/day (38%) treatment groups compared to the placebo group (25%).

Adverse events

Treatment-emergent adverse events (%) occurring in at least 10% of patients in any treatment group

	Placebo	LCM 200mg/d	LCM 400mg/d	LCM 600mg/d
600mg/d Lacosamide Total				
Adverse events	(n = 97)	(n = 107)	(n = 108)	(n = 106)
Any event	68 (70)	85 (79)	87 (81)	98 (92)
Dizziness (55)	10 (10)	26 (24)	28 (26)	58
Headache (13)	9 (9)	12 (11)	26 (24)	14
Nausea (18)	9 (9)	11 (10)	16 (15)	19
Fatigue (20)	5 (5)	11 (10)	13 (12)	21
Ataxia (23)	3 (3)	4 (4)	14 (13)	24
Vision abnormal (20)	5 (5)	4 (4)	12 (11)	21
Vomiting (12)	3 (3)	11 (10)	13 (12)	13
Diplopia (14)	2 (2)	4 (4)	12 (11)	15
Somnolence (9)	6 (6)	8 (7)	13 (12)	10
URI (6)	11 (11)	12 (11)	13 (12)	6
Accident NOS (5)	12 (12)	15 (14)	6 (6)	5
Nystagmus (10)	5 (5)	3 (3)	5 (5)	11

aPatients reporting the same adverse event more than once are counted once per adverse event and randomized dose.

NOS, not otherwise specified; URI, upper respiratory infection.

Of the 418 patients who received at least one dose of trial medication, 69 (17%) discontinued from the trial during the treatment period because of TEAEs; 5 patients randomized to placebo, and 12, 20, and 32 patients randomized to lacosamide 200, 400, and 600 mg/day, respectively.

The most frequently reported SAEs were dizziness and convulsions (3 patients each), as well as vomiting, accident not otherwise specified, nystagmus, nausea, and aggravated convulsions (2 patients each).

Safety and adverse effects

Does the study answer the question?

Yes. Lacosamide, at doses of 400 mg/day and 600 mg/day, produced a statistically significant reduction in seizure frequency for patients with partial-onset seizures, with or without secondary generalization, when added to 1 or 2 concomitant AEDs.

Effect due to factor in study?

Yes. The study was powered sufficiently well to detect differences between lacosamide groups and placebo.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in this study were adults with uncontrolled partial-onset seizures.

Internal Validity

Ben-Menachem E;Falter U;

Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. European Levetiracetam Study Group

Ref ID 4741

2000

Study Type Randomised Controlled Trial **Funding** Grant from UCB S.A. Pharma Sector, Braine l'Alleud, Belgium

Number of participant A total of 286 patients (placebo, n = 105; Levetiracetam 3000mg/d (LEV), n = 181) entered the add-on phase, and 86 patients (placebo, n = 17; LEV, n = 69) were eligible for the monotherapy phase.

Inclusion/Exclusion Criteria Included: Men and women aged 16 to 70 years with seizures refractory to one AED; women had to be using contraception. Excluded: hx of status, progressive disease, CVA or CV disease; diabetes, impaired hepatic or renal function, drug or alcohol abuse, psychiatric disorder, CNS drugs, digitalis, glucosides or coumarins

Patient Characteristics 286 enrolled patients (ITT population)

	Placebo, n=105	LEV n=181	Total n=286
Mean age (yrs)	36(12)	37(12)	36(12)
Mean BMI (SD)	24.5(3.9)	24.8 (4.3)	24.7 (4.2)
Gender (%male/female)	49/51	48/52	48/52
Age at epilepsy onset (yrs) (SD)	18(13)	18(14)	18(14)

Recruitment Unknown

Setting 47 institutions throughout Europe

Interventions/ Test/ Factor being investigated To evaluate the efficacy and tolerability of levetiracetam (LEV) monotherapy in selected patients with refractory partial seizures

Comparisons Comparison is made between treatment and placebo

Length of Study/ Follow-up 60 weeks

Outcome measures studied Primary: Percentage of patients who completed the monotherapy phase relative to the number of patients randomized to receive the study medication
Secondary: Seizure frequency, reported as the number of partial seizures per week; the responder rate.

Results A total of 286 patients (placebo, n = 105; LEV, n = 181) entered the add-on phase, and 86 patients (placebo, n = 17; LEV, n = 69) were eligible for the monotherapy phase. Thirty-six of 181 patients (19.9%) who received LEV completed the entire study compared with only 10 of 105 patients (9.5%) in the placebo group (p = 0.029). The odds of completing the study on LEV were 2.36 times (95% confidence interval, 1.08, 5.57) higher than on placebo. The responder rate during the add-on phase was significantly higher in the LEV group compared with the placebo group (42.1% vs. 16.7%, respectively; p < 0.001). In the LEV monotherapy group, the median percent reduction in partial seizure frequency compared with baseline was 73.8% (p = 0.037), with a responder rate of 59.2%. Nine patients (18.4%) remained seizure-free on LEV monotherapy

Safety and adverse effects	The incidence of adverse events in the add on phase was comparable between treatment groups (placebo 53%; LEV 55%). Asthenia, infection and somnolence had an incidence >5%.
Does the study answer the question?	Conversion to LEV monotherapy (1500 mg twice daily) is effective and well tolerated in patients a small group of patients with refractory partial seizures who responded to 3000 mg/d LEV as add-on therapy
Effect due to factor in study?	The ultimate patient population is small and this drug needs to be studied further.
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Small study population completed study

Ben-Menachem E;Henriksen O;Dam M;Mikkelsen M;Schmidt D;Reid S;Reife R;Kramer L;Pledger G;Karim R;

Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures

Ref ID 4748

1996

Study Type	Randomised Controlled Trial	Funding	Not reported, 1 co author from Johnson Pharmaceutical
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Number of participant Total 56, 28 topiramate, 28 placebo

Inclusion/Exclusion Criteria

Inclusion criteria:

- Healthy men and women aged 18 to 65 with history of partial seizures which had not responded to treatment with one or two AEDs
- Had secondary generalised seizures
- Presence of lateralised epileptic form pattern consistent with a diagnosis of localised related epilepsy documented by EEG within the past 5 years
- Women should be post menopausal, or surgically rendered incapable of having children, or used an acceptable method of birth control
- At least 8 partial seizures during the 8 week baseline period while maintained on therapeutic doses and plasma levels of one or two appropriate AEDs. Seizure free period must not be longer than 3 weeks, and only one such period permitted.

Exclusion criteria:

- Treatable cause of seizure
- Progressive neurologic disorder
- Significant laboratory abnormalities,
- History of alcohol or drug abuse, serious psychiatric disorders, nephrolithiasis,
- History of poor compliance

Patient Characteristics	Both groups
Male:	84%
Mean age, year:	37.2
Mean weight,:	75.2
Number of AEDs:	
One:	38%
Two:	62%
	Median baseline monthly seizure: 14.2 for TPM, 11.4 for placebo
Recruitment	Multicentre trial, Sweden, Norway, Denmark, Germany
Setting	Multicentre - Sweden, Norway, Denmark, Germany

Interventions/ Test/ Factor being investigated	TPM or placebo as adjunctive therapy																					
Comparisons	Adjunctive therapy: TPM vs placebo																					
Length of Study/ Follow-up	8 weeks baseline period, 13 week double blinded period – 5 week titration and 8 week maintenance																					
Outcome measures studied	Primary: % reduction in monthly seizure rate vs baseline Secondary: % of treatment responders (≥50% reduction in seizure rate), reduction in generalised seizures, the investigator's global rating, the patient's rating of study medication.																					
Results	<p>Proportion of seizure free (GENERALISED seizure) participants (100% reduction vs baseline) TPM: 6/11(46%) Placebo: 2/13(18%) P no reported</p> <p>Proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders) TPM: 12/28(43%) Placebo: 0/28 (0%) P=0.001</p> <p>Proportion of participants experiencing at least a 50% reduction in GENERALISED seizure frequency (i.e. responders) TPM: 9/11(69%) Placebo: 3/13(27%) P no reported</p> <p>The proportion of participants having treatment withdrawn due to adverse event: TPM: 6/28 (21%) Placebo: 0/28 (0%) P not reported</p> <p>Incidence of adverse events >10%</p> <table border="0"> <thead> <tr> <th></th> <th>Placebo</th> <th>TPM</th> </tr> </thead> <tbody> <tr> <td>Fatigue:</td> <td>10/28(36%)</td> <td>22/28(79%)</td> </tr> <tr> <td>Headache:</td> <td>10/28(36%)</td> <td>6/28(21%)</td> </tr> <tr> <td>Concentration impaired:</td> <td>0/28</td> <td>7/28(25%)</td> </tr> <tr> <td>Weight loss:</td> <td>0/28</td> <td>7/28(25%)</td> </tr> <tr> <td>Dizziness:</td> <td>1/28(4%)</td> <td>6/28(21%)</td> </tr> <tr> <td>Paraesthesia:</td> <td>1/28(4%)</td> <td>5/28(18%)</td> </tr> </tbody> </table> <p>(study only reported adverse events which affected ≥15% of patients in either treatment arm) Adverse events occurring in 10-14% were abdominal pain, anorexia, ataxia, diplopia, dry mouth, tremor (TPM group); accidental injury, diarrhoea, dyspepsia, insomnia and nystagmus in the (placebo group); respiratory infection (both groups)</p>		Placebo	TPM	Fatigue:	10/28(36%)	22/28(79%)	Headache:	10/28(36%)	6/28(21%)	Concentration impaired:	0/28	7/28(25%)	Weight loss:	0/28	7/28(25%)	Dizziness:	1/28(4%)	6/28(21%)	Paraesthesia:	1/28(4%)	5/28(18%)
	Placebo	TPM																				
Fatigue:	10/28(36%)	22/28(79%)																				
Headache:	10/28(36%)	6/28(21%)																				
Concentration impaired:	0/28	7/28(25%)																				
Weight loss:	0/28	7/28(25%)																				
Dizziness:	1/28(4%)	6/28(21%)																				
Paraesthesia:	1/28(4%)	5/28(18%)																				
Safety and adverse effects	No death or serious AE reported.																					
Does the study answer the question?	NO serious AE or laboratory changes reported. The present study established the risk/benefit profile of treatment of TPM in refractory epilepsy																					
Effect due to factor in study?	Uncertain. Method of randomisation allocation, concealment and blinding not described. Sample size may not be large enough to detect significant differences in some effects.																					
Consistency of results with other studies?	Baseline characteristics not reported for each group Median monthly baseline seizure rate higher in treatment group.																					

Directly applicable to guideline population? unsure

Internal Validity

Beydoun A;Uthman BM;Kugler AR;Greiner MJ;Knapp LE;Garofalo EA;Study Group;

Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy

Ref ID 4277

2005

Study Type Randomised Controlled Trial **Funding** Supported by Pfizer inc.

Number of participant N=313 randomised. Placebo n=98; BID n=103 and TID n=111.

Inclusion/Exclusion Criteria Inclusion: patients had to experience a minimum of six partial-onset seizures during a prospective 8 week baseline period, with no 28-day seizure-free period, while maintained on stable doses of one to three AEDs. Patients also had to have failed two or more AEDS at maximally tolerated doses.
Exclusions: No pregnant or lactating women and women were to be using a reliable method of contraception. Patients with a treatable cause of their seizures were excluded, as were those with absence seizures, Lennox-Gastaut syndrome, or a progressive neurologic, psychiatric or systemic disorder. Patients with clinically relevant disease were excluded. Patients with a history of status epilepticus, illicit drug use or alcohol abuse within the previous year, progressive abnormalities on neuroimaging, or noteworthy abnormalities on a chest radiograph or those treated with any investigational drug within 30 days prior to screening or concomitantly treated with Gabapentin were excluded.

Patient Characteristics All patients had medically refractory epilepsy, with a mean baseline frequency per 28 days ranging from 21.3 to 25.1 across the 3 treatment groups. The mean patient age at diagnosis was 16.6 years for the placebo, 13.0 years for the BID and 11.9 years for the TID treatment groups.

Recruitment Not reported

Setting Not clear

Interventions/ Test/ Factor being investigated Pregabalin versus placebo

Comparisons Pregabalin 600mg/day BID (twice a day), Pregabalin 600mg/day TID (three times a day) versus placebo

Length of Study/ Follow-up 12 weeks treatment period.

Outcome measures studied Reduction in seizure frequency during the double-blind period, responder rate (≥ 50 reduction in seizures) and median percentage change in seizure frequency compared to baseline.

Results Both TID and BID were more efficacious than placebo in reducing the frequency of partial-onset seizures ($p \leq 0.0001$). The percentage reduction in seizure frequency from baseline was 53.0% for the TID and 44.3% for the BID groups compared to an increase of 1.2% for placebo.
Responder rates between pregabalin and placebo (9%) for both TID (49%. $p \leq 0.001$) and BID (43%; $p \leq 0.001$) groups. BID and TID were not significantly different from one another.
The median percentage seizure frequency reductions were greater for patients receiving pregabalin (48.1% for TID and 35.6% for BID) than those to placebo (0.8%).

BID (n=%) (D= discontinuation): Dizziness n=43 (D=7), somnolence n=31 (D=6), ataxia n=17(D=3), weight gain n=21(D=1), amplyopia n=10 (D=2), asthenia n=14 (D=2), Diplopia n=10 (D=3), and thinking abnormal n=9 (D=2).

TID: Dizziness n=42 (D=7), somnolence n=26 (D=4), ataxia n=30 (D=7), amblyopia n=19 (D=1), weight gain n=17(D=0) and asthenia n=13 (D=1), , diplopia n=15 (D=1)

and thinking abnormal n=12 (D=3).

Placebo: dizziness n=12 and somnolence n=12, ataxia n=6 (D=0), amblyopia n=4 (D=0), weight gain n=2 (D=0) and asthenia n=5 (D=1), diplopia n=4 (D=1) and thinking abnormal n=1 (D=0).

Safety and adverse effects

19% for the pregabalin TID and 26% from the BID group due to AEs.

Does the study answer the question?

Pregabalin is efficacious as adjunctive therapy in the treatment of patients with partial seizures.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Directly applicable to guideline population?

Relevant population.

Internal Validity

Randomisation details not given.

Bill PA;Vigoni U;Pohlmann H;Guerreiro CA;Kochen S;Saffer D;Moore A;

A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy

Ref ID 4726

1997

Study Type	Randomised Controlled Trial	Funding	International Adult Oxcarbazepine/Phenytoin Trial Group and Novartis Pharma
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Number of participant 287 total: 143 to OXC and 144 to PHT

Inclusion/Exclusion Criteria Inclusion: Ages 16-65 years with newly diagnosed epilepsy with two seizures separated by at least 48 hours within 6 months before trial
Exclusion: No AED drug except for emergency treatment; Pregnancy risk, status, psychiatric illness or mental retardation, progressive neurological disorder, alcoholism, drug abuse or significant organic disease.

Patient Characteristics	OXC (n=143)	PHT (n=144)
Age (mean; range)	27.1(16-63)yrs	26.6(15-91)yrs
Gender (M/F)	82/61	92/52
Race (Cauc/B/Other)	72/22/49	68/23/53
Body wt.	63.6 (41-104)kg	64.9 (43-101)kg

Recruitment Unknown

Setting Argentina, Brazil, Mexico and South Africa

Interventions/ Test/ Factor being investigated Use of oxcarbazepine vs. phenytoin as monotherapy in newly diagnosed epilepsy patients

Comparisons oxcarbazepine vs. phenytoin

Length of Study/ Follow-up A flexible titration period of 8 weeks followed by 48 weeks of maintenance treatment

Outcome measures studied The primary efficacy variable was the proportion of seizure free patients who had at least one seizure assessment during the maintenance period.
Secondary outcomes: Treatment group differences in time and rate of premature discontinuation

Results	OXC (n=118)	PHT (n=119)	P-value
Seizure frequency per week: Mean/median	0.08/0	0.06/0	p=0.72
Total number of seizures mean/median	3.57/0	2.13/0	
Number of patients with:			
No seizures	70	69	
1 seizure	17	20	
2-15 seizures	26	26	
16-50 seizures	3	4	
More than 50 seizures	2	0	

Five patients receiving OXC and 16 patients receiving PHT treatment were withdrawn due to adverse experiences. There was a statistically significant difference between groups in favour of the OXC treatment (p=0.02). There was no significant treatment difference due to premature discontinuations (p=0.63). Physicians and patients' overall assessment of tolerability on a 4 point scale, favoured the OXC treatment (p=0.032 for physicians and p=0.026 for patients).

Safety and adverse effects 5 patients in the OXC group and 16 in the PHT group discontinued for tolerability reasons. The most common side effects were somnolence, headache, dizziness, nausea, rash.

Does the study answer the question? This trial provides support for the efficacy and safety of OXC as first line treatment in adults with PS

Effect due to factor in study? Yes

Consistency of results with other studies?

Directly applicable to guideline population? See GRADE

Internal Validity

Binnie CD;Debets RM;Engelsman M;Meijer JW;Meinardi H;Overweg J;Peck AW;Van WA;Yuen WC;

Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy

Ref ID 4756

1989

Study Type Randomised Controlled Trial **Funding** Not reported. However, one of the authors was from the Wellcome Research Laboratories, Beckenham, UK.

Number of participant 34 patients were recruited to the randomised within-patient, crossover designed study.

Inclusion/Exclusion Criteria Inclusion criteria: age 16 to 65 years, confident diagnosis of epilepsy, partial seizures, seizure frequency at least 4 per month, seizures resistant to drugs of first choice, co-medication unchanged for previous 3 months and unlikely to be changed during study.
Exclusion criteria: severe psychiatric, mental, neurological or haematological disease; status epilepticus in the preceding 6 months; use of investigative AEDs; pregnancy.

Patient Characteristics Summary statistics n=30

Age (yrs)	
Range	16-51
Mean (+/- SD)	37.1(10.26)
Males/Females	22/8
Height (cm)	
Mean (+/-SD)	175(8)

Weight (kg)	
Mean (+/-SD)	70.7 (12.1)
Age of onset epilepsy	
Mean (+/- SD)	14.3(10.7)
Duration of seizures	
Mean (+/- SD)	22.8(11.0)

No. of uncontrolled seizure types

1	9
2	16
3	4
4	1

Recruitment	Epilepsy out-patient clinics x 3 in Netherlands.
Setting	Institute voor Epilepsiebestrijding, Netherlands.
Interventions/ Test/ Factor being investigated	Lamotrigine (vs. placebo) adjunctive to currently used AEDs. Target dose 200mg, 100mg or 75 mg based on currently used AEDs. For the first week half the target dose was given. Dose doubled at end of first week. Reduced for side effects. 12 weeks treatment with lamotrigine and 12 weeks with placebo.
Comparisons	Lamotrigine vs. placebo adjunctive to currently used AEDs.
Length of Study/ Follow-up	Total of 44 weeks. Baseline = 8 weeks. Treatment period 1 = 12 weeks. Washout period 1 = 6 weeks. Treatment period 2 = 12 weeks. Washout period 2 = 6 weeks.
Outcome measures studied	Primary outcome was seizure frequency defined as the total count of all seizures. No secondary outcomes defined although adverse events were reported.
Results	<p>The journal article reports that there was a significant treatment effect in favour of lamotrigine ($P > 0.02$). The median percentage reduction in seizure count attributable to lamotrigine was 17% with a confidence interval of 0-30%. 19 (63%) patients had fewer seizures on lamotrigine compared to 9 (30%) who had fewer seizures on placebo and 2(7%) who had same number of seizures on each.</p> <p>No other summary statistics are reported. One table presents a seizure count for each of the 30 patients when they have been treated with lamotrigine and placebo. Summing these from the table the total no. of seizures when on lamotrigine for all 30 patients is 1242 compared to 1647 on placebo (One patient had 444 seizures on lamotrigine and 697 on placebo).</p> <p>A total of 39 adverse experiences were reported in 29 patients. Nine of these were classified as serious. Only 2 of these occurred on lamotrigine. One was a maculo-papular rash appeared to be drug related and resolved after withdrawal. The other was depression. The latter had been previously reported by the same patient when on placebo.</p>
Safety and adverse effects	There were no differences in adverse experiences between lamotrigine and placebo periods. The plasma concentrations of concomitantly administered AEDs were not affected by lamotrigine treatment.
Does the study answer the question?	To some extent yes. The authors conclude that lamotrigine produced a clinically modest but statistically significant reduction in seizure counts in patients with poorly controlled partial seizures. However, no sample size calculation was performed and the power of the study to detect a significant difference is unknown. The study did however employ a complex procedure of targeting plasma lamotrigine levels by means of an unblinded observer. Its use avoided the problems of under dosing or intoxication which would otherwise probably have resulted from the effects of co-medication on lamotrigine metabolism. It therefore enabled subsequent studies to employ a simpler design with lamotrigine dosing determined by co-medication.
Effect due to factor in study?	No. The authors conclude that lamotrigine produced a clinically modest but statistically significant reduction in seizure counts in patients with poorly controlled partial seizures. However, no sample size calculation was performed and the power of the study to detect a significant difference is unknown.

Consistency of results with other studies?

Directly applicable to guideline population?

The patient population is directly comparable with the that of this guideline since patients in this study were required to have seizures which must include partial seizures together possibly with other types. Indirectness (?) (see comments on validity)

Internal Validity

Brodie MJ;

Zonisamide clinical trials: European experience

Ref ID 2599

2004

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant N=144 at 10 sites.
ZNS n=73; PCB n=71.

Inclusion/Exclusion Criteria
Inclusion criteria:
18 to 59 years of age;
history of refractory partial seizures (at least 4 seizures per month in previous 4 months);
treated with one or two AEDs but no more than 2 of the following: phenytoin, carbamazepine, sodium valproate, phenobarbital, or primidone;
capable of counting no. Of seizures experienced;
Exclusion criteria:
progressive central nervous system disease;
more than

Patient Characteristics
ZNS vs PCB:
Male 43/73 (59%) vs 42/71 (59%)
Female 30/73 (41%) vs 29/71 (41%)
Race:
Caucasian 73/73 (100%) vs 71/71 (100%)
Age (years, mean): 35 (s.d 11) vs 34 (s.d 12);
Monthly seizures, median (range):
All partial: 11.3 (2.5-763) vs 11 (2.8 -435)
Complex partial: 10 (2.5-763) vs 10 (2.8-217)
Other (including generalised): 0 (0-5) vs 0 (0-4.5)

Recruitment Not stated.

Setting 10 sites in UK.

Interventions/ Test/ Factor being investigated Zonisamide versus placebo.

Comparisons Treatment versus placebo.

Length of Study/ Follow-up Open label extension study to look at long-term safety and efficacy of zonisamide after the double-blind study.

Outcome measures studied Median change from baseline in seizure frequency; % responders(over 50% reduction in seizure frequency) for 8 week treatment period;

Results
ZNS:
Responders: n=17
Nonresponders n=52.

ZNS vs PCB
Withdrawal due to adverse events: 5 vs 0.
Adverse events:
fatigue: 17/73 vs 8/71

dizziness 12/73 vs 3/71
 somnolence 11/73 vs 6/71;
 anorexia 9/73 vs 1/71;
 ataxia 9/73 vs 0/71;
 Trouble concentrating 9/73 vs 1/71

Safety and adverse effects

2 patients experienced serious or potentially serious Aes during this study including carcinoma and renal calculi and a third patient died. The cause of death was stated as not being related to the study drug.

Does the study answer the question?

This does not give the placebo results for the % responders but does for those in the zonisamide trial. The adverse events are reported adequately. The results for 9 of the centres is reported by Schmidt et al (1993).

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Brodie MJ;Duncan R;Vespignani H;Solyom A;Bitensky V;Lucas C;

Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures

Ref ID 4286

2005

Study Type Randomised Controlled Trial **Funding** Elan Pharmaceuticals.

Number of participant n=351 randomized (n=120 placebo, n=57 in ZNS 100mg/day group, n=56 in ZNS 300mg/day group and n=118 in the ZNS 500mg/day).

Inclusion/Exclusion Criteria Inclusion criteria: at least 12 years old with partial seizures with or without secondary generalization unsatisfactorily controlled despite a stable regimen of one to three AEDs.

Exclusion: history of nonepileptic seizures, alcoholism, drug abuse, or significant drug sensitivity were excluded, as were those with progressive neurologic disease.

Patient Characteristics

Patient demographics and baseline characteristics (safety population)				
	Placebo	ZNS 100 mg/day	ZNS 300 mg/day	ZNS 500
mg/day	(n = 120)	(n = 56)	(n = 55)	(n = 118)
Gender: no (%)				
Male	68 (56.7)	30 (53.6)	27 (49.1)	53
(44.9)				
Age at screening (yr)				
Mean	36.5	36.1	32.9	36.1
Range	12-64	12-65	12-73	
12-77				
Time since epilepsy onset (mo)				
Median	254.0	279.5	188.0	
227.0				
Range	22-586	5-672	7-670	
11-776				
Seizure start date: median (range) (yr)				
CP seizure	20.0 (0-48)	16.0 (0-56)	14.0 (3-55)	16.0
(1-64)				
SP+CP seizures	19.5 (0-48)	16.0 (0-56)	13.5 (0-55)	16.0
(1-64)				
All seizures	21.0 (1-48)	22.5 (0-56)	14.0 (0-55)	17.0
(1-64)				

Historic SP frequency/28 days				
Mean (SD)	10.9 (44.5)	9.2 (24.7)	12.5 (32.0)	9.5 (33.7)
Median (range)	0.0 (0–459)	0.0 (0–139)	3.0 (0–212)	0.0 (0–318)
Historic CP frequency/28 days				
Mean (SD)	12.5 (22.0)	11.8 (2.1)	9.6 (13.0)	12.7 (20.3)
Median (range)	5.7 (0–153)	6.3 (0–121)	2.9 (0–56)	6.2 (0–119)
Historic SG frequency/28 days				
Mean (SD)	2.7 (9.5)	2.7 (5.5)	2.4 (6.5)	2.9 (8.6)
Median (range)	0.0 (0–81)	0.0 (0–27)	0.0 (0–45)	0.0 (0–64)
Concomitant AEDs: N (%)				
0	0	0	0	
1	22 (18.3)	17 (30.4)	15 (27.3)	32 (27.1)
2	68 (56.7)	21 (37.5)	27 (49.1)	50 (42.4)
3	26 (21.7)	17 (30.4)	13 (23.6)	34 (28.8)
>3a	4 (3.3)	1 (1.8)	0	2 (1.7)

AEDs, antiepileptic drugs; CP, complex partial; SG, secondarily generalized; SP, simple partial; SD, standard deviation; ZNS, zonisamide.

Although seven patients were reported as taking more than three AEDs, these were not considered protocol violators, as the fourth medication was used only as rescue therapy.

Recruitment

Not reported.

Setting

54 centres in Europe (n=49) and S.Africa (n=5)

Interventions/ Test/ Factor being investigated

Zonisamide (ZNS) in three doses: 100mg, 300mg and 500mg per day as adjunctive therapy with currently used AEDs.

Comparisons

The comparison is between ZNS in three different doses (100mg, 300mg and 500mg per day) and placebo as adjunctive therapy.

Length of Study/ Follow-up

36 weeks: 12 week baseline, 6 week titration and 18 week fixed dose.

Outcome measures studied

Primary outcome: a) median % change in frequency of complex partial seizures and b) response rate. Secondary: % change in all partial seizures and all seizures and corresponding response rates.

Results

Primary outcome

Primary efficacy-analysis population (all patients in the ITT population with partial seizure frequency data collected during the fixed dose phase)

Median reduction in complex partial (CP) seizures

ZNS, 500 mg/day, produced a significantly greater median reduction in CP seizure frequency from baseline than did placebo [51.2% (n = 86 subjects included in the analysis) vs. 16.3% (n = 89)]. The difference between the two groups was 31.2% (95% CI, 15.7–44.6; p < 0.0001).

Response rates

The proportion of responders for CP seizures was significantly higher (p < 0.001) in the ZNS, 500 mg/day, group compared with placebo (52.3% vs. 21.3%). Odds ratio (95% CI) for the ZNS, 500 mg/day, group relative to placebo was 4.07 (1.94–8.56).

Secondary outcomes

Median reduction in simple partial (SP) and complex partial (CP) seizures

For all seizures and for SP+CP seizures, median baseline frequencies were broadly similar across treatment groups. The median percentage reduction in all seizure frequency from baseline was significantly greater than that with placebo [18.1% (n=112)] for both ZNS, 500 mg/day [51.3% (n = 101); p < 0.0001] and 300 mg/day [41.8% (n = 45); p = 0.0005]. The median reduction in SP+CP seizure frequency from baseline also was significantly greater for both ZNS, 500 mg/day [50.6% (n = 99); p < 0.0001], and 300 mg/day [46.4% (n = 42); p = 0.0007] than for placebo [19.4% (n = 109)]. The median reduction in the frequency of all seizures and SP+CP seizures with ZNS, 100 mg/day, was not statistically different from placebo.

Response rates

For all seizures, the proportion of responders was higher in each ZNS group (500 mg, 52.5%; 300 mg, 42.2%; 100 mg, 29.6%) than for placebo (17.9%). The treatment difference was significant (p < 0.001) for the ZNS, 500 mg/day, group compared with placebo; the odds ratio (95% CI) for the ZNS, 500 mg/day group relative to placebo was 4.63 (2.28–9.39). For SP+CP seizures, the proportion of responders also was higher in each

ZNS group (500 mg, 50.5%; 300 mg, 42.9%; 100 mg, 28.8%) than in the placebo group (20.2%). Again, the treatment difference was significant (p < 0.001) for the ZNS, 500 mg/day, group compared with placebo; the odds ratio (95% CI) for the ZNS, 500 mg/day, group relative to placebo was 4.25 (2.01–8.95).

Adverse events

Adverse events (%) reported by ≥10% of patients during the titration phase and during the fixed-dose assessment phase (safety population)

	Placebo	ZNS 100 mg/day	ZNS 300 mg/day	ZNS 500
mg/day	(n = 120)	(n = 56)	(n = 55)	(n = 118)
Titration phase				
Any AE	60 (50.0)	32 (57.1)	34 (61.8)	73 (61.9)
Dizziness	3 (2.5)	1 (1.8)	4 (7.3)	14 (11.9)
Headache	8 (6.7)	4 (7.1)	7 (12.7)	8 (6.8)
Nausea	7 (5.8)	2 (3.6)	6 (10.9)	9 (7.6)
Somnolence (14.4)	3 (2.5)	3 (5.4)	2 (3.6)	17
Fixed-dose assessment phase				
Any AE	58 (48.3)	29 (51.8)	23 (41.8)	59 (50.0)
Headache	15 (12.5)	6 (10.7)	6 (10.9)	5 (4.2)
Pharyngitis	3 (2.5)	6 (10.7)	1 (1.8)	3 (2.5)

The incidence of withdrawals due to AEs was higher for the 300-mg/day and 500-mg/day groups (18.2% and 27.1%, respectively) than for the 100-mg/day and placebo groups (1.8% and 10.0%, respectively). The higher incidence of AEs leading to withdrawal in the 500-mg/day group compared with other groups was mainly because of more events of dizziness, difficulty concentrating, nausea, and somnolence during the titration phase.

Safety and adverse effects

There was a higher incidence of AEs leading to withdrawal in the 500-mg/day group compared with other groups. This was mainly because of more events of dizziness, difficulty concentrating, nausea, and somnolence during the titration phase.

Does the study answer the question?

Yes. This is a well conducted study and it concludes that zonisamide provides dose-dependent, effective and generally well-tolerated adjunctive therapy in patients with partial seizures.

Effect due to factor in study?

Yes. The study is sufficiently powered to detect significant differences in seizure frequency between treatment groups and placebo.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in the study had a diagnosis of refractory partial seizures.

Internal Validity

Study Type	Randomised Controlled Trial	Funding	UCB SA
Number of participant	n=285 in the LEV arm and n=291 in the CBZ-CR group.		
Inclusion/Exclusion Criteria	<p>Inclusion criteria: aged >=16 years, newly diagnosed partial or generalized seizures with clear focal origin or tonic-clonic seizures without clear focal origin if >= 2 seizures separated by >=48 hrs during the past year and >=1 seizure during the previous 3 months.</p> <p>Exclusion criteria: pseudo seizures, seizures in clusters, and clinical or electroencephalographic findings suggestive of idiopathic generalized epilepsy.</p>		
Patient Characteristics	CBZ-CR	LEV	
	N=291	N=285	
	Age, years Mean (SD)	39.8 (16.6)	
	39.0 (15.8)		
	Sex		
	Male n (%)	146 (51.2)	171
	(58.8)		
	Female n (%)	139 (48.8)	
	120 (41.2)		
	Ethnicity		
	White n (%)	262 (91.9)	
	268 (92.1)		
	Black n (%)	5 (1.8)	10
	(3.4)		
	Asian n (%)	1 (0.4)	4
	(1.4)		
	Other n (%)	17 (6.0)	9
	(3.1)		
	Height, cm Mean (SD)	170.0 (9.7)	
	171.1 (9.7)		
	Weight, kg Mean (SD)	73.7 (16.8)	
	73.6 (15.2)		
	BMI, kg/m ² Mean (SD)	25.5 (5.2)	
	25.1 (4.6)		
	No. of seizures in past year Median	4.0	
	3.0		
	No. of seizures in past 3 months Median	2.0	
	2.0		
	Epilepsy duration, years Median	0.8	
	0.8		
	Age at onset, years Median	34.7	
	31.9		
	Time since last seizure, days Median	9.0	
	11.0		
Recruitment	Unknown.		
Setting	85 centres in Europe and in South Africa.		
Interventions/ Test/ Factor being investigated	Levetiracetam (LEV) 1000mg to 3000mg/day vs. Carbamazepine (CBZ-CR) 400mg to 1200mg/day		
Comparisons	Comparison is between LEV and CBZ-CR in this non-inferiority trial, which aims to show that FEV has at least a similar benefit-risk balance to CBZ-CR.		
Length of Study/ Follow-up	For the purposes of the primary outcome follow-up was 30 weeks (1 week screening, 2 weeks titration, 1 week stabilization and 26 weeks evaluation period). Patients who remained seizure free for 6 months entered an additional 26-week maintenance		

period.

Outcome measures studied

Primary outcome was proportion of study subjects in each arm who were seizure-free at 6 month, using per protocol (PP) population. Secondary outcome was proportion of patients seizure free at 6 months using ITT population. Also, adverse events.

Results

Primary outcome: In the PP population 73.0% (173/237) of patients in the LEV group and 72.8% (171/235) in the CBZ-CR group were seizure free for ≥ 6 months. Adjusted absolute difference (95% two-sided CI) = 0.2% (95% CI -7.8% to 8.2%)
Secondary outcome: Seizure free at 6 months in ITT population LEV=66.7% and CBZ-CR 66.7%. No significant difference between the two groups in proportion seizure free at 12 months. Patients reporting ≥ 3 seizures in the 3 months before study start were less likely to achieve seizure free at 6 months than those experiencing ≤ 2 seizures prior to study. (LEV 63.8% and CBZ-CR 62.9%) vs. (LEV 81.8% and CBZ-CR 79.7%).

Adverse events: A similar proportion of patients in the LEV (79.6%) and CBZ-CR groups (80.8%) experienced at least one AE during the treatment period with most events being of mild or moderate intensity. Depression and insomnia were more common in the LEV group and back pain more common in the CBZ-CR group ($p < 0.05$). 14.4% discontinued in the LEV group because of AEs compared to 19.2% in the CBZ-CR group.

Safety and adverse effects

Significantly more patients in the LEV group experienced depression (6.3% vs. 2.1%) and insomnia (6.0% vs. 2.4%) than in the CBZ-CR group.

Does the study answer the question?

Yes. Levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy.

Effect due to factor in study?

Yes. This study was powered to detect no inferiority between populations using two proportions.

Consistency of results with other studies?

Directly applicable to guideline population?

This study includes a population of newly diagnosed epilepsy patients.

Internal Validity

Callaghan N;Kenny RA;O'Neill B;Crowley M;Goggin T;

A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy

Ref ID 4629

1985

Study Type

Randomised Controlled Trial

Funding

Supported by grants from Labaz, Geigy and Warner-Lambert.

Number of participant

181 recruited. 102 had generalised seizures, 79 had partial seizures. Generalised tonic clonic seizures: 28 in the carbamazepine group; 37 in the phenytoin group; 37 in the valproate group.

Inclusion/Exclusion Criteria

Inclusion criteria:
Previously untreated;
Recently diagnosed;
General or partial seizures;
Minimum of 2 seizures over six months period before referral for assessment;

Patient Characteristics

Patients with generalised tonic clonic seizures (without focal features):

Carbamazepine vs phenytoin vs valproate:
Sex: male: 13 vs 21 vs 20; female: 15 vs 16 vs 17;
Age (year) range (mean): 4-72 (26) vs 7-69 (26) vs 5-71 (23);
Duration of seizures prior to treatment months range (median): 0-132 (18) vs 3-156 (9) vs 0-120 (9);

Duration of treatment months range (median): 3-44 (15) vs 3-42 (18) vs 3-44 (24);
Total no of seizures since the onset of and range (median):
2-1277 (4) vs 2-900 vs 2-720 (3).

Patients with partial seizures with or without secondary generalised attacks:

Carbamazepine vs phenytoin vs valproate:
Sex: male: 15 vs 12 vs 14; female: 16 vs 9 vs 13;
Age (yr) range (mean): 8-75 (28) vs 7-64 vs 6-68 (25);
Duration prior to treatment months range (median): 0-180 (12) vs 6-168 (24) vs 3-36
(12);
Duration of treatment months range (median): 3-42 (14) vs 3-47 (24) vs 3-48 (24);
Total no. of seizures since the onset of attacks range (median):
2-1095 (6) vs 3-300 (6) vs 2-732 (26).

Recruitment

Not reported.

Setting

Cork, Ireland.

**Interventions/ Test/
Factor being
investigated**

Assessments at seizure clinic of response to treatment and side effects documented
and sample of blood taken to estimate serum AED levels.

The participants were instructed to take the drug twice daily. If they did not respond
to the first preference of drug the dose of that drug was decreased by 200mg
decrements of sodium valproate and carbamazepine and by 100mg phenytoin at two
weekly intervals and then second preference drug was allocated from randomisation
list.

CBZ was prescribed in a dosage of 600mg daily for adults and 5-10mg/kg body
weight for children; phenytoin in a dose of 300mg daily for adults and 5-10mg/kg
body weight for children; sodium valproate in a dose of 600mg daily for adults and 5-
10mg/kg body weight for children.

Comparisons

Carbamazepine versus phenytoin vs sodium valproate.

**Length of Study/
Follow-up**

Patients are seen at one month after prescription then intervals of one to three
months, depending on how they responded to treatment.

Follow up ranged from 3 to 9 weeks.

**Outcome measures
studied**

Response to treatment: excellent control - complete freedom from seizures; good
control - greater than 50% reduction in seizure frequency; poor control no response
or less than 50% reduction in seizure frequency.

Results

Response in patients with generalised seizures:

Phenytoin vs carbamazepine vs valproate: Control (number (%)):

Excellent control (complete freedom from seizures): 27 (73%) vs 11 (39%) vs 22
(59%). Total 60 (59%);

Good control (greater than 50% reduction in seizure frequency): 3 (8%) vs 10 (36%)
vs 7 (19%). Total 20 (20%).

Poor control (no response or less than 50% reduction in seizure frequency): 7 (19%)
vs 7 (25%) vs 8 (22%). Total 22 (21%).

Phenytoin vs carbamazepine - excellent control, $p < 0.01$.

Overall patients with primary generalised attacks: 71% achieved excellent or good
control.

Overall response in patients with partial seizures with or without secondary
generalised attacks:

Phenytoin vs carbamazepine vs valproate: Control (number (%)):

Excellent control: 12 (57.1%) vs 11 (33.5%) vs 12 (44.4%). Total 35 (44.3%).

Good control: 4 (19%) vs 12 (38.7%) vs 9 (33.3%). Total 25 (31.6%).

Poor control: 5 (23.8%) vs 8 (25.8%) vs 6 (22.2%). Total 19 (24%).

[partial also subdivided for partial complex and simple partial].

When compared response in patients with generalised seizures and those with

partial seizures, with or without secondary generalised attacks, the overall response was better in patients with generalised seizures ($p < 0.05$).

Withdrawal of treatment: 26 patients, 8 taking carbamazepine, 7 valproate and 11 phenytoin. 4 relapsed, 1 taking carbamazepine, 2 taking phenytoin and one taking sodium valproate. Not mentioned whether these were generalised or partial seizure types.

Safety and adverse effects

12 patients dropped out. 10 with generalised seizures and 2 with partial seizures.

Of these 5 with generalised took phenytoin, 3 carbamazepine and 2 sodium valproate.

One with partial seizures was taking phenytoin, one carbamazepine.

Does the study answer the question?

Yes.

Authors conclusion was that sodium valproate, carbamazepine and phenytoin are effective in the control of generalised and partial seizures, and that all three drugs can be prescribed as anti-convulsant of first choice. Irrespective of the drug prescribed, partial seizures were less responsive to treatment.

Effect due to factor in study?

Unsure as no blinding and no power calculation given.

Consistency of results with other studies?

Directly applicable to guideline population?

Yes.

Internal Validity

Cereghino JJ;Biton V;bou-Khalil B;Dreifuss F;Gauer LJ;Leppik I;

Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial

Ref ID 4740

2000

Study Type

Randomised Controlled Trial

Funding

UCB Pharma.

Number of participant

95 in the placebo group, 98 in the levetiracetam 1000mg/day group and 101 in the levetiracetam 3000mg/day group.

Inclusion/Exclusion Criteria

Inclusion criteria: age 16 to 70, uncontrolled partial seizures for ≥ 2 years, min of 12 seizures in last 12 wks, min of 2 per 4 wks in baseline period, taking ≥ 2 AEDs. Exclusion criteria: pregnancy, co morbidities, use of investigational AED in last 4 wks, history of drug abuse, or renal or hepatic impairment.

Patient Characteristics

	Placebo	Lev 1000mg/d	3000mg/d
n	95	98	101
Male/female	50/45	62/36	66/35
Race			
White	81	82	88
Black	7	10	9
Other	7	6	4
Age mean (SD)	38(11)	38(11)	38(11)
Weight kg mean (SD)	77.3(17.9)	79.4(19.1)	80.3(16.7)
Median weekly partial seizure frequency	1.77	2.53	2.08
Concomitant AEDs			
1	25	35	36
2	67	57	59
>2	3	6	6

Recruitment	Unknown.		
Setting	41 study sites in North America		
Interventions/ Test/ Factor being investigated	Levetiracetam 1000mg and 3000mg per day compared to placebo.		
Comparisons	Comparison is between levetiracetam (1000mg and 3000 per day doses) and placebo as adjunctive therapy with currently used AEDs.		
Length of Study/ Follow-up	38 weeks: 12-week, single-blind placebo baseline period, a 4-week double-blind drug titration period; a 14 week double-blind treatment period; and an 8 week double-blind study medication withdrawal period.		
Outcome measures studied	Primary efficacy variable was the mean number of partial seizures per week over the entire 14-week evaluation period. Secondary outcomes were median percent reduction compared to baseline, responder rate, and number of seizure-free patients.		
Results	Primary outcome (14 wk treatment period)		
	Placebo	Lev 1000mg/d	3000mg/d
	Least squares mean (LSM) number of seizures per wk (SE).		
	1.366(-0.053)	1.131 (0.050)	1.041(0.049)
	Secondary outcomes		
	Median % reduction vs. placebo	20.9*	27.7*
	Median % reduction vs baseline	6.8	32.5*
	50% responder rate	10.0	33.0*
	*p<0.001		
	Sub group analysis		
	Median percent reduction in seizure frequency from baseline by seizure subtype		
	Seizure 1a (p value)	34.4	54.7(NS)
	44.8(NS)		
	Seizure 1b (p value)	6.4	34.2(0.003)
	45.6(<0.001)		
	Seizure 1c (p value)	24.4	84.7(0.018)
			64.5(0.015)
	Adverse events		
	At least one, % of pts	88.4	88.8
			89.1
	Very few AEs were severe: (<=4%). 5/95 (5.3%) of placebo group withdrew for AE reasons; 6/98 in the levetiracetam 1000mg/d group; 7/101 6.9% in the levetiracetam 3000mg/d group. Treatment -emergent AE s (>=10%) with incidences higher than placebo were infection, headache, somnolence, dizziness, asthenia, rhinitis, and flu syndrome.		
Safety and adverse effects	Number of patients experiencing AEs were high but were similar in placebo and treatment groups. Very few AEs were severe: (<=4%).		
Does the study answer the question?	Yes. Adjunctive therapy with levetiracetam appears to be effective and well tolerated in controlling partial seizures.		
Effect due to factor in study?	Yes. This was a well conducted study with a low risk of bias. The sample size was calculated to ensure the study was powered to detect a difference between treatment groups and placebo.		
Consistency of results with other studies?			

Directly applicable to guideline population? The study population is similar to the population of interest in the guideline. Inclusion criteria ensured that all of those enrolled had partial seizures.

Internal Validity

Chadwick D;

Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group

Ref ID 4718

1999

Study Type Randomised Controlled Trial **Funding** Industry: Hoechst Marion Roussel (HMR)

Number of participant Carbamazepine , n=230. Vigabatrin, n=229. Total =459 enrolled.

Inclusion/Exclusion Criteria Patients with newly diagnosed epilepsy, ages 12-65 and had at least 2 seizures in the previous 12 months (simple or complex partial seizures with or without secondary generalisation).

The occurrence of generalised seizures types qas an exclusion criterion.

Patient Characteristics Male: 122 (54%) in carbamazepine and 117 (53%) in Vigabatrin. Mean age (sd): 36(16) in carbamazepine and 35(15) in Vigabatrin

Recruitment Recruited from 44 centres after approval of local ethics committee - not stated how recruitment was done.

Setting 44 multinational centres - recruitment: 1993-1996

Interventions/ Test/ Factor being investigated Vigabatrin vs Carbamazepine (mono-therapies). All were divided into twice daily dosing.

Comparisons Comparison were made between active treatments. The control - carbamazepine was the accepted first line therapy for newly diagnosed individuals with partial epilepsy in Europe.

Length of Study/ Follow-up 52 weeks. After that, patients on Vigabatrin continued on an open follow up study.

Outcome measures studied Primary: time to treatment failure (withdrawal due to lack of efficacy or adverse events). Secondary: efficacy (time to 6 month-remission and time to 1st seizure after initial dose stabilisation); adverse events (incidence & severity)

Results Time to treatment failure (withdrawal): ITT analysis hazard ratio: 0.83, 95% CI 0.57 to 1.20, hazard ratio adjusted for covariates (centre, reciprocal of seizure frequency at baseline, duration of epilepsy, age, number of secondary generalised seizures): 0.75, 95%CI 0.52 to 1.10. Per protocol analysis (n=400),adjusted hazard ratio: 0.74 95% CI 0.50 to 1.12.

Time to withdrawal due to lack of efficacy: Adjusted hazard ratio 2.37 95% CI 1.09 to 5.18, p=0.0298 (23 in Vigabatrin and 9 in carbamazepine)

Number of patients with 6 month remission by end of study: 107/220 in Vigabatrin, 116/226 in carbamazepine. Hazard ratio (unadjusted): 1.20 95% CI 0.93 to 1.57, adjusted hazard ratio: 1.15(0.88 to 1.55)

Time to first seizure after dose stabilisation: adjusted and unadjusted hazard ratio: 1.58 95% CI 1.09 to 5.18, p=0.0298

Time to withdrawal due to adverse events: adjusted hazard ratio 0.63 95%CI 0.43 to 0.94, unadjusted hazard ratio: 0.70 95% CI 0.47 to 1.03

Time to first seizure after randomisation: adjusted and unadjusted hazard ratio: 1.57 95% CI 1.23 to 2.02, p =0.0003.

Number and percentage of patients with adverse events:
 Central nervous system (total): Carbamazepine - 144(63%) Vigabatrin - 141(62%)
 Amnesia : Carbamazepine - 17(7%) Vigabatrin - 16(7%)
 Drowsiness : Carbamazepine - 63 (28%) Vigabatrin - 49(21%)
 Fatigue : Carbamazepine - 50(22%) Vigabatrin - 45(20%)
 Headache : Carbamazepine -48(21%) Vigabatrin - 47(21%)

Psychiatry (total): Carbamazepine - 34 (15%) Vigabatrin - 58(25%) p<0.05
 Agitation : Carbamazepine - 13 (6%) Vigabatrin - 16(7%)
 Depression : Carbamazepine - 7 (3%) Vigabatrin - 15(7%)
 Insomnia : Carbamazepine - 5 (2%) Vigabatrin - 15(7%)
 Other : Carbamazepine - 9 (4%) Vigabatrin - 12(5%)

Skin and appendages (total): Carbamazepine - 52 (23%) Vigabatrin - 31(14%)
 p<0.05
 Rash : Carbamazepine - 22 (10%) Vigabatrin - 7(3%)
 Other : Carbamazepine - 30 (13%) Vigabatrin - 27(12%)

Other events:
 Asthenia : Carbamazepine - 15 (7%) Vigabatrin - 5(2%)
 Weight increase : Carbamazepine - 12 (5%) Vigabatrin - 25(11%) p<0.05
 Other : Carbamazepine - 29 (13%) Vigabatrin - 29(13%)

Safety and adverse effects

195(85%) of patients on carbamazepine and 191(84%) on Vigabatrin had an adverse event. 26(11%) on Vigabatrin and 21(9%) in carbamazepine had serious adverse events. There were three deaths - 1 carbamazepine and 2 Vigabatrin.

No clinically important haematological and biochemical parameters were noted, but there was an increase in alkaline phosphates and decreases in uric acid and bilirubin concentrations and decrease in white blood cell counts in the carbamazepine patients.

Does the study answer the question?

Carbamazepine showed better efficacy (time to 1st seizure after randomisation, and time to 1st seizure after dose stabilisation and withdrawal due to lack of efficacy).

There were significantly more psychiatric and skin or appendages adverse events in the carbamazepine group more patients with weight increase in the Vigabatrin group.

Effect due to factor in study?

Unclear.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Chadwick DW;Anhut H;Greiner MJ;Alexander J;Murray GH;Garofalo EA;Pierce MW;

A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945-77

Ref ID 4767

1998

Study Type Randomised Controlled Trial

Funding Parke Davis

Number of participant 292 patients were randomised: 74 to carbamazepine (CBZ) 600 mg; 72 to Gabapentin (GBP) 300mg; 72 to GBP 900 mg and 74 to GBP 74.

Inclusion/Exclusion Criteria
 Inclusion: newly diagnosed untreated partial epilepsy; at least 12 years old and weighing between 40-110 kg; women of childbearing age using contraception
 Exclusions: idiopathic generalized Epilepsy; hx of status; progressive encephalopathy; medical or psychiatric condition that could affect study outcome

Patient Characteristics	300 (n=72)	900 (n=72)	1800 (n=74)	CBZ 600 (n=72)
Gender				
Men	56%	49%	55%	55%
Women	44%	51%	45%	45%
Age, y				
Mean (SD)	37(17.3)	34(16.0)	37(16.9)	34(16.4)
Duration of epilepsy, m				
Mean (SD)	1.0(2.2)	0.0(1.0)	1.5(4.5)	1.3(2.3)

Recruitment Unknown

Setting Multicentre - Europe, Australia, S. Africa, Canada

Interventions/ Test/ Factor being investigated Gabapentin monotherapy for newly diagnosed partial seizures

Comparisons GBP doses of 300 mg vs. 900 mg and 1800 mg/day vs. CBZ 600 mg/day

Length of Study/ Follow-up 24 week evaluation phase

Outcome measures studied Primary efficacy variable was time to exit event.

Results

	GBP 300 mg/d	GBP 900 mg/d	GBP1800 mg/d	CBZ 600mg/d
	n=72	n=72	n=74	n=74
Completion rate	18(25%)	28(38.9%)	28(37.8%)	27(36.5%)
Exit event rate	45(62.5%)	29(40.3%)	32 (43.2%)	22(29.7%)
AE withdrawal rate	0(0.0%)	3(4.2%)	10(13.5%)	18(24.3%)
Exit +				
AE withdrawal rate	45(62.5%)	32(44.4%)	42(56.8%)	40(54.1%)

Safety and adverse effects No unexpected new adverse events emerged with GBP monotherapy

Does the study answer the question? GBP at 900 or 1800 mg/day is effective and safe as monotherapy for patients with newly diagnosed partial epilepsy.

Effect due to factor in study? Yes

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity Multi centre study

Christe W;Kramer G;Vigoni U;Pohlmann H;Steinhoff BJ;Brodie MJ;Moore A;

A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy

Ref ID 4770

1997

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant 249 in total, 128 in oxcarbazepine, 121 in sodium valproate

Inclusion/Exclusion Criteria Inclusion: aged 15 to 65 years, newly diagnosed epilepsy with PS or GTCS, at least 2 seizures at least 48 hours apart in previous 6 months, no previous AED except for emergency treatment in previous 3 weeks
Exclusion: pregnancy or risk of becoming pregnant, history of status epilepticus,

severe psychiatric illness or severe mental retardation, progressive neurological disorder, alcoholism or drug abuse, significant other organic disease

Patient Characteristics In the oxcarbazepine group the mean age was 32.45 years (range 15 to 65 years), 60 out of 128 were male. The mean weight was 69.9 kg (range 42 to 119 kg). 76 patients had partial seizures with or without secondary generalised seizures and 52 had generalised seizures without partial onset.

In the sodium valporate group the mean age was 32.47 years (range 15 to 64 years), 67 out of 121 were male. The mean weight was 70.2 kg (range 44 to 115 kg). 78 patients had partial seizures with or without secondary generalised seizures and 43 had generalised seizures without partial onset.

Recruitment Between November 1990 and first quarter 1995

Setting europe, brazil, south africa

**Interventions/ Test/
Factor being
investigated** 300mg oxcarbazepine

Comparisons 300 mg sodium valporate

**Length of Study/
Follow-up** No follow up reported

**Outcome measures
studied** Number of patients who were seizure free, side effects, withdrawal

Results The trial was conducted in Belgium, Brazil, France, Germany, Netherlands, South Africa, Spain, UK

The trial was split into two periods, an 8 week titration and 48 week maintenance period. No concomitant AEDs were allowed. During the titration period patients received 300 mg oxcarbazepine or sodium valporate, this was gradually increased depending upon response, there was no fixed titration schedule. After 8 weeks patients were on daily doses of 900 to 2400 mg oxcarbazepine or sodium valporate, this dose was continued for the maintenance period. However this dose could be changed according to response.

214 patients reached the maintenance period, of these 212 had at least 1 seizure assessment during the maintenance period and were therefore included in the results

Number of patients who were seizure free:
In the oxcarbazepine group 60 out of 106 were seizure free compared to 57 out of 106 in the sodium valporate group

In the oxcarbazepine group 46% of patients with partial seizures (with or without secondary generalised seizures) were seizure free compared to 48% of patients with partial seizures (with or without secondary generalised seizures) in the sodium valporate group

In the oxcarbazepine group 72% of patients with generalised seizures (without partial onset) were seizure free compared to 62% of patients with generalised seizures (without partial onset) in the sodium valporate group

Withdrawal:

A total of 52 patients in the oxcarbazepine group withdrew compared to 41 in the sodium valporate group. In the oxcarbazepine group 15 patients withdrew due to adverse events compared to 10 in the sodium valporate group.

In the oxcarbazepine group 6 withdrew due to allergic reaction, 1 due to pregnancy, 1 due to nausea, 1 due to drowsiness, 5 due to other adverse experiences, 14 due to non-compliance, 6 due to unsatisfactory therapeutic effect, 4 due to lost to follow up, 7 due to protocol violation, 3 due to administrative reasons, 2 due to concomitant illness and 1 due to death.

In the sodium valporate group 4 withdrew due to hair loss, 2 due to pregnancy, 2 due to nausea, 5 due to other adverse experiences, 7 due to non-compliance, 6 due to unsatisfactory therapeutic effect, 7 due to lost to follow up, 3 due to protocol violation, 5 due to administrative reasons, 2 due to concomitant illness, and 1 due to abnormal laboratory results.

Side effects:

In the oxcarbazepine group 115 out of 128 had at least 1 adverse event compared to 106 out of 121 in the sodium valporate group

Safety and adverse effects

In the oxcarbazepine group 115 out of 128 had at least 1 adverse event compared to 106 out of 121 in the sodium valporate group. In the oxcarbazepine group 15 patients withdrew due to adverse events compared to 10 in the sodium valporate group.

Does the study answer the question?

There was no significant difference in the number of patients becoming seizure free, withdrew or had at least 1 adverse event between the oxcarbazepine group and the sodium valporate group.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Cramer JA;Arrigo C;Van HG;Gauer LJ;Cereghino JJ;

Effect of levetiracetam on epilepsy-related quality of life. N132 Study Group

Ref ID 4763

2000

Study Type Randomised Controlled Trial

Funding Please see database entry for Cereghino study for details of methods and results of RCT.

Number of participant This publication reports only on the analysis of QoL data from a previously reported RCT (Cereghino et al, 2000, RID= 210, Ref Man ID 4740). Please see database entry for Cereghino study for details of methods and results of RCT.

Inclusion/Exclusion Criteria Please see database entry for Cereghino study for details of methods and results of RCT.

Patient Characteristics Baseline characteristics for patients for whom quality of life data available.

	Placebo	LEV 1000mg	LEV
3000mg			
	(n=81)	(n=80)	(n=85)
Age (mean years)	38.5(11.3)	39.1(11.3)	38.5(10.2)
Gender (% male)	54.3%	61.3%	64.7%
Age at epilepsy onset (mean years)	13.9(11.9)	15.3(12.7)	13.6(10.8)
Duration of epilepsy (mean years)	24.6(12.0)	23.8(12.7)	24.9(12.1)
No. of AEDs (%)			
One	29.6	36.3	38.8
Two	69.2	60.0	60.0
Three or more	1.2	3.7	1.2
Mean no. of partial-onset seizures per week at baseline	5.6(18.79)	7.55(13.99)	5.15(15.58)
Seizure type (%)			
SPS or CPS	64.2	65.0	69.4
SPS or CPS + PSSG	35.8	31.3	29.4
PSSG	0.0	3.7	1.2

Recruitment Please see database entry for Cereghino study for details of methods and results of RCT.

Setting

Interventions/ Test/ Factor being investigated Please see database entry for Cereghino study for details of methods and results of RCT.

Comparisons Please see database entry for Cereghino study for details of methods and results of RCT.

Length of Study/ Follow-up Health related quality of life (HRQoL) was assessed at end of baseline period and at end of treatment (18 weeks between the two time points).

Outcome measures studied HRQoL as measured by the QOLIE-31 (quality of life in epilepsy), a self administered questionnaire. It includes 7 subscales: Seizure Worry, Overall QOL, Emotional Well-Being, Energy-Fatigue, Cognitive Functioning, and the Health Status item.

Results Mean values of QOLIE-31 at follow-up assessment

	Placebo	LEV 1000mg	LEV 3000mg	p value*
Seizure Worry	55.9	65.8	65.7	0.0003
Overall QOL	62.7	67.3	67.6	0.04
Emotional Well-Being	67.2	69.7	67.4	0.41
Energy-Fatigue	52.7	54.4	55.2	0.62
Cognitive Functioning	60.0	64.6	66.6	0.01
Medication Effects	61.7	66.1	69.6	0.10
Social Function	55.6	58.6	59.9	0.36
Health Status	65.2	66.6	67.9	0.64
Total Score	59.4	63.4	64.1	0.0009

*p-value for difference between treatment groups on adjusted mean values at follow-up assessment (with baseline as covariate).

There were statistically significant changes among responders in all subscale scores (all $p < 0.0006$ to $p < 0.0001$)

Safety and adverse effects Please see database entry for Cereghino study for details of methods and results of RCT.

Does the study answer the question? Please see database entry for Cereghino study for details of methods and results of RCT.

Effect due to factor in study? The clinical trial was not powered for an HRQOL outcome. Thus, the QOLIE-31 analyses were exploratory.

Consistency of results with other studies?

Directly applicable to guideline population? Please see database entry for Cereghino study for details of methods and results of RCT.

Internal Validity

Duchowny M;Pellock JM;Graf WD;Billard C;Gilman J;Casale E;Womble G;Risner M;Manasco P;

A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. Lamictal Pediatric Partial Seizure Study Group

Ref ID 4611

1999

Study Type Randomised Controlled Trial **Funding** Glaxo Wellcome Research and Development

Number of participant 199 patients randomized: 98 patients lamotrigine group and 101 placebo

Inclusion/Exclusion Criteria Inclusion: 2-16 years in US or 2-12 years in France, weighed at least 10 kg, had diagnosis of partial seizures and were incompletely controlled on AED. Exclusion: Previous been exposed to lamotrigine; were using corticosteroid therapy for asthma; had intracerebral, structural lesions or history of status within previous 12 weeks; hx of medical non-compliance, drug abuse, psychiatric disorders or progressive neurological disease or had chronic cardiac, renal or hepatic condition, pregnancy or were awaiting surgery for epilepsy

Patient Characteristics	Lamotrigine (n=98)	Placebo (n=101)
Age (y)		
<6	27	30
6-12	58	62
>12	13	9
Sex M/F	47/51	56/45
Race		
White	78	85
Black	14	7
Other	6	9
Weight, kg mean +/- SD	36.1+/-19.4	32.5 +/-19.1
Height, m, mean +/- SD	1.31+/-0.22	1.26+/-0.23
Recruitment	Not described	
Setting	40 study sites in US and France	
Interventions/ Test/ Factor being investigated	Efficacy and safety of lamotrigine when added to the current AED regimen in children and adolescents with partial seizures	
Comparisons	Treatment (lamotrigine) and placebo	
Length of Study/ Follow-up	8 week baseline and 18 week trial periods	
Outcome measures studied	Primary: Percentage change in seizure frequency between the 8 week baseline stage of the study and either the entire 18 week treatment stage or the 12 week period of maintenance dosing. Secondary: Percent reductions	
Results	<p>The median percentage changes from baseline in seizure counts with lamotrigine and placebo for weeks 1-18 were 36.1% vs. 6.7% respectively (p=0.008) and for weeks 7-18, 44.0% vs. 12.8% respectively (p=0.012). The frequency of secondarily generalized seizures was also significantly reduced from baseline. The median percentage changes from baseline in seizure counts with lamotrigine and placebo for weeks 1-18 were 53.0% vs. 8.6% respectively (p=0.003) and for weeks 7-18, 66.7% vs. 11.2% respectively (p=0.013). The percentage of patients who achieved at least a 50% reduction in the frequency of all partial seizures during weeks 1-18 was 42% with lamotrigine compared with 16% placebo (p<0.001) and during weeks 7-18 was 45% with lamotrigine compared with 25% with placebo (p=0.004). The percentage of patients who achieved at least a 50% reduction in the frequency of partial seizures with secondary generalization during weeks 1-18 was 53% with lamotrigine compared with 26% placebo (p<0.015) and during weeks 7-18 was 45.7% with lamotrigine compared with 30% with placebo (p=0.0023).</p>	
Safety and adverse effects	The most commonly reported adverse events in the lamotrigine treated patients were vomiting, somnolence, and infection; the frequency of these and other adverse events was similar to that in the placebo treated group with the exception of ataxia, dizziness, tremor and nausea which were more frequent and statistically significant (less than or equal to 0.05) in the lamotrigine treated group. Two patients were hospitalized for skin rash, which resolved after discontinuation of lamotrigine.	
Does the study answer the question?	Lamotrigine was effective for adjunctive treatment of partial seizures in children and demonstrated an acceptable safety profile.	
Effect due to factor in study?	Yes	
Consistency of results with other studies?	See GRADE	
Directly applicable to guideline population?	See GRADE	
Internal Validity	Multi-centre	

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=341 (n=131 in PGB 150-600mg/day pregabalin (flexible dose), n=137 in the PGB 300mg/day fixed dose, and n=73 in the placebo group.)

Inclusion/Exclusion Criteria
 Inclusion criteria: aged 18 years or older, weight at least 50 kg, diagnosis of epilepsy with partial seizures, and not previously received pregabalin. They must have experienced at least 4 partial seizures during the 6- week baseline period with no 28-day period free of partial seizures, and to be currently receiving between 1 and 3 AEDs.
 Exclusion criteria: seizures with a treatable cause, absence seizures, Lennox–Gastaut syndrome, or status epilepticus within the previous year.

Patient characteristic	Patient Characteristics		
	Placebo (n = 73)	Pregabalin flexible dose 150–600 mg/day (n = 131)	Pregabalin fixed dose 600 mg/day (n = 137)
Age in yr			
Mean (SD)	40.3 (12.5)	40.0 (13.5)	41.1 (12.2)
Race, n (%)			
White	71 (97.3)	128 (97.7)	133 (97.1)
Black	0	0	1 (0.7)
Other	2 (2.7)	3 (2.3)	3 (2.2)
Gender, n (%)			
Male	37 (50.7)	64 (48.9)	69 (50.4)
Weight (kg)			
Mean (SD)	72.6 (15.6)	74.0 (17.4)	75.1 (16.3)
Estimated creatinine clearance (ml/min)			
Mean (SD)	107.2 (28.9)	109.4 (33.8)	108.0 (31.7)

Recruitment Unknown.

Setting 53 centres worldwide

Interventions/ Test/ Factor being investigated Flexible dose PGB (150-600mg PGB titrated to clinical response and adverse events in 150mg increments) and fixed dose PGB (300mg daily).

Comparisons Comparisons are between two regimens of PGB and placebo as add-on therapy to currently used AEDs.

Length of Study/ Follow-up 18 weeks: a 6 week baseline phase and a 12 week treatment period.

Outcome measures studied The primary efficacy measure was a reduction in the 28-day seizure rate. Secondary outcomes: responder rate, % pts seizure free, % completing study, reduction in proportion of sec. gen. tonic-clonic seizures.

Results Primary outcome

Both pregabalin treatment regimens were significantly more effective than placebo in reducing the frequency of all partial seizures. Mean R Ratios for the pregabalin flexible-dose group (-21.5, p = 0.0091) and the pregabalin fixed-dose group (-32.7, p = 0.0001) were both significantly lower than for the placebo group (-5.6), indicating a greater reduction in seizure frequency.

The corresponding percentage reduction in seizure frequency between baseline and treatment was 35.4% for the pregabalin flexible-dose group, and 49.3% for the pregabalin fixed-dose group compared with 10.6% for the placebo group (Fig. 2, left y-

axis). Differences in the treatment means (95% confidence intervals) compared with the placebo group were -15.8 (-27.4, -4.3) for the pregabalin flexible-dose (150–600 mg/day) group, and -27.0 (-38.5, -15.6) for the pregabalin fixed-dose group. The pregabalin fixed-dose group was significantly superior to the pregabalin flexible-dose (150–600 mg/day) group ($p = 0.0337$), with a mean RRatio treatment difference of -11.2 (-20.8, -1.6).

Secondary outcomes

Responder rate

The responder rate ($\geq 50\%$ reduction) was significantly greater in both the pregabalin flexible-dose group (31.3%, $p=0.001$) and the pregabalin fixed-dose group (45.3%, $p=0.001$) compared with the placebo group (11.0%). The responder rate for the pregabalin fixed-dose group was also significantly higher than the rate in the pregabalin flexible-dose group ($p=0.016$).

Free of seizures

During the last 28 days of treatment, 16 (12.2%) patients in the pregabalin flexible-dose group, 17 (12.4%) in the pregabalin fixed-dose group, and 6 (8.2%) in the placebo group were completely free of seizures.

Completing study

Significantly more patients in the pregabalin flexible dose group (76.3%) completed the trial than did patients in the fixed-dose group (58.4%; $p = 0.0019$).

Reduction in secondary generalized tonic-clonic seizures

Compared with the placebo group (33%, $n = 27$), a higher proportion of patients in both the pregabalin flexible-dose group (53%, $n = 28$) and pregabalin fixed dose group (68%, $n = 45$) exhibited a decrease in the proportion of SGTC seizures by 28-day seizure rates for all partial seizures with the difference between the pregabalin fixed dose and placebo reaching statistical significance ($p = 0.015$).

Adverse events

Pregabalin dose mg/day	Frequency of adverse event Pregabalin		
	Placebo	150–600 mg/day	fixed 600
Adverse event (n = 137)	(n = 73)	(n = 131)	(n = 137)
Overall adverse events (%)	63.0	86.3	87.6
Frequency of most common adverse events (%) ^b			
Dizziness	8.2	24.4	43.1
Ataxia	4.1	9.2	21.2
Weight gain	6.8	19.1	20.4
Asthenia	13.7	16.8	18.2
Somnolence	8.2	19.1	17.5
Vertigo	2.7	10.7	13.9
Diplopia	1.4	6.1	11.7
Amblyopia (blurred vision)	1.4	2.3	10.2
Headache	11.0	13.7	7.3

Withdrawal due to an adverse event was 33% in the pregabalin fixed-dose group followed by the pregabalin flexible-dose group (12%), and placebo group (7%).

Safety and adverse effects

More patients discontinued study drug due to adverse events in the fixed dose pregabalin group. Significant weight gain is a relatively common adverse effect.

Does the study answer the question?

Yes. Pregabalin administered either as fixed (600 mg/day), or as flexible (150–600 mg/day) dose, was effective as add-on therapy for partial seizures with or without secondary generalization. Lower incidence of adverse events and discontinuations were achieved in patients receiving a flexible dose.

Effect due to factor in study? Yes. The sample size was derived from a power calculation which was based on previous pregabalin trials.

Consistency of results with other studies?

Directly applicable to guideline population? The study population comprised patients who all had suffered from partial seizures.

Internal Validity

Elterman RD;Glaser TA;Wyllie E;Reife R;Wu SC;Pledger G;

A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children.
Topiramate YP Study Group

Ref ID 4608

1999

Study Type Randomised Controlled Trial **Funding** R.W. Johnson
Pharmaceutical Research
Institute

Number of participant 41 patients in topiramate treatment and 45 patients in placebo group

Inclusion/Exclusion Criteria Inclusion: Ages 1-16 years, weighing more than 16 kg and had partial onset seizures. Six or more seizures during the baseline phase with at least one during each 4 week interval while maintained on at least one but not more than two AEDs. Exclusion: Progressive neurologic disease, status, Lennox-Gastaut, EKG abnormalities, significant medical disease, drug or alcohol abuse, psychiatric condition and use of drugs that increased risk of renal stones.

Patient Characteristics Age range 2-16; mean age placebo (n=45) 9.0+/-3.4 and topiramate (n=41) 8.8+/-3.6. Male/female placebo (n=45) 25/20 and topiramate (n=41)23/18; mean weight placebo (n=45)35.1+/-16.3 and topiramate (n=41) 34.7 +/-15.8.

Recruitment Not described

Setting 16 sites in the US and one in Costa Rico

Interventions/ Test/ Factor being investigated Use of topiramate as adjunctive therapy for partial onset seizures in children

Comparisons Topiramate versus placebo

Length of Study/ Follow-up 8 week baseline and 16 week treatment phase (8 week titration and 8 week stabilization)

Outcome measures studied The primary efficacy variable was percent reduction in average monthly partial seizure frequency during the double blind phase. Secondary variable included percent reduction in various seizure types and parental global evaluation of seizure activity.

Results Topiramate treated patients: greater median percent reduction from baseline in average monthly partial onset seizure rate than placebo (33.1% versus 10.5%, p=0.034); a greater proportion of responders (>50%, 39% vs. 20%, p=0.08) (>75%, 17% vs. 2% p=0.019) and better parental global evaluations of concentration or attention (12% versus 2%).

Safety and adverse effects No patients withdrew due to adverse experiences. One topiramate treated patient had a serious treatment emergent event not related to the drug (dehydration)

Does the study answer the question? Topiramate appears to be safe and effective in the treatment of partial onset seizures in children.

Effect due to factor in study? Yes

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity Multi-centre

Faught E;Ayala R;Montouris GG;Leppik IE;Trial Group.;

Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures.[see comment]

Ref ID 1043

2001 Nov 27

Study Type Randomised Controlled Trial **Funding** Dainippon Pharmaceutical USA Corp. Teaneck NJ.

Number of participant n=203(n=85 in group A, n=60 in group B and n=58 in group C)

Inclusion/Exclusion Criteria Inclusion criteria: at least 12 years of age, refractory partial-onset seizures (complex partial or simple partial with an observable motor component, with or without secondary generalization to tonic-clonic seizures). Patients had at least four seizures per month for 3 months before entry, with no seizure-free period over 30 days, while taking one or two standard antiepilepsy drugs. At least one baseline antiepilepsy drug was required to be phenytoin, carbamazepine, valproic acid, phenobarbital, or primidone. Exclusion criteria were pregnancy, nursing, progressive neurologic disease, unstable systemic or psychiatric disease, allergy to sulfonamides, use of acetazolamide within a year, hemolytic anemia, glucose-6-phosphate dehydrogenase deficiency, acute intermittent porphyria, history of drug or alcohol abuse within 2 years, previous treatment with zonisamide, use of intermittent benzodiazepines for seizure flurries, or unacceptable laboratory results.

Patient Characteristics	Characteristic	Group A (n=85)	Group B1 (n=60)	Group B2 (n=58)
	Sex, n (%)*			
	Men	35 (41)	37 (62)	32 (55)
	Women	50 (59)	23 (38)	26 (45)
	Race, n (%)			
	White	72 (85)	50 (83)	51 (88)
	African-American	9 (11)	7 (12)	4 (7)
	Asian	1 (1)	1 (2)	0 (0)
	Other	3 (4)	2 (3)	3 (5)
	Age, y			
	Mean (SD)	34.2(11.4)	35.8(11.4)	33.6(11.2)
	Range	14–67	13–66	15–68
	Age at seizure onset, y			
	Mean(SD)	12.2(12.2)	12.0(10.7)	12.9(11.7)
	Weight, kg			
	Mean(SD)	75.0(18.4)	81.(20.3)	75.6(18.7)
	Range	45–140	44–133	44–128
	Median baseline seizure frequency			
	All partial-onset	13.0	11.2	13.0
	Complex partial	7.0	6.2	8.0
	Seizure characteristics, n (%)			
	Complex partial	81 (95)	57 (95)	57 (98)
	Simple partial	4 (5)	3 (5)	1 (2)
	Secondarily generalized tonic-clonic	20 (24)	14 (23)	12 (21)

Recruitment Not reported.

Setting 20 epilepsy centres in the United States.

**Interventions/ Test/
Factor being
investigated**

Zonisamide in three different doses.

Comparisons

Zonisamide with a target dose of 400 mg/day in three different titration doses.

**Length of Study/
Follow-up**

24 weeks: 4 weeks baseline and 20 weeks treatment which includes titration.

**Outcome measures
studied**

Primary outcome: median % reduction in seizure frequency from the baseline period. Primary comparison is Group A(placebo) and Groups B1 and B2 (receiving zonisamide 400mg/d). Secondary outcomes:comparison over different weeks. And others e.g. response

Results

The primary population for each analysis was a "modified intent-to-treat" population, including all patients who received at least one dose of study drug during the time period (n =170).

Primary outcome

Zonisamide at 400 mg/d yielded a median reduction in the frequency of all seizures of 40.5% from baseline for pooled patient groups B1 and B2 over weeks 8 through 12 (n=98), compared with a median reduction of 9% for patients on placebo (n=72, p= 0.009).

"Worst case" intent to treat population

The same efficacy outcome is presented using the "worst case" intent to treat population: all patients who were randomly assigned with imputation of seizure frequency beyond the dropout period (n=203 randomised).

Zonisamide at 400 mg/d yielded a median reduction in the frequency of all seizures of 32.3% from baseline for pooled patient groups B1 and B2 over weeks 8 through 12, compared with a median reduction of 5.6% for patients on placebo (p=0.016).

Other outcomes

43% (41/98) of patients on zonisamide 400 mg/d had a >=50% reduction in all seizures, a responder rate that was significantly higher than that observed for the placebo group (16/72, 22%) (p=0.014).

Group A (placebo) patients crossed over to 400 mg/d zonisamide (weeks 17 through 20) had a median reduction of 40.1% in all seizures (p=0.0003) and 55% in complex partial seizures, compared with their previous seizure rates on placebo (p=0.0012).

Zonisamide 100 and 200 mg/d.

The median reduction in seizure frequency for the 100-mg/d group (B1, n=56) was 24.7% for all seizures, compared with 8.3% for the placebo (group A, n=80, p=0.038). For complex partial seizures, there was a 33.3% reduction in group B1 compared with 8.6% for placebo (p=0.0095). The reduction in seizure frequency for the 200-mg/d dosage (group B2, n=55) was 20.4% for all seizures, compared with 4.0% for placebo (group A, n=82, p=0.003). The reduction in complex partial seizures for the 200-mg group (17.2%) did not differ significantly from the 9.5% reduction noted for the placebo group.

Adverse events

Treatment-emergent adverse events reported by >=10% of patients

Adverse event

	Weeks 1-5 Group A (placebo)	Weeks 1-12 Group B1 and B2 (100,200 and 400mg)
	n=85	n=118
Somnolence	13 (15.3)	18 (15.3)
Anorexia	8 (9.4)	17 (14.4)
Rhinitis	13 (15.3)	17 (14.4)
Dizziness	12 (14.1)	16 (13.6)
Nausea or vomiting	15 (17.6)	14 (11.9)
Ataxia	6 (7.1)	12 (10.2)
Fatigue	12 (14.1)	11 (9.3)
Headache	11 (12.9)	11 (9.3)

Safety and adverse effects

Does the study answer the question?

Yes. Zonisamide is effective as an adjunctive agent for refractory partial-onset seizures. The minimal effective dosage was 100mg/d, but 400mg/d was the most effective dosage.

Effect due to factor in study?

Yes. The study had 85% power to detect a difference between groups in the primary outcome.

Consistency of results with other studies?

Directly applicable to guideline population?

The study enrolled patients with epilepsy who had refractory partial-onset seizures (complex partial or simple partial with or without secondary generalization to tonic-clonic seizures.) Directness of comparisons to the intervention group.

Internal Validity

Faught E;Wilder BJ;Ramsay RE;Reife RA;Kramer LD;Pledger GW;Karim RM;

Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group

Ref ID 4699

1996

Study Type Randomised Controlled Trial

Funding Robert Wood Johnson

Number of participant

181 were randomised: placebo (n=45), 200 mg/day (n=45), , 400 mg/day (n=45), , 600 mg/day (n=46)

Inclusion/Exclusion Criteria

Inclusion: History of partial onset seizures with EEG verification; experienced 12 partial seizures during 12 week baseline period preceding the double blind study phase while maintained on therapeutic AEDs. Age 18-65. Exclusion: Progressive neurological disease. Status, child-bearing potential, alcohol or drug abuse, psychiatric disorder, nephrolithiasis, non-compliance history, abnormal baseline lab tests.

Patient Characteristics

Gender: Male 143
Female 38
Race: White 159
Black 21
Other 1
Age (yr)
Mean 36.9
Range 19-68

Recruitment

Unknown

Setting

Multicentre - USA

Interventions/ Test/ Factor being investigated

Comparison of three doses of topiramate (200, 400 and 600 mg) with the placebo.

Comparisons

Comparison of three doses of Topiramate (200, 400 and 600 mg/day) and placebo as adjunctive therapy in patients with refractory partial onset epilepsy

Length of Study/ Follow-up

12 week baseline and 16 week double blind phase divided into 4 week titration segment and a 12 week stabilization period

Outcome measures studied

Primary: percent reduction in average monthly seizure rate in the double blind phase relative to the baseline phase.
Secondary: percent treatment responders (those with greater than or equal to 50% reduction in seizure rate);

Results		Placebo	200 mg	400mg	600mg
	% seizure reduction				
	Median	13.1	29.6	47.8	44.7
	p-value		0.051	0.007	<0.001
	Treatment responders				
	Number	8/45	12/45	21/45	21/46
	Percent	18	27	47	46
	p-value		0.620	0.013	0.027
	Number withdrawn due to adverse events:				
		3/45 (7%)	2/45 (4%)	4/45 (9%)	6/46 (13%) -
	although the table in the study says 45 in order to be 13% and match the data elsewhere in the study.				
Safety and adverse effects	CNS events were the most common adverse events including dizziness, fatigue, abnormal thinking, somnolence, headache and ataxia. Discontinuations due to adverse events were: 7% placebo; 4% 200mg; 9% 400 mg and 13% 600 mg. No remarkable abnormal clinical lab findings				
Does the study answer the question?	To primate may be a promising AED for adjunctive therapy in refractory partial onset seizures				
Effect due to factor in study?	Yes				
Consistency of results with other studies?	See GRADE				
Directly applicable to guideline population?	See GRADE				
Internal Validity	Multi centre				

French JA;Kugler AR;Robbins JL;Knapp LE;Garofalo EA;

Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures

Ref ID 4589

2003

Study Type Randomised Controlled Trial **Funding** Pfizer. Inc.

Number of participant n=455 randomized (n=100 in placebo group, n=88 in PGB 50mg/day group, n=88 in PGB 150mg/day group, n=90 in 300mg/day group and n=89 in 600mg/day group)

Inclusion/Exclusion Criteria
 Inclusion criteria: aged 12 to 70 years, experienced at least three observable partial seizures in the month prior to screening and six partial seizures in the 8 weeks between screening and baseline; their disease was refractory to at least two AEDs at maximally tolerated doses; and currently receiving at least one but no more than three AEDs.
 Exclusion criteria: seizures caused by an underlying medical illness, absence seizures, Lennox-Gastaut syndrome, and status epilepticus in the past year. Patients who had received gabapentin within a week of screening were also excluded. Patients with clinically relevant medical illness were excluded. Women were not pregnant or breastfeeding and were reliably using barrier or hormonal contraception.

Patient Characteristics			Pregabalin dose (mg/d)*			
		Placebo	50	150		
	300					
	600					
	n=89	n = 100	n=88	n=86	n=90	
	Age, mean (SD) (11.1)	39.5 (12.6)	38.9 (11.0)	37.4 (13.3)	37.8 (11.4)	38.0
	Women, n (%) (51.7)	48 (48.0)	49 (55.7)	50 (58.1)	42 (46.7)	46

Race, white, n (%)	84 (84.0)	76 (86.4)	73 (84.9)	78 (86.7)	74 (83.1)
Weight, mean (SD), kg	80 (19.7)	79 (19.4)	73 (17.8)	80 (23.8)	80 (21.6)
28-Day seizure rate					
Mean (SD)	22.3 (42.1)	27.4 (50.2)	23.1 (36.5)	19.1 (26.7)	18.6 (26.9)
Epilepsy duration, mean (SD), y	24 (10)	25 (11.8)	24 (12.8)	26.2 (13.5)	25.5 (13.7)
Partial seizures with secondary generalization					
n (%)	26 (26.0)	33 (37.5)	34 (39.5)	29 (32.2)	29 (32.6)
28-Day seizure rate					
Mean (SD)	4.3 (9.4)	1.8 (2.4)	3.8 (8.5)	3.9 (7.6)	3.9 (4.5)
Concurrent AED, n (%)					
1 AED	26 (26.0)	30 (34.1)	27 (31.4)	30 (33.3)	22 (24.7)
2 AED	48 (48.0)	39 (44.3)	44 (51.2)	46 (51.1)	49 (55.1)
3 AED	24 (24.0)	18 (20.5)	15 (17.4)	14 (15.6)	18 (20.2)

Recruitment

Not reported.

Setting

76 centres in the United States and Canada.

Interventions/ Test/ Factor being investigated

Pregabalin in doses of 50, 150, 300, and 600 mg/day.

Comparisons

Comparisons are made between all the above doses of PGB and placebo, as add-on therapy to currently used AEDs.

Length of Study/ Follow-up

20 weeks: 8 week baseline period and 12 week treatment period.

Outcome measures studied

The primary outcome was reduction in seizure frequency as measured by response ratio (RRatio). Efficacy was also assessed on basis of responder rate ($\geq 50\%$ reduction)

Results

Primary outcome

Seizure reduction

Seizure reduction for all partial seizures was lower in the pregabalin 150-, 300-, and 600-mg/d groups compared with the placebo group at endpoint ($p \leq 0.0001$). There was a percentage reduction in seizure frequency between baseline and endpoint of 7% (placebo; $n=100$), 12% (50 mg/d; $n=88$), 34% (150 mg/d; $n=86$), 44% (300 mg/d; $n=90$), and 54% (600 mg/d; $n=89$). Seizure reduction for all partial seizures was lower in the pregabalin 150-, 300-, and 600-mg/d groups compared with the placebo group at endpoint ($p \leq 0.0001$). There was a percentage reduction in seizure frequency between baseline and endpoint of 7% (placebo; $n=100$), 12% (50 mg/d; $n=88$), 34% (150 mg/d; $n=86$), 44% (300 mg/d; $n=90$), and 54% (600 mg/d; $n=89$).

Secondary outcomes

Seizure reduction by responder ($\geq 50\%$ reduction)

The responder rate was greater than placebo in the pregabalin 150 ($p=0.006$), 300 ($p \leq 0.001$), and 600 ($p \leq 0.001$) mg/d groups and was also dose related. The analyses of RRatio ($p \leq 0.0001$) and responder rate ($p \leq 0.001$) indicate that pregabalin exhibits a dose-response relationship.

Reduction by seizure type

In the analysis of seizure type, the reductions in simple partial seizures, complex partial seizures, and seizures without generalization were similar to those observed for all partial seizures across dose groups, as measured by RRatio. Too few patients experienced partial seizures with generalization during the baseline and treatment periods to provide meaningful data. However, the number of partial-onset seizures

with generalization decreased in the pregabalin 300- and 600-mg/d groups.

Adverse events

	300	600	Pregabalin dose (mg/d)*			
			Placebo	50	150	
			n = 100	n=88	n=86	n=90
n=89						
Any AE Incidence (88.8)			74 (74.0)	59 (67.0)	61 (70.9)	76 (84.4) 79
AEs of severe intensity Incidence (14.6)			6 (6.0)	6 (6.8)	4 (4.7)	7 (7.8) 13
Dizziness Incidence (42.7)			9 (9.0)	8 (9.1)	14 (16.3)	28 (31.1) 38
Somnolence Incidence (28.1)			11 (11.0)	9 (10.2)	15 (17.4)	16 (17.8) 25
Accidental injury Incidence (12.4)			5 (5.0)	13 (14.8)	5 (5.8)	10 (11.1) 11
Ataxia Incidence (14.6)			3 (3.0)	3 (3.4)	9 (10.5)	9 (10.0) 13
Asthenia Incidence (10.1)			8 (8.0)	5 (5.7)	7 (8.1)	11 (12.2) 9
Headache Incidence (5.6)			13 (13.0)	6 (6.8)	8 (9.3)	5 (5.6) 5
Infection Incidence (10.1)			10 (10.0)	8 (9.1)	8 (9.3)	5 (5.6) 3 (3.4)
Blurred vision* Incidence (10.1)			5 (5.0)	3 (3.4)	3 (3.5)	7 (7.8) 9
Tremor Incidence (11.2)			3 (3.0)	3 (3.4)	3 (3.5)	6 (6.7) 10
Weight gain Incidence (12.4)			0	1 (1.1)	2 (2.3)	6 (6.7) 11
In coordination Incidence (10.1)			1 (1.0)	2 (2.3)	2 (2.3)	3 (3.3) 9
Dry mouth Incidence (10.1)			1 (1.0)	2 (2.3)	1 (1.2)	2 (2.2) 9

Overall, adverse events resulted in the discontinuation of five patients (5.0%) from the placebo group, six (6.8%) from the 50- mg/d group, one (1.2%) from the 150- mg/d group, 13 (14.4%) from the 300-mg/d group, and 21 (23.6%) from the 600-mg/d group.

Safety and adverse effects

There is a dose-related increase in the incidence of discontinuation due to adverse events in the 600 and 300mg/day groups compared with placebo. Significant weight gain is a relatively common adverse effect.

Does the study answer the question?

Yes. Adjunctive therapy with pregabalin 150, 300, and 600 mg/d, given in twice-daily doses without titration, is significantly effective in the treatment of patients with partial seizures.

Effect due to factor in study?

Yes. The sample size was derived from a power calculation which was based on results from earlier trials of pregabalin.

Consistency of results with other studies?

Directly applicable to guideline population?

This study population comprised patients with epilepsy all of whom suffered from partial seizures.

Internal Validity

French JA; Mosier M; Walker S; Sommerville K; Sussman N;

A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. Vigabatrin Protocol 024 Investigative Cohort

Ref ID 4752

1996

Study Type Randomised Controlled Trial **Funding** Marion Merrell Dow Inc.

Number of participant n=182 (n=90 in placebo group and n=92 in the vigabatrin group.)

Inclusion/Exclusion Criteria
 Inclusion criteria: age 18 to 60 years with a diagnosis of complex partial seizures, with or without secondary generalization; seizures unsatisfactorily controlled with AEDs; at least six documented complex partial seizures during the last 8 weeks of a 12-week period; at least one, but not more than two AEDs; Prior treatment with phenytoin or carbamazepine; must not have experienced a seizure-free interval of 28 days or more over the last 8 weeks; MRI, demonstrated an abnormal EEG.
 Exclusion criteria: treatable seizure etiology (e.g., metabolic or neoplastic cause) or progressive neurologic disorders; experienced more than one episode of status epilepticus during the previous 6 months; had a history of alcoholism or drug addiction, were unable to comply with completing the seizure frequency diaries; or evidence of other systemic diseases that would subject them to undue risk or would compromise the objective of the study.

Patient Characteristics The 182 patients (80 men and 102 women) included in the analyses ranged in age from 18 to 60 years (mean, 34 years). The majority of patients (113, 62%) received two concurrent antiepilepsy drugs. No significant differences were observed between treatment groups for any baseline demographic or clinical characteristic or in the use of any concomitant antiseizure medication.

Recruitment Not reported.

Setting Multiple centres in the United States.

Interventions/ Test/ Factor being investigated Vigabatrin 3 g/day.

Comparisons Comparison is between vigabatrin 3g/day and placebo as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up 28 weeks: 12 week evaluation period, 4 week titration phase and 12-week treatment phase.

Outcome measures studied
 Primary outcome: monthly freq complex partial seizures plus partial seizures with secondary gen during the last 8 weeks of the treatment phase vs. the last 8 weeks of the baseline phase.
 Secondary outcomes: response rate, freq seizures, global eval.

Results
 Primary outcome
 There was a significant lower frequency of seizures (complex seizures plus partial seizures with secondary generalization) during the last 8 weeks of the study for patients receiving vigabatrin than for those receiving placebo. The median monthly frequency was reduced by three seizures per 28 days in the vigabatrin group (baseline, 8.3; end of study, 5.3) versus 0.8 seizures per 28 days in the placebo group (baseline, 8.3; end of study, 7.5) (p = 0.0002).

Percent change in total seizure frequency

	Placebo N (%)	Vigabatrin N (%)
Percent change in seizures		
<50% increase	14 (15.6)	4 (4.4)
1-50% increase	21 (23.3)	14 (15.2)
0-49% reduction	38 (42.2)	34 (36.9)
50-99% reduction	16 (17.8)	34 (36.9)
100% reduction	1(1.1)	6 (6.5)

Overall, median percent reduction in seizures (1B + 1C) was 7.5% for the placebo group, versus 39.5% in the vigabatrin group (p > 0.001).

Secondary outcomes

Therapeutic success ($\geq 50\%$ reduction) was attained in 40 of the vigabatrin patients (43%) compared with 17 of those treated with placebo (19%) ($p < 0.001$). An analysis of response by seizure type showed the frequency of complex partial seizures at the end of study was significantly lower for vigabatrin-treated patients. The median monthly rate of these seizures was reduced by 3.5 seizures in the vigabatrin group and by 1.0 seizure in the placebo group (5.0 seizures per 28 days on vigabatrin versus 7.0 seizures per 28 days on placebo at end of study; $p < 0.001$). The median monthly rate of partial seizures with secondary generalization was reduced by 1.5 seizures per 28 days in the vigabatrin group and was unaffected by placebo therapy (2.5 seizures per 28 days on vigabatrin versus 1.5 seizures per 28 days on placebo at end of study; $p = 0.3881$).

Percent change in seizures for IB and IC subtypes (complex partial seizures and partial seizures with secondary generalization)

Percent change in seizures	Complex (N = 173)		Partial seizures with secondary partial generalization (N = 84)	
	Placebo (N = 89)	Vigabatrin (N = 84)	Placebo (N = 29)	Vigabatrin (N = 31)
<50% increase	13 (14.6)	4 (4.8)	5 (17.2)	5 (16.1)
1-50% increase	21 (23.6)	15 (17.6)	6 (20.7)	1 (3.2)
0-49% reduction	38 (42.7)	26 (30.9)	3 (10.3)	10 (32.2)
50-99% reduction	13 (14.6)	31 (36.9)	8 (27.6)	8 (25.8)
100% reduction	4 (4.5)	8 (9.5)	7 (24.1)	7 (22.6)

Adverse events

The most common treatment-related adverse events were drowsiness (vigabatrin group, 29.3%; placebo group, 13.3%), light-headedness (vigabatrin group, 21.7%; placebo group, 14.4%), headache (vigabatrin group, 21.7%; placebo group, 16.7%), fatigue (vigabatrin group, 19.6%; placebo group, 13.3%), and tremor (vigabatrin group, 13.0%; placebo group, 4.4%).

Nine patients (2 placebo [2%]; 7 vigabatrin [7.6%]) discontinued from the study because of adverse events. Other treatment-related events that occurred in 10% or more of patients in either group were depression, vision abnormalities, nystagmus, and paresthesia.

Safety and adverse effects

Depression was the only behavioural change reported consistently during vigabatrin treatment. One patient on vigabatrin committed suicide and another experienced a behavioural abnormality, consisting of hyperactivity, paranoia and grandiose thoughts, which resolved when vigabatrin was discontinued.

Does the study answer the question?

Yes. Vigabatrin is more effective than placebo as add-on therapy.

Effect due to factor in study?

Unsure. No statistical power calculation performed.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in this study had complex partial seizures which were difficult to control with established AED therapy.

Internal Validity

Gilliam F; Vazquez B; Sackellares JC; Chang GY; Messenheimer J; Nyberg J; Risner ME; Rudd GD;

An active-control trial of lamotrigine monotherapy for partial seizures

Ref ID 4719

1998

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=156 (n=76 in LTG group and n=80 in VPA group)

Inclusion/Exclusion Criteria Inclusion criteria: >=13 years, partial seizures with or without sec. gen. tonic-clonic seizures, unresponsive to at least one AED, at least four seizures every 4 weeks during the baseline phase, no more than 20 consecutive seizure-free days during baseline.

Patient Characteristics Intent to treat population patient characteristics

Characteristic	LTG n=76	VPA n=80
Age, y, mean (range)	37(13-73)	36(14-71)
Weight, kg, mean (range)	78(49-137)	70(43-121)
Sex, n(%)		
Male	33(43)	32(40)
Race, n (%)		
White	52(68)	55(69)
Black	8(11)	11(14)
Other	16(21)	14(17)
Baseline seizure frequency		
Median/28 days (range)	9(1-737)	10(3-226)
Presenting seizure type* n(%)		
Simple partial	31(41)	35(44)
Complex partial	64(84)	71(89)
Sec. gen.	38(50)	27(34)
No. previous AEDs, mean (range)	4.4(1-13)	4.6(1-14)
AED at baseline, n(%)		
Carbamazepine	48(63)	46(58)
Phenytoin	28(37)	34(42)

Recruitment Not reported.

Setting 36 centres in United States.

Interventions/ Test/ Factor being investigated Lamotrigine (LTG) 150 to 250mg twice daily as monotherapy.

Comparisons The comparison is between LTG and valproic acid (VPA: target low dose of 500mg twice daily).

Length of Study/ Follow-up 28 weeks: 8 week baseline phase and 20 weeks treatment phase.

Outcome measures studied Primary: proportion of pts meeting escape criteria (1) doubling of average monthly seizure rate, 2) doubling of highest consecutive 2-day seizure rate 3) new more severe seizure type, 4) clinically sig. prolongation of gen. tonic-clonic seizure.)

Results Results of primary efficacy analyses

N(%) of completed patients

Median to escaped	Total	Completed			time
		monotherapy	Escaped	Withdrawn	
Per protocol analysis					
LTG	50	28(56)*	22(44)	NA	168*
VPA	64	13(20)	51(80)	NA	57
Intent to treat analysis					
LTG	76	28(37)*	32(42)	16(21)	NA
VPA	80	13(16)	55(69)	12(15)	NA

*p<=0.005 versus VPA.

Adverse events

Intent to treat population: adverse experiences (AE)

	Treatment group	
	Monotherapy period LTG n=43, n(%)	Monotherapy period VPA n=44, n(%)
Patients with >=1 AE	26(60)	19(43)
Dizziness	3(7)	0(0)
Nausea	3(7)	1(2)
Headache	3(7)	6(14)
Dyspepsia	3(7)	1(2)
Somnolence	0(0)	1(2)
Asthenia	1(2)	0(0)
Coordination abnormalities	3(7)	0(0)
Vomiting	4(9)	0(0)
Rash	1(2)	1(2)
Tremor	2(5)	3(7)

Safety and adverse effects

The most common AEs during LTG monotherapy were vomiting, headache, dizziness, nausea, dyspepsia, and coordination abnormalities (7% to 9%).

Does the study answer the question?

Yes. Results show that Lamotrigine therapy is effective in adults with partial seizures. The proportion of patients who successfully completed 12 weeks of LTG monotherapy was more than two and half times greater than the proportion of patients completing monotherapy treatment with a low dose of VPA.

Effect due to factor in study?

No. The study did not perform a statistical power calculation. A low dose of valproic acid was chosen as the control.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients were diagnosed with partial seizures (simple partial, complex partial, or secondarily generalized).

Internal Validity

Gil-Nagel A;Lopes-Lima J;Almeida L;Maia J;Soares-da-Silva P;Investigators Study Group.;

Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures

Ref ID 5082

2009 Nov

Study Type Randomised Controlled Trial

Funding BIAL (Portela & Ca SA).

Number of participant n=252. Placebo n=87; ESL 800mg n=85; ESL 1200mg n=80.

Inclusion/Exclusion Criteria

Inclusion:
 aged 18 or over;
 general good health, other than epilepsy;
 diagnosed with simple or complex partial seizures (with or without secondary generalisation) for a minimum of 12 months prior to screening;
 experienced at least four partial-onset seizures in the two 4-week periods prior to screening as well as during each of the two 4-week periods of the 8-week baseline period;
 treated with one to two concomitant AEDs in a stable dose regimen for at least 2 months prior to screening.
 Exclusion:
 If at time specified had: an uncontrolled, relevant medical disorder;
 visual field loss caused by vigabatrin use (at least 1 year);
 Simple partial seizures without motor symptoms;

primary generalised epilepsy;
 rapidly progressive neurological disorder;
 status epilepticus ;
 cluster seizures (within 3 months);
 history of seizures of psychogenic origin (within 2 years)
 history of schizophrenia or suicide attempts;
 a known hypersensitivity to CBZ or OXC, or chemically-related substances;
 Receiving OXC, felbamate, or a benzodiazepine except when used chronically as an AED;
 Pregnant or breastfeeding women.

Patient Characteristics	<p>Mean age placebo 37.7 +/-12.07 vs ESL 800mg 36.8 +/-10.65 and ESL 1200mg 36 +/-11.43 Malels: placebo 43 (49.4) vs ESL 800mg 35 (41.2); ESL 1200mg 35 (43.8). Ethnic origin: hispanic 54 (62.1) vs 52 (61.2) vs 53 (66.3); Caucasian 33 (37.9) vs 32 (37.6) vs 27 (33.8); Asian ESL 800mg 1 (1.2). Seizure types: simple partial, complex partial, secondary generalised epilepsy and unclassified. Up to 4 concomitant AEDs. Types of AEDs: Carbamazepine, valproic acid, phenytoin, levetiracetam, topirimate, lamotrigine, phenobarbital, clobazam, primidone, clonazepam.</p>
Recruitment	Not reported.
Setting	39 sites in Mexico, Portugal and Spain between Dec
Interventions/ Test/ Factor being investigated	Eslicarbazepine 800mg and 1200mg and placebo once daily.
Comparisons	Comparisons between two doses and placebo.
Length of Study/ Follow-up	No follow-up.
Outcome measures studied	Proportion with at least 50% reduction in seizure frequency, seizure freedom, seizure exacerbation; incidence of adverse events, withdrawal due to adverse events.
Results	<p>Placebo vs eslicarbazepine 800mg vs eslicarbazepine 1200mg:</p> <p>At least 50% reduction in seizure frequency (titration and maintenance): placebo 22.6%, 800mg 34.5%; 1200mg 37.7% .</p> <p>Proportion of seizure free (titration and maintenance) : placebo 1.2%, 800mg 4.8%; 1200mg 3.9%.</p> <p>Exacerbation in seizure frequency >=25% placebo 22.5; 800mg 16.7% , 1200mg 13%.</p> <p>Adverse events (over 10%) n (%): dizziness 9 (10.3) vs 16 (18.8) vs 24 (30) somnolence 8 (9.2) vs 11 (12.9) vs 11 (13.8) headache 10 (11.5) vs 5 (5.9) vs 8 (10) nausea 1 (1.1) vs 5 (5.9) vs 8 (10)</p> <p>Withdrawal due to treatment emergent adverse events: 6 (6.9) vs 7 (8.2) vs 9 (11.3) from abnormal coordination, dizziness and nausea.</p>
Safety and adverse effects	<p>See results for adverse events over 10%. Serious TEAEs: placebo 0% vs 800mg 0% vs 1200mg 1.3%) - the one case in the eslicarbazepine 1200mg group was cerebellar syndrome and led to study discontinuation. No deaths.</p>
Does the study answer the question?	Yes.
Effect due to factor in study?	Yes.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Glauser TA;Ayala R;Elterman RD;Mitchell WG;Van Orman CB;Gauer LJ;Lu Z;Study Group.;

Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures.[see comment]

Ref ID 382

2006 Jun 13

Study Type Randomised Controlled Trial **Funding** UCB Inc.

Number of participant n=198 (n=101 in the LEV group and n=97 in the placebo group)

Inclusion/Exclusion Criteria Inclusion criteria: children aged 4 to 16 years, inclusive, and weighing 13.5 to 80 kg (30 to 177 lb), partial seizures (including the subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures) that at the time of enrollment were inadequately controlled with one or two concomitant AEDs, diagnosis made at least 6 months before the screening visit, at least four partial seizures during the 4 weeks preceding the screening visit and at least four partial seizures during each 4-week interval of the 8-week baseline period.
Exclusion criteria: pregnant females; a treatable seizure etiology; epilepsy secondary to a progressive cerebral disease or any other progressively neurodegenerative disease; seizures too close together to accurately count; status epilepticus that required hospitalization during the 3 months before the screening visit; history of or the presence of pseudoseizures; current diagnosis of Lennox-Gastaut syndrome; a cardiovascular, respiratory, hepatic, renal, gastrointestinal, hematologic, oncologic, psychiatric, or progressive neurologic disorder likely to have an impact on the outcome of the trial.

Patient Characteristics Demographic and baseline characteristics (intent-to-treat population)

Variable	Levetiracetam, n=101	Placebo, n=97
% Male	53.5	47.4
% White	73.3	67.0
Age, median (range), y	10.4 (4–17)	9.7 (3–17)
% Receiving concomitant AEDs (in >10% of patients)		
Carbamazepine	34.7	38.1
Topiramate	28.7	32.0
Valproate	25.7	28.9
Lamotrigine	22.8	20.6
Oxcarbazepine	12.9	10.3
Partial seizure frequency, median (range)	4.7 (0–696)	5.3(0-467)

Recruitment Not reported.

Setting 60 centres in the United States and Canada.

Interventions/ Test/ Factor being investigated Levetiracetam up to 60mg/kg /day as adjunctive therapy to currently used AEDs.

Comparisons The comparison is between levetiracetam up to 60mg/kg/day and placebo as adjunctive therapy to currently used AEDs.

**Length of Study/
Follow-up**

22 weeks: 8 week baseline, 4 weeks titration and 10 weeks maintenance period.

**Outcome measures
studied**

Primary outcome: partial seizure frequency (including simple, complex, and secondarily generalized partial seizures) per week during treatment period. Secondary outcomes: responder rates, % reduction in partial seizure freq, % reduction by cat (>25% etc)

Results

Primary outcome

Levetiracetam resulted in a reduction in partial-onset seizure frequency per week, and % reduction over placebo during the treatment period was 26.8% (p=0.0002; 95% CI 14% to 37.6%).

The median percentage reduction from baseline during the treatment period in weekly partial seizure frequency was higher in the levetiracetam group compared with the placebo group (43.3% vs 16.3%; Kruskal–Wallis, p=0.0001).

Secondary outcomes

Categorical summary of percent reduction

Reduction from baseline in partial seizure frequency during treatment favored levetiracetam over placebo (Mantel–Haenszel, p=0.001), with 24.8% and 12.9% of levetiracetam-treated patients achieving reductions of 50% to less than 75% and 75% to less than 100%, compared with 14.4% and 4.1%, for placebo.

Absolute change in seizure frequency

The median absolute change from baseline in seizure frequency per week during the treatment period was -1.6 seizures/week in the levetiracetam group vs -0.7 seizures/week for placebo (Kruskal–Wallis, p 0.003).

Adverse events

Incidence (%) of treatment-emergent adverse events by COSTART body system and by individual adverse event*

	Levetiracetam, % (n=101)	Placebo, % (n= 97)
COSTART body system†		
Body as a whole	58.4	64.9
Digestive	36.6	38.1
Hematologic and lymphatic	5.9	2.1
Metabolic and nutritional	4.0	10.3
Nervous	58.4	47.7
Respiratory	30.0	28.9
Skin and appendages	9.9	13.4
Special senses	12.9	9.3
Urogenital system	9.9	9.3
Specific adverse event		
Somnolence	23	11
Accidental injury	17	10
Vomiting	15	13
Anorexia	13	8
Rhinitis	13	8
Hostility	12	6
Cough increased	11	7
Pharyngitis	10	8
Nervousness	10	2
Asthenia	9	3
Diarrhea	8	7
Personality disorder	8	7
Dizziness	7	2
Emotional lability	6	4
Pain	6	3
Agitation	6	1

* Adverse events had to occur in at least 5% of levetiracetam-treated patients and be more frequent than in placebo patients.

† Investigator term describing each adverse event was coded to a body system and preferred term using the COSTART (Coding Symbols for Thesaurus

of Adverse Reaction Terms) dictionary (version 5).

Five patients randomized to levetiracetam (5.0%) discontinued treatment because of an adverse event. Eight patients (7.9%) in the levetiracetam group and nine patients (9.3%) in the placebo group experienced a serious adverse event.

Safety and adverse effects

Most adverse events were mild to moderate.

Does the study answer the question?

Yes. The results demonstrated that levetiracetam was efficacious and well tolerated at a target dose of 60mg/kg/day when given as adjunctive therapy in pediatric patients with inadequately controlled partial seizures.

Effect due to factor in study?

Yes. The study had sufficient power to detect a 20% difference in seizure reduction between the placebo and levetiracetam groups.

Consistency of results with other studies?

Directly applicable to guideline population?

Those enrolled in the trial were children aged 4 to 16 years with partial seizures including the subtypes of simple, complex and partial seizures evolving to secondarily generalized seizures.

Internal Validity

Glauser TA;Nigro M;Sachdeo R;Pasteris LA;Weinstein S;bou-Khalil B;Frank LM;Grinspan A;Guarino T;Bettis D;Kerrigan J;Geoffroy G;Mandelbaum D;Jacobs T;Mesenbrink P;Kramer L;D'Souza J;

Adjunctive therapy with oxcarbazepine in children with partial seizures. The Oxcarbazepine Pediatric Study Group

Ref ID 4603

2000

Study Type Randomised Controlled Trial **Funding** Novartis Pharmaceuticals Corporation

Number of participant 267 patients were randomised; oxcarbazepine (OXC) = 138 and placebo = 129.

Inclusion/Exclusion Criteria Inclusion:8 partial seizures during the 56 day baseline phase, had serum sodium concentration of at least 130 mmol/l, positive EEG, no progressive lesion, no possibility of pregnancy. Exclusion: status during 6 months preceding; non-compliance; a CV, respiratory, hepatic, renal, GI, haematological, oncology, substance abuse, psychiatric or progressive neurologic disorder; participation in other trial of OXC

Patient Characteristics	OXC (n=138)	Placebo (n=129)
Sex		
Male	51%(70)	55%(71)
Female	49%(68)	45%(58)
Race		
White	87%(120)	87%(112)
Other	13%(18)	13%(17)
Age, y mean (range)	11%(3-17)	11%(3-17)
Weight, kg mean (range)	44%(16-130)	44%(16-89)

Recruitment Unknown

Setting Multi centre -47 centres

Interventions/ Test/ Factor being investigated Evaluate the safety and efficacy of OXC as adjunctive therapy in children 3-17 years of age with inadequately controlled partial seizures.

Comparisons OXC vs. placebo

Length of Study/ Follow-up 112 days

Outcome measures studied	Primary: percentage of reduction from baseline in partial seizure frequency per 28 days during double blind treatment Secondary: response to treatment and change in other seizure types
Results	Patients treated with OXC experienced a significantly greater median percent reduction from baseline in partial seizure frequency than patients treated with placebo (p=0.0001; 35% vs. 9% respectively). Forty one percent of patients treated with OXC experienced a 50% or greater reduction from baseline in partial seizure frequency per 28 days compared with 22% of patients treated with placebo (p=0.0005).
Safety and adverse effects	Ninety one percent of the group treated with OXC and 82% of the group treated with placebo report one or more adverse event; vomiting, somnolence, dizziness and nausea occurred more frequently in the group treated with OXC (twofold or greater)
Does the study answer the question?	OXC adjunctive therapy is safe, effective and well tolerated in children with partial seizures.
Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Multi - centre

Guberman A;Neto W;Gassmann-Mayer C;

Low-dose topiramate in adults with treatment-resistant partial-onset seizures

Ref ID 4747

2002

Study Type Randomised Controlled Trial **Funding** Industry : Johnson and Johnson Pharmaceutical

Number of participant 263 patients were enrolled. 171 were in Topiramate groups, and 92 to placebo.

Inclusion/Exclusion Criteria Age 18 to 65 years old, weigh >45 kg, had at least 3 partial-onset seizures, with or without secondary generalisation within the 4 week baseline. These seizures could not be clustered, patients had to be receiving Carbamazepine with and without another AED in stable doses for at least 30 days before entering the baseline phase. Women had to be postmenopausal or incapable of childbearing; women of childbearing potential had to be practising a medically acceptable methods of birth control.

Exclusion criteria: treatable cause of seizures, progressive neurological disorder, or primary generalised seizure. Documented history of status epilepticus during the past 3 months were also excluded.

Patient Characteristics Age, mean (range): Placebo: 36(18-67), Topiramate: 37 (18-64)
 Female (%): Placebo: 50%, Topiramate: 54%
 Time since diagnosis, year, median (range): placebo: 18 year (0.4 -42), Topiramate: 19 year (0.2 to 54)
 Carbamazepine dose, median (range): Placebo: 1200mg/day (200-1800), Topiramate: 100mg/day (100-2400)
 Number of AEDS on baseline (1AED/2AED): Placebo: 42%/58%, Topiramate: 45%/55%
 Baseline seizure type (simple partial/complex partial/secondary generalised): Placebo : 29%/74%/39%, Topiramate: 27%/77%/32%
 Monthly seizure frequency, median (range):
 Partial onset : Placebo: 7 (2-462), Topiramate: 7(2-184)
 Secondary generalised: Placebo: 0 (0-27), Topiramate: 0(0-37)
 Number of patients with secondary generalised seizures:: Placebo: 36 Topiramate :55

Recruitment	Not stated
Setting	Multicentre trial, mainly European centres
Interventions/ Test/ Factor being investigated	g/day, dose administered twice daily. In one group Topiramate was titrated to 200 mg/day over 8 weeks (25mg/day starting dose, with a 25mg/week increment) and in the other it was done over 4 weeks (50 mg/day starting dose with 50mg/week increment)
Comparisons	Active treatment vs. placebo addition to stabilised AED regimen
Length of Study/ Follow-up	12 weeks plus 4 weeks baseline.
Outcome measures studied	Primary outcome measure: median % reduction from baseline in monthly partial onset seizure frequency for the combine Topiramate groups vs. placebo Secondary outcome measure: percent of patients who were treatment responders(50% seizure reduction)
Results	<p>Proportion of seizure free participants: Week 1-12 (double blind period): Placebo:/91(2%) All topiramate:/168 (6%)**</p> <p>Week 9-12 (Maintenance period): Placebo:79/88(9%) All topiramate:30/150 (20%)**</p> <p>Proportion of patients experiencing at least a 50% reduction in seizure frequency (i.e. responders): Week 1-12 (double blind period): Placebo:22/91(24%) Topiramate 25/25: 33/85(39%)* Topiramate50/50:42/83** (51%) All topiramate:75/168 (45%)**</p> <p>Week 9-12 (Maintenance period): Placebo:29/88(33%) Topiramate 25/25:49/76(64%)** Topiramate50/50:38/74 (51%) * All topiramate:87/150 (58%)**</p> <p>Week 1-2 (early titration period): Placebo:27/91(30%) Topiramate 25/25: 30/85(35%)* Topiramate50/50:40/84 (48%) All topiramate:70/169 (41%) * p<0.05, **p=0.001</p> <p>Double blind phase: Proportion of patients experiencing at least a 50% reduction in seizure (secondary generalised) frequency (i.e. responders): Placebo : 12/36(34%) All topiramate:27/55 (50%) p=0.05</p> <p>Proportion of participants having treatment withdrawn due to adverse events: Placebo: 2/92 (2%) Topiramate 25/25: 7/85(8%) Topiramate 50/50:6/86(7%) All topiramate: 13/171(8%)</p> <p>Adverse events (≥ 10% incidence): Somnolence: Placebo: 8/92(9%) TPM25/25:13/85(15%) TPM50/50:12/86(14%) All topiramate:25/171 (15%) Paraesthesia: Placebo:2/92(2%) TPM25/25: 6/85(7%) TPM50/50: 9/86(10%) All topiramate:15/171 (9%) Nervousness: Placebo: 2/92(2%) TPM25/25: 9/85(11%) TPM50/50: 6/86(7%) All topiramate: 15/171 (9%) Anorexia: Placebo: 6/92(7%) TPM25/25: 7/85(8%) TPM50/50: 9/86(10%) All topiramate: 16/171 (9%)</p>
Safety and adverse effects	<p>In the TPM group, 45% of discontinuations occurred within the first 3 weeks - during the titration period.</p> <p>There were no significant difference between the two topiramate groups in terms of incidence of adverse events, time to onset of adverse events resulting in study</p>

discontinuation and in cumulative incidence rate of study drug discontinuations due to adverse events.

Mean body weight reduction was 1.9kg (2.6% of baseline) in topiramate group vs 0.1kg (1%) in placebo patients. Weight loss was occurred within the first two weeks and stabilised there after. One patient discontinued because of weight reduction.

Does the study answer the question?

Among adults with treatment resistant partial onset seizures, significantly more patients treated with topiramate(200mg/day) were treatment responders (at least 50% reduction in seizures) for partial seizures and secondary generalised seizures compared to patients receiving placebo.

Effect due to factor in study?

The study did not report sample size calculation and power.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in this study had treatment resistant partial onset seizures. Topiramate dose used was low - target maintenance dose was 200mg

Internal Validity

Guerreiro MM;Vigoni U;Pohlmann H;de M;Fejerman N;Antoniuk SA;Moore A;

A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy

Ref ID 4615

1997

Study Type Randomised Controlled Trial

Funding None reported

Number of participant 193 in total, 97 in oxcarbazepine, 96 in phenytoin

Inclusion/Exclusion Criteria

Inclusion: aged 5 to 18 years, newly diagnosed epilepsy with PS or GTCS, at least 2 seizures at least 48 hours apart in previous 6 months, no previous AED except for emergency treatment in previous 3 weeks
Exclusion: pregnancy or risk of becoming pregnant, history of status epilepticus, severe psychiatric illness or severe mental retardation, progressive neurological disorder, alcoholism or drug abuse, significant other organic disease

Patient Characteristics

In the oxcarbazepine group the mean age was 10.22 years (range 5 to 17 years), 41 out of 97 were male. 80 were Caucasian, 11 were black, 6 were of other race. The mean weight was 36.4 kg (range 16 to 72 kg). 73 patients had partial seizures with or without secondary generalised seizures, 22 had generalised seizures without partial onset and 2 had no main type of seizure. 18 patients had localization-related idiopathic syndrome, 7 had localization-related symptomatic syndrome, 46 had localization-related cryptogenic syndrome, 11 had generalised idiopathic syndrome, 6 had generalised cryptogenic or symptomatic syndrome, 2 had had generalised symptomatic syndrome, 6 had other syndromes and 1 was not classified.

In the phenytoin group the mean age was 10.85 years (range 6 to 17 years), 50 out of 96 were male. 80 were Caucasian, 6 were black, 10 were of other race. The mean weight was 40.7 kg (range 21 to 96 kg). 78 patients had partial seizures with or without secondary generalised seizures, 17 had generalised seizures without partial onset and 1 had no main type of seizure. 20 patients had localization-related idiopathic syndrome, 5 had localization-related symptomatic syndrome, 50 had localization-related cryptogenic syndrome, 11 had generalised idiopathic syndrome, 5 had generalised cryptogenic or symptomatic syndrome, 1 had had generalised symptomatic syndrome, and 4 had other syndromes.

Recruitment

Between 1991 and first quarter 1995

Setting

Brazil and Argentina

Interventions/ Test/ Factor being investigated	oxcarbazepine versus phenytoin.
Comparisons	Between treatments.
Length of Study/ Follow-up	No follow up reported.
Outcome measures studied	Number of patients who were seizure free, side effects, withdrawal
Results	<p>The trial was split into two periods, an 8 week titration and 48 week maintenance period. No concomitant AEDs were allowed. During the titration period patients received 150 mg oxcarbazepine or 50 mg phenytoin, this was gradually increased depending upon response, there was no fixed titration schedule. After 8 weeks patients were on daily doses of 450 to 2400 mg oxcarbazepine or 150 to 800 mg phenytoin, this dose was continued for the maintenance period. However this dose could be changed according to response.</p> <p>161 patients reached the maintenance period, of these 158 had at least 1 seizure assessment during the maintenance period and were therefore included in the results</p> <p>Number of patients who were seizure free: In the oxcarbazepine group 49 out of 81 were seizure free compared to 46 out of 77 in the phenytoin group</p> <p>In the oxcarbazepine group 60% of patients with partial seizures (with or without secondary generalised seizures) were seizure free compared to 62% of patients with partial seizures (with or without secondary generalised seizures) in the phenytoin group</p> <p>In the oxcarbazepine group 59% of patients with generalised seizures (without partial onset) were seizure free compared to 54% of patients with generalised seizures (without partial onset) in the phenytoin group</p> <p>Withdrawal: In total 24 patients withdrew from the oxcarbazepine group compared to 34 in the phenytoin group. In the oxcarbazepine group 8 patients withdrew due lost to follow up, 2 due to adverse events, 6 due to non-compliance, 4 due to unsatisfactory therapeutic effect, 3 due to protocol violation and 1 due to concomitant illness In the phenytoin group 9 patients withdrew due lost to follow up, 14 due to adverse events, 5 due to non-compliance, 3 due to unsatisfactory therapeutic effect, 2 due to protocol violation and 1 due to discontinuations at baseline</p> <p>Side effects: In the oxcarbazepine group 79 out of 96 had at least 1 adverse event compared to 84 out of 94 in the phenytoin group</p>
Safety and adverse effects	In the oxcarbazepine group 79 out of 96 had at least 1 adverse event compared to 84 out of 94 in the phenytoin group. In the oxcarbazepine group 2 patients withdrew due to adverse events compared to 14 in the phenytoin group.
Does the study answer the question?	There was no significant difference in the number of patients becoming seizure free between the oxcarbazepine group and the phenytoin group. More patients in the phenytoin group experienced side effects and more patients withdrew from the phenytoin group due to adverse events compared to the oxcarbazepine group.
Effect due to factor in study?	No details of allocation concealment.
Consistency of results with other studies?	
Directly applicable to guideline population?	Had to impute the figures for partial seizures as partial and generalised.
Internal Validity	

Study Type Randomised Controlled Trial

Funding UCB Group, Research Triangle Park, NC, USA, sponsored and funded the trial.

Number of participant n=485 (n=163 in placebo group, n=163 in lacosamide 200mg/d group and n=159 in lacosamide 400mg/d group).

Inclusion/Exclusion Criteria Inclusion criteria: age 16 to 70 years, diagnosis of partial-onset seizures with or without secondary generalizations, seizures for at least 2 years, therapy with at least two AEDs, at least four partial -onset seizures per 28 days on average, no seizure-free period longer than 21 days during the 8 week period prior to enrollment. Exclusion criteria: pregnant, breast-feeding or childbearing potential, history of alcohol or drug abuse, medical condition that might jeopardize the trial.

Patient Characteristics Demographic characteristics of patients receiving trial medication (safety set)

	Placebo	200 mg/day	Lacosamide 400mg/day	
Total	(n=163)	n=163	n=159	
n=485				
Age, year				
Mean ± SD	38.5 ± 10.93	36.9 ± 11.70	37.9 ± 12.96	37.8 ± 11.88
Range	17–63	16–66	16–70	
Sex, n (%)				
Male	91 (55.8)	90 (55.2)	69 (43.4)	250 (51.5)
Female	72 (44.2)	73 (44.8)	90 (56.6)	235 (48.5)
Race, n (%)				
Caucasian	162 (99.4)	162 (99.4)	157 (98.7)	481 (99.2)
Black	0 (0)	1 (0.6)	0 (0)	1 (0.2)
Asian	1 (0.6)	0 (0)	2 (1.3)	3 (0.6)
Weight, kg (mean ± SD)	74.7 ± 17.06	74.9 ± 16.93	72.2 ± 16.90	74.0 ± 16.97
BMI, kg/m ² (mean ± SD)	25.9 ± 5.01	25.2 ± 4.79	25.3 ± 5.09	25.4 ± 4.96
Mean time since diagnosis, year (mean ± SD)	21.1 ± 12.23	22.9 ± 12.30	22.8 ± 13.15	22.3 ± 12.56
Seizure classification, n (%)				
Simple partial-onset seizures	61 (37.4)	67 (41.1)	58 (36.5)	186 (38.4)
Complex partial-onset seizures	138 (84.7)	142 (87.1)	146 (91.8)	426 (87.8)
Partial-onset seizures with secondary generalization	130 (79.8)	125 (76.7)	127 (79.9)	382 (78.8)

A total of 87% of patients were taking at least two AEDs, with 37% of these taking three AEDs in addition to their assigned trial medication.

Recruitment Not reported.

Setting 75 sites worldwide inc. UK.

Interventions/ Test/ Factor being investigated Lacosamide 200mg/day and lacosamide 400mg/day as adjunctive therapy.

Comparisons The comparisons are between the lacosamide doses (200mg and 400mg) and placebo.

Length of Study/ Follow-up 24 weeks: 8 week baseline, 4 week titration and 12 week maintenance period.

Outcome measures studied Primary outcome: seizure freq (ITT pop) 1) change in seizure freq per 28 days from baseline to maintenance phase 2) 50% responder rate per 28 days. Secondary: % change in seizure freq per 28 days and seizure-free for those completing maintenance phase.

Results Primary outcome

Median percent reduction (ITT population) per 28 days
The median percent reduction in seizure frequency per 28 days from baseline to the maintenance period was 20.5% for placebo, 35.3% for lacosamide 200 mg/day (p=0.02, diff from placebo), and 36.4% for lacosamide 400 mg/day (p=0.03, diff from placebo).

Responder rate (ITT population)
The 50% responder rate for lacosamide 400 mg/day (40.5%) was statistically significant (p = 0.01) over placebo (25.8%). Although not statistically significant (p = 0.07), the 50% responder rate for lacosamide 200 mg/day (35.0%) was numerically higher than placebo.

Secondary outcomes

Seizure-free days (those completing the maintenance period)

Among patients completing the maintenance period, 5 (3.6%) of 137 patients in the lacosamide 200 mg/day group and 3 (2.4%) of 123 patients in the lacosamide 400 mg/day group were seizure-free throughout the 12-week maintenance period compared with 3 (2.1%) of 143 in the placebo group. A statistically significant increase of 5% in the percentage of seizure-free days over placebo during the maintenance period was observed for lacosamide 400 mg/day (p = 0.01; 95% CI 1.5, 8.5).

Adverse events

Incidence of treatment-emergent adverse events occurring in at least 5% of patients in any treatment group during the treatment period (titration plus maintenance periods)

Adverse event	Placebo	200mg/d	Lacosamide 400mg/d	Total
	n=163 n(%)	n=163 n(%)	n=159 n(%)	n=322 n(%)
Dizziness	8 (4.9)	17 (10.4)	25 (15.7)	42 (13.0)
Headache	12 (7.4)	18 (11.0)	13 (8.2)	31 (9.6)
Diplopia	2 (1.2)	13 (8.0)	16 (10.1)	29 (9.0)
Nausea	2 (1.2)	9 (5.5)	13 (8.2)	22 (6.8)
Vertigo	3 (1.8)	11 (6.7)	10 (6.3)	21 (6.5)
Fatigue	6 (3.7)	8 (4.9)	10 (6.3)	18 (5.6)
Nasopharyngitis	6 (3.7)	8 (4.9)	10 (6.3)	18 (5.6)
Coordination abnormal	1 (0.6)	7 (4.3)	10 (6.3)	17 (5.3)
Vomiting	3 (1.8)	5 (3.1)	9 (5.7)	14 (4.3)

Overall, 42 patients (8.7%) discontinued participation in the trial during the treatment period because of AEs: 8 patients (4.9%) randomized to placebo, 10 (6.1%) to lacosamide 200 mg/day, and 24 (15.1%) to 400 mg/day.

The overall percentage of patients experiencing serious AEs (SAEs) during the

treatment period was greater in the lacosamide treatment groups compared to placebo (3.7%, 8.0%, and 9.4% of patients in the placebo, lacosamide 200 mg/day, and 400 mg/day treatment groups, respectively).

Safety and adverse effects

The most clearly dose related treatment emergent adverse events include dizziness, nausea and vomiting.

Does the study answer the question?

Yes. This is a well conducted effectiveness study. Lacosamide 200 mg/day and 400 mg/day significantly reduced seizure frequency in patients with uncontrolled partial-onset seizures when added to one to three concomitant AEDs.

Effect due to factor in study?

Yes. The study was sufficiently well powered to detect differences between lacosamide and placebo.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients enrolled in this study had a diagnosis of uncontrolled partial-onset seizures.

Internal Validity

Kalviainen R;Aikia M;Mervaala E;Saukkonen AM;Pitkanen A;Riekkinen PJ;

Long-term cognitive and EEG effects of tiagabine in drug-resistant partial epilepsy

Ref ID 4689

1996

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant In double blind phase: 20 placebo and 17 tiagabine (TGB). In the open label phase 25 TGB.

Inclusion/Exclusion Criteria Inclusion: Adults, ages 18-75; male and female with partial seizures refractory to 1-3 AEDs

Patient Characteristics

	Double blind phase		Open label phase
	Placebo	TGB	TGB
Gender			
Men	10	7	10
Women	10	10	15
Age, y			
Mean (SD)	40(14)	37(9)	37(10)
Full Scale IQ			
Mean (SD)	88(20)	82(18)	84(22)

Recruitment Unknown

Setting Finland

Interventions/ Test/ Factor being investigated The long-term effects of tiagabine on cognition and EEG in 37 patients with partial epilepsy.

Comparisons TGB vs. placebo in double blind phase; open label phase is TGB only

Length of Study/ Follow-up 12 week baseline period during which cognitive testing and EEG were performed to all patients. 12 week fixed dose period after which second cognitive testing and EEG were performed. Further 6-12 months and 18-24 months open label with two more evaluation

Outcome measures studied Primary: Cognitive function as measured in a battery of 10 neuropsychological tests and scored by a blinded neuropsychologist; EEG tracings

Results	There were no differential changes across the TGB and placebo groups from the end of the baseline to the end of the drug treatment period in any of the cognitive measures. There were also no changes in cognitive function during long term TGB treatment at higher doses after 6-12 months. There was no deterioration seen in the 18-24 month phase but there was improvement in the List learning test and in auditory reaction times. There was no new rhythmic slow-wave activity or other constant, new abnormalities on EEG during longer follow-up with successful treatment on higher doses after 6-12 months (mean 65.7 mg/day, range 30-80 mg/day) and after 18-24 months (mean dose 67.6 mg/day, range 24-80 mg/day).
Safety and adverse effects	Reported separately in multicentre evaluation of TGB by the Northern European tiagabine Study Group
Does the study answer the question?	In this study the neuropsychological and neurophysiological evaluation did not indicate any adverse effects of TGB .
Effect due to factor in study?	This is a small study and should be repeated
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Validity and reliability of neuro tests not stated

Kalviainen R;Brodie MJ;Duncan J;Chadwick D;Edwards D;Lyby K;

A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. Northern European Tiagabine Study Group

Ref ID 4761

1998

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant A total of 77 patients were randomised to treatment in each arm.

Inclusion/Exclusion Criteria Inclusion: Male and female patients aged between 16 and 75 years with history of partial seizures refractory to one to three AEDs.
Exclusion: pseudo seizures, progressive CNS disease or serious medical disorder requiring frequent medication changes. Also, a hx of drug or alcohol abuse and poor compliance were reasons for exclusion.

Patient Characteristics	TGB, n=77	Placebo, n=77
Age (years)	36.4 (18.7-59.7)	36.0 (17.9-71.3)
Sex		
Female	34 (44%)	30 (39%)
Male	43 (56%)	47 (61%)
Years with epilepsy	24.9 (2-52)	23.0 (1-49)

Study population was entirely Caucasian.

Recruitment Unknown

Setting Multicentre - Finland, UK, Denmark

Interventions/ Test/ Factor being investigated A three-times daily regimen of tiagabine was evaluated as add-on therapy in 154 adult patients with refractory partial seizures.

Comparisons Treatment with fixed dose vs. placebo

Length of Study/ Follow-up 4 week titration period; 12 week fixed dose period

Outcome measures studied	Primary: proportion of responders (50% or more reduction in 4 weekly seizure rate). Secondary. Median percentage reduction in the 4 weekly seizure rate and the number of seizure free days attained.
Results	During the 12-week fixed-dose period, there was a significant reduction in the median 4-weekly seizure rate for all partial seizures and simple partial seizures (P < 0.05 in each case). Furthermore, the proportion of patients with a reduction of 50% or more in all partial seizures was higher in the tiagabine group than in the placebo group (14 versus 6%), though the difference did not achieve statistical significance. The difference with respect to simple partial seizures was significant (21 versus 6%, P < 0.01). The percentage of patients achieving an increase of at least 50% in the proportion of days free of all partial seizures was significantly greater in the tiagabine group compared to placebo (14 versus 4%, P<0.01).
Safety and adverse effects	Tiagabine did not appear to influence the plasma concentrations of other concomitant antiepileptic drugs and was generally well tolerated, with most drug-related adverse events being mild or moderate in severity. The most common adverse events were dizziness, asthenia, headache and somnolence. Adverse event incidence was similar between tiagabine and placebo groups, except for dizziness which was more common with tiagabine (29 versus 10%, P < 0.01). Tiagabine had no significant effects on laboratory tests or vital signs.
Does the study answer the question?	The present study shows that tiagabine, at a dose of 10 mg administered three-times daily, which is at the lower end of the usual recommended dose range (30-50 mg/day, tiagabine base), is generally well tolerated and demonstrates efficacy for the treatment of refractory partial seizures
Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See Grade
Internal Validity	Multi centre; high discontinuation rate in TGB

Koeppen D;Baruzzi A;Capozza M;Chauvel P;Courjon J;Favel P;Harmant J;Lorenz H;Oller FV;Procaccianti G;,
 Clobazam in therapy-resistant patients with partial epilepsy: a double-blind placebo-controlled crossover study
 Ref ID 4645 1987

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant 129 patients began this cross over study

Inclusion/Exclusion Criteria Inclusion: Patients with refractory epilepsy who were on basic antiepileptic medication
 Exclusion: Not addressed

Patient Characteristics Age: 33 +/- 12
 Gender
 Male 56
 Female 73

Recruitment Not discussed

Setting Five European centres

Interventions/ Test/ Factor being investigated Clobazam in therapy resistant patients with partial epilepsy

Comparisons Clobazam vs. placebo

Length of Study/ Follow-up	7 months
Outcome measures studied	Primary: Difference in seizure reduction Secondary: EEG signs, mood ratings and global impressions
Results	The difference in seizure reduction between Clobazam and placebo was significant ($p < 0.05$). Nineteen percent of patients receiving Clobazam became seizure free during the maintenance dose period compared to none in the placebo group. EEG signs, mood ratings and global impressions also indicated therapeutic effects of Clobazam.
	Withdrawal due to adverse events: Clobazam: 0/129 Placebo: 3/129
	Withdrawal due to lack of adverse events: Clobazam: 4/129 Placebo : 8/129
Safety and adverse effects	The most frequent adverse reactions to Clobazam were drowsiness and dizziness.
Does the study answer the question?	There is evidence of the therapeutic value of Clobazam as adjunct medication in therapy resistant partial seizures.
Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Multi-centre

Korean Topiramate Study Group

Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. Korean Topiramate Study Group

Ref ID 4746

1999

Study Type Randomised Controlled Trial **Funding** Janssen Korea Ltd.

Number of participant n=91 in topiramate arm and n=86 in placebo arm.

**Inclusion/Exclusion
Criteria** Patients were eligible if: aged 16 to 65 years; well-established partial epilepsies; treatment with 1 or 2 AEDs; at least 2 seizures per 4 wks during 3 consecutive 4-wk periods.
Excluded if: history of pseudo seizures; systemic or neurologic disease; history of drug or alcohol abuse; history of non-compliance; use of drugs known to cause nephrolithiasis.

Patient Characteristics

	Topiramate n=91	Placebo n=86	Total n=177
Gender			
Men	47	48	95
Women	44	38	81
Age			
Mean (+/-)	29.58(7.80)	29.77(8.71)	
Weight (kg)			
Mean (+/-)	63.7(10.9)	63(10.5)	

Seizure types		
Simple partial	11(12.1%)	5(5.8%)
Complex partial	70(76.9%)	72(83.7%)
Secondary generalization		
tonic-clonic	31(34.1%)	39(45.4%)
Seizure freq (episodes per wk)		
Median	5.6	5.6

Recruitment

Not reported.

Setting

8 clinical centers in Korea. No further info.

**Interventions/ Test/
Factor being
investigated**

Topiramate vs. placebo as adjunctive therapy.

Comparisons

Comparisons made between topiramate and placebo when used in addition to one or two currently prescribed antiepileptic drugs.

**Length of Study/
Follow-up**

18 weeks post randomisation.

**Outcome measures
studied**

Primary outcome: Median seizure frequency reduction rate (MSFRR)
Secondary outcomes: responder rate; seizure-free rate; global evaluations by patient and physician; adverse events (AEs).

Results

Primary outcome	Topiramate (n=89)	Placebo (n=85)	p-value
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Median seizure freq
(episodes per 4wks)

Baseline phase	5.6	5.6	
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Experimental phase	2.4	5.1	0.0001
MSFRR	51.3%	9.1%	0.0001

Secondary outcomes

Responder rate	45(50.6%)	11(12.9%)	0.04
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Global eval physician Excellent or good	46(60.5%)	19(24.7%)	
Global eval pts Excellent or good	50(65.8%)	19(24.7%)	

Incidence of AEs	74(81.3%)	42(48.8%)	0.001
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Anorexia	19(20.9%)	5(5.8%)	0.003
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Abdominal. Discomfort	19(20.9%)	2(2.3%)	0.001
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Dizziness	18(19.8%)	18(21%)	0.85
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Somnolence	18(19.8%)	8(9.3%)	0.85
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Nausea/vomiting	15(16.5%)	7(8.1%)	0.09
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Headache	10(11%)	6(7.0%)	0.52
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Amblyopia	10(11%)	4(4.7%)	0.12
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Subgroup analysis

Type of seizure	Median seizure frequency reduction rate (MSFFR)		
	Topiramate	Placebo	p value
SPMS	(n=9) 87.5	(n=4) 72.9	0.94
CPS	(n=70) 49.4	(n=72) -14.3	0.0001
GTCS	(n=28) 100	(n=35) 40.26	0.25

SPMS=simple partial motor seizure, CPS=complex partial seizure, GTCS=secondarily generalized tonic-clonic seizure.

**Safety and adverse
effects**

The AEs more frequently found in the topiramate group compared with the placebo group were abdominal discomfort or pain, anorexia, weight loss, speech disturbance, psychomotor slowing, and somnolence, with abdominal discomfort or pain and

anorexia being the most common AEs. Severe AEs are not common. Rapid dose escalation increases rate of AEs.

Does the study answer the question?

Yes.
Topiramate appears to be effective as add on therapy in medically intractable partial epilepsies. However, the incidence of adverse events is high.

Effect due to factor in study?

Yes, it appears that the overall effect seen in this study is due to the add-on effect of topiramate. However, there is insufficient reporting of randomisation methods and concealment of allocation.

Consistency of results with other studies?

Directly applicable to guideline population?

The comparisons used here (topiramate vs. placebo as adjunctive therapy) are relevant to the question in this guideline as is the study population.

Internal Validity

Labiner DM;Ettinger AB;Fakhoury TA;Chung SS;Shneker B;Tatum Iv WO;Mitchell MJ;Vuong A;Hammer AE;Messenheimer JA;

Effects of lamotrigine compared with levetiracetam on anger, hostility, and total mood in patients with partial epilepsy

Ref ID 40

2009 Mar

Study Type Randomised Controlled Trial **Funding** GlaxoSmithKline Research and Development.

Number of participant n=132 in lamotrigine group and n=136 in levetiracetam group were randomised to treatment.

Inclusion/Exclusion Criteria Inclusion criteria: age >=16: IQ >=80, confident diagnosis of epilepsy, two partial seizures in previous 6 months, monotherapy with carbamazepine or phenytoin or polytherapy that included carbamazepine or phenytoin and one other AED. Exclusion criteria: taking antidepressants or antipsychotic or clinically significant comorbidity that could prevent completion of questionnaires.

Patient Characteristics	Lamotrigine n=132	Levetiracetam n=136
Mean Age (SD)	38.3(12.3)	39.1(11.6)
Female n(%)	63(48)	56(41)
Race n(%)		
Asian	0(0)	2(1)
Black	22(17)	23(17)
Hispanic	11(8)	11(8)
White	94(71)	99(73)
Other	5(4)	1(<1)
Mean (SD) age at first seizure.	22.2(14.3)	21.2(15.6)
Mean (SD) seizures in past 8 weeks.	12.0(37.7)	18.6(51.8)
Epilepsy classification n(%)		
Any seizure type	132(100)	136(100)
Simple partial	37(28)	52(38)
Complex partial	110(83)	97(71)
Partial evolving to secondarily generalized.	63(48)	82(60)
Gen. tonic-clonic	9(7)	15(11)

Recruitment Not reported.

Setting 62 North American study sites.

Interventions/ Test/ Factor being investigated lamotrigine as adjunctive therapy is compared with levetiracetam as adjunctive therapy. Lamotrigine is the intervention drug and levetiracetam is the control group.

Comparisons The comparison is between lamotrigine and the active treatment levetiracetam. Both are used in the trial as adjunctive therapy. Patients are already taking a stable dose of at least one AED.

Length of Study/ Follow-up Approximately 22 weeks. Up to 2 weeks for the screening phase, 8 weeks for the drug escalation phase and 12 weeks maintenance phase.

Outcome measures studied Primary measure is the change from baseline to end of maintenance phase in the Anger-Hostility subscale of the Profile of Mood States (POMS). Secondary outcomes included a no. of depression outcomes. Also seizure frequency and clinical global improvement.

Results Primary outcome: change in score from baseline to end of treatment in Anger-Hostility subscale of Profile of Mood states (POMS).

	Lamotrigine (n=125)	Levetiracetam (n=126)	p value
Baseline score Anger-Hostility Mean (SD).	10.6(9.0)	9.1(8.7)	
Mean change (SD)	-2.0(8.2)	-0.3(8.4)	0.024
Seizure frequency			
Median % decrease	60	65	0.501
Pts showing any improvement in CGI- %	89	85	NR
Adverse events			
% patients >=1 event	82	85	
AEs leading to discontinuation			
% patients	11	18	
Most common AEs as % of AEs			
Headaches	32	25	
Dizziness	13	15	
Nausea	11	10	

No significant differences were observed for CGI scores at end of maintenance phase.
NR=Not reported. CGI=Clinical Global Improvement.

Safety and adverse effects The most common adverse events were headache, dizziness and nausea. 11% of patients in the lamotrigine and 18% in the levetiracetam groups discontinued because of AEs.

Does the study answer the question? Yes. The study sets out to measure efficacy and quality of life from adjunctive treatment with lamotrigine.

The authors conclude that lamotrigine significantly improved Anger-Hostility subscale scores relative to adjunctive levetiracetam in patients with partial seizures at the end of 20 weeks. However, it is unclear how clinically significant the changes are. There were no significant differences between groups with regard to the efficacy outcome (seizure frequency) or the clinical global improvement (CGI) scores at study end.

Effect due to factor in study? No. For the primary outcome (change in Anger-Hostility subscale) it is unclear how clinically significant the changes are. The change from baseline to study end for the lamotrigine group was 2 points compared to -0.3 for the control group. The study was powered to detect a difference of 4 points (>=90% power) yet they acknowledge that the threshold for clinically meaningful change in this scale has not been defined.

Efficacy outcome (seizure frequency) and clinically global improvement (CGI) scores were not significantly different between the two groups at study end.

Consistency of results with other studies?

Directly applicable to guideline population?

This study enrolled a population which is similar to the patient population of interest in this guideline. Patients were only enrolled in the study if they had partial seizures.

Internal Validity

Lee BI;Yi S;Hong SB;Kim M;Lee SA;Lee SK;Shin D;Kim JM;Song HK;Heo K;Lowe W;Leon T;

Pregabalin add-on therapy using a flexible, optimized dose schedule in refractory partial epilepsies: A double-blind, randomized, placebo-controlled, multicenter trial

Ref ID 1032

2009

Study Type Randomised Controlled Trial **Funding** Pfizer Inc.

Number of participant n=178 (n=119 in the PGB group and n=59 in the placebo group).

Inclusion/Exclusion Criteria Inclusion criteria: aged ≥ 18 years and weighing ≥ 40 kg with a diagnosis of partial seizures (simple, complex, or SGTC); at least one AED at the maximally tolerable dose and had to be taking one to three AEDs. Additional inclusion criteria included a minimum of four seizures that had occurred over at least 2 days during a 6-week baseline period with no 28-day seizure-free period.
Exclusion criteria: patients with absence seizures, Lennox-Gastaut syndrome, status epilepticus within the previous year, clinically relevant medical illness, electrocardiography (ECG) abnormalities, or significant psychiatric disorders.

Patient Characteristics

	Pregabalin n=119	Placebo n=59
Sex: male (%)	52 (44)	34 (58)
Age (years): mean (SD)	33.3 (9.7)	35.1 (8.8)
Height (cm): mean (SD)	163.8 (8.1)	164.1 (8.2)
Weight (kg): mean (SD)	62.2 (10.4)	64.0 (12.9)
Duration of illness (year) Mean (range)	16.5 (0.3–48.0)	18.0 (0.7–48.1)
Etiology of epilepsy		
Symptomatic (%)	55 (46.2)	31 (52.5)
Cryptogenic (%)	64 (53.8)	28 (47.5)
Seizure types		
Simple partial (%)	66 (55.5)	30 (50.8)
Complex partial (%)	93 (78.2)	49 (83.1)
SGTC (%)	49 (41.2)	26 (44.1)
Partial w/o generalization (%)	116 (97.5)	59 (100)
Concomitant AEDs (%)		
One	8 (6.7)	3 (5.1)
Two	34 (28.6)	12 (20.3)
Three	76 (63.9)	44 (74.6)
Four	1 (0.8)	0
Seizure frequency per 28 days		
Mean (SD)	13.2 (14.5)	13.2 (19.2)
Median (range)	6.7 (2.4–69.3)	5.2 (2.5–91.8)

Recruitment Not reported.

Setting 9 centres in Korea.

Interventions/ Test/ Factor being investigated Pregabalin in a flexible dose (up to 600mg/day).

Comparisons Comparison is between PGB (flexible dose) and placebo as add-on therapy to currently used AEDs.

Length of Study/ Follow-up 19 weeks: 6-week baseline phase, 12-week treatment phase, and 1 week taper period.

Outcome measures studied

The primary efficacy outcome was seizure frequency change expressed as the response ratio (RRatio). Secondary outcomes: responder rate, PCH in 28 day seizure rate, % SGTC responders, QoL measures.

Results

Primary outcome

Response ratio

The Rratio least mean was -35.8 for the PGB group and -23.2 for the placebo group, corresponding to 52.7% and 37.7% seizure frequency reduction, respectively. The estimated treatment difference in RRatio between the two groups was -12.6 (95% CI: -22.7 to -2.5), which was statistically significant (p = 0.015).

Secondary analysis

Response rate by seizure type

Rratio defined by seizure types favoured PGB in all types of seizure; however, the result was statistically significant only in “complex partial seizures” and “partial seizure without generalization”. (Data presented only in figures.)

Secondary outcomes

	Pregabalin	Placebo	p-value
Responder rate (%)			
All seizures ^a	55 (46.2)	19 (32.2)	p = 0.068b
SGTCs	28 (62.2)	20 (80.0)	p = 0.143b
PCH in 28 days seizure rate			
Mean (median)	-38.3 (-48.2)	-20.3 (-32.4)	p = 0.012d
95% CI for median	-53.1 to -36.5	-44.1 to -11.9	
Seizure free rate			
Double-blind phase (%)	5 (4.2)	2 (3.4)	p = 1.00e
Any 28-day period (%)	51 (43)	22 (37)	p = 0.52e
Change in number of SFD per 28 days			
RDB:BL (95% CI) *	1.09 (1.07 to 1.10)	1.05 (1.03 to 1.08)	
RDB:BL of PGB/Placebo (95% CI)*	1.03 (1.01 to 1.06)		

SGTC, secondarily generalized tonic-clonic seizures; PCH, percent change; CI, confidence interval; SFD, seizure free days.

*Ratio of ratios of change in number of SFD per 28 days from baseline to double-blind phase (pregabalin-RDB:BL/placebo-RDB:BL).

	Pregabalin	Placebo	p-value
HAD-A			
Baseline score (SD)	8.23 (3.87)	8.41 (3.67)	
Week-12 score (SD)	7.87 (3.96)	7.69 (3.97)	
ANCOVA of week-12 score:			
LS mean (SE)	7.91 (0.32)	7.56 (0.44)	
Difference in LS means (95% CI)	0.35 (-0.70 to 1.41)		0.507
HAD-D			
Baseline score (SD)	9.29 (3.65)	9.02 (3.85)	
Week-12 score (SD)	8.82 (4.16)	7.69 (3.89)	
ANCOVA of week-12 score:			
LS mean (SE)	8.71 (0.33)	7.79 (0.46)	
Difference in LS means (95% CI) ^a	0.92 (-0.16 to 2.00)		0.095
SIS			
Baseline SIS (SD)	2.06 (2.09)	2.21 (2.36)	
Endpoint SIS (SD)	1.67 (2.00)	2.22 (2.51)	
ANCOVA of endpoint SIS:			
LS mean (SE)	1.62 (0.13)	2.07 (0.18)	
Difference in endpoints SIS (95% CI) ^a	-0.45 (-0.87 to -0.02)		0.039
QOLIE-31			
Baseline score	48.0 (7.96)	49.0 (9.08)	
Week-12 score	50.4 (8.45)	49.3 (8.31)	
ANCOVA of week-12 score:			

LS mean (SE)	50.7 (0.73)	49.2 (1.01)
Difference in endpoints (95% CI) ^a	1.4 (-1.0 to 3.8)	0.245

95% CI: 95% confidence interval; HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; SIS, sleep interference scale (scores) from Daily Sleep Interference Scale; QOLIE-31, quality of life in epilepsy-31 questions.

^aDifference between the pregabalin group and the placebo group; except for QOLIE-31, negative value indicated a result favoring pregabalin.

Adverse events

	Pregabalin n=119		Placebo n=59	
	All causality	Treatment related	All causality	Treatment related
Dizziness	46 (38.7)	42 (35.3)	6 (10.2)	5 (8.5)
Somnolence	26 (21.8)	26 (21.8)	3 (5.1)	3 (5.1)
Weight increase	14 (11.8)	14 (11.8)	2 (3.4)	2 (3.4)
Fatigue	11 (9.2)	11 (9.2)	3 (5.1)	3 (5.1)
Headache	9 (7.6)	6 (5.0)	7 (11.9)	6 (10.2)
Increased appetite	6 (5.0)	5 (4.2)	1 (1.7)	1 (1.7)
Tremor	6 (5.0)	6 (5.0)	0	0
Constipation	5 (4.2)	5 (4.2)	0	0
Coordination abnormal	5 (4.2)	4 (3.4)	0	0
Vision blurred	3 (2.5)	3 (2.5)	1 (1.7)	1 (1.7)
Dyspepsia	4 (3.4)	3 (2.5)	5 (8.5)	2 (3.4)
Paraesthesia	4 (3.4)	3 (2.5)	0	0
Convulsion	3 (2.5)	3 (2.5)	1 (1.7)	1 (1.7)
Nasopharyngitis	4 (3.4)	0	4 (6.8)	0
Memory impairment	3 (2.5)	0	0	0
Insomnia	1 (0.8)	1 (0.8)	5 (8.5)	2 (3.4)
Sleep disorder	3 (2.5)	3 (2.5)	2 (3.4)	1 (1.7)

n=7 (5.9%) patients in the PGB group discontinued because of adverse events and n=0 in the placebo group.

Safety and adverse effects

Weight gain was reported as AEs in 14 patients (11.8%) taking PGB compared with 2 patients (3.5%) of the PLC group; however, post hoc analysis indicated that a significant weight gain, defined as "≥7% of baseline body weight gain," was found in 29 patients (24.8%) of the PGB group and in only 2 patients (3.5%) of the placebo group.

Does the study answer the question?

Yes. PGB was effective as add-on treatment in an Asian population with refractory partial-onset seizures.

Effect due to factor in study?

Yes. Sample size was derived from a power calculation which was based on results from previous PGB studies.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in this study had a diagnosis of partial seizures.

Internal Validity

Lindberger M;Alenius M;Frisen L;Johannessen SI;Larsson S;Malmgren K;Tomson T;

Gabapentin versus vigabatrin as first add-on for patients with partial seizures that failed to respond to monotherapy: a randomized, double-blind, dose titration study. GREAT Study Investigators Group. Gabapentin in Refractory Epilepsy Add-on Treatment

Ref ID 4730

2000

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant 102 total; 35 patients in Gabapentin (GBP) group and 44 in Vigabatrin (VGB) group.

Inclusion/Exclusion Criteria
 Inclusion: Refractory partial epilepsy with no more than two AED monotherapy regimens.
 Exclusion: status within 6 months before study; progressive CNS disease; psychosis; severe liver or renal disease; pregnancy or nursing; treatment with phenytoin, antipsychotic or antidepressant drugs or antacids at the time of inclusion.

Patient Characteristics

	GBP (n=50)	VGB (n=52)
Gender		
Men	28(56%)	23(44%)
Women	22(44%)	29(56%)
Age, y		
Median (range)	34.5(13-68)	33(14-56)
Weight (kg)		
Median (range)	77.5(53-135)	69.0(46-104)
Duration of epilepsy, m		
Median (range)	3.5(0-36)	9.5(0-43)

Recruitment Unknown

Setting Nordic countries

Interventions/ Test/ Factor being investigated The efficacy and safety of gabapentin and vigabatrin as first-line add-on treatment in patients with partial epilepsy.

Comparisons Gabapentin vs. vigabatrin as first-line add-on treatment in patients with partial epilepsy.

Length of Study/ Follow-up 8 week baseline; maximum treatment period at each dosage level was 8 weeks. Dosage changes were allowed after a 4 week period of receiving each dosage level if the patient had experienced seizures or intolerable side effects

Outcome measures studied Primary outcome: Improvement rate defined as the proportion of patients with a reduction in seizure frequency of at least 50% during the 8 week evaluation period compared with baseline. Secondary outcomes: seizure reduction rate, responder rate.

Results

ITT population	GBP (n=50)	VGB (n=52)	Estimated difference	95%CI
Improvement rate	24%(48)	29%(56)	-0.08	[-0.27;0.12]
Seizure reduction	27%(54)	34%(65)	-0.10	[-0.29;0.09]
Responder rate	13%(26)	18%(35)	-0.11	[-0.28;0.07]

Withdrawal due to adverse events: VGB 7/52; GBP 7/50.

Safety and adverse effects The recruitment was stopped when it became apparent that vigabatrin could induce visual field defects. One patient taking VGB developed agitative depression and one had weight gain. 38 (76%) of patients in the GBP group and 45 (86.5%) in the VGB group had one or more adverse events. The five most common adverse events were tiredness, dizziness, respiratory infection, headache and diarrhoea.

Does the study answer the question? This study failed to exclude a 15% difference in efficacy between GBP and VGB; the low statistical power may have contributed to this due to premature discontinuation of recruitment. The results offer little guidance as to which drug to choose when monotherapy fails.

Effect due to factor in study? Not applicable

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity Reduced statistical power as study was stopped.

Loiseau P;Yuen AW;Duche B;Menager T;rne-Bes MC;

A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures

Ref ID 4716

1990

Study Type Randomised Controlled Trial **Funding** GlaxoSmithKline

Number of participant N=25
2 patients did not complete the trial (1 was withdrawn because of protocol violation (receiving another investigative drug) and 1 withdrew his consent after 1st treatment)

Inclusion/Exclusion Criteria
Inclusion: 16–65 years; confident diagnosis of epilepsy uncomplicated by suspected psychogenic attacks; partial seizures easily recognisable by patient/carer and classifiable by ICS; minimum of 4 partial seizures/month in each of previous 3 months and baseline period; AED unchanged for previous 3 months; seizures resistant to first-choice AEDs to therapeutic plasma concentrations.
Exclusion: severe organic or psychiatric disease; severe mental subnormalities; progressive neurological disease; abnormal values of laboratory screen considered to be of clinical significance and not attributable to enzyme induction; status epilepticus in previous 6 months or more than once in previous 2 years; use of other investigational drugs in previous 6 months; more than 2 AEDs; other chronic medication; abuse of alcohol or other substances; inability to fulfil protocol requirements; pregnancy, lactation or current risk of pregnancy

Patient Characteristics
Mean Age
Total (n = 23): 34.2 years (SD 12.41);
LTG/placebo (n = 10): 38.1 years (SD 12.91);
Placebo/LTG (n = 13): 31.2 years (SD 11.62);
Age range
total (n = 23): 20–54 years;
LTG/placebo (n = 10): 21–54 years;
placebo/LTG (n = 13): 20–52 years

Gender
Total (n = 23): men = 12, women = 11;
LTG/placebo (n = 10): men = 5, women = 5;
placebo/LTG (n = 13): men = 7, women = 6

Duration of seizures (years):
total (n = 23): 17.4 years (SD 10.81);
LTG/placebo (n = 10): 17.0 years (SD 12.17);
placebo/LTG (n = 13): 17.8 years (SD 10.14)

Pre-trial medication
No. of AEDs at entry:
One AED: total (n = 23): 8;
LTG/placebo (n = 10): 4;
placebo/LTG (n = 13): 4
Two AEDs: total (n = 23): 15;
LTG/placebo (n = 10): 6;
placebo/LTG (n = 13): 9

Ongoing concurrent medication
One patient was receiving thyroxine for hypothyroidism.
One concurrent (AED) (n = 8/23)
Two concurrent AEDs (n = 15/23)
Concurrent AEDs were: CBZ (n = 10/23); PHT (n = 10/23); PB

	(n = 11/23); VPA (n = 5/23); CLB (n = 2/23) Co-morbidities One patient had hypothyroidism
Recruitment	Not stated
Setting	Outpatient setting in European country (France)
Interventions/ Test/ Factor being investigated	LTG 150 or 300 mg/day
Comparisons	randomised double blind placebo-controlled crossover trial of LTG added on to existing AEDs Comparing LTG to placebo
Length of Study/ Follow-up	Trial lasted 28 weeks.
Outcome measures studied	Efficacy parameters: countable seizures during each phase, number of days during which seizures occurred Safety parameters: clinical and neurological examinations, adverse events, haematology, routine blood chemistry
Results	<p>1/ CHANGE IN SEIZURE FREQUENCY; reported as the percentage reduction in total seizure counts for each patient. Percentage change expressed relative to the larger of the two treatment period totals</p> <p>Intervention: LTG/placebo sequence group: patient no. 1 (23.12% decrease on LTG); no. 3 (36.3% decrease on LTG); no. 6 (15.15% decrease on placebo); no. 7 (20.0% decrease on LTG); no. 10 (52.38% decrease on LTG); no. 11 (27.27% decrease on LTG); no. 18 (10.0% decrease on placebo); no. 20 (58.87% decrease on placebo); no. 23 (66.66% decrease on LTG); no. 34 (no change) Median change in seizure count on LTG: 23% (95% CI: -11 to 52%) Placebo vs LTG (p < 0.05)</p> <p>Comparator Placebo/LTG sequence group: patient no. 2 (35.06% decrease on LTG); no. 4 (18.18% decrease on LTG); no. 5 (19.35% decrease on LTG); no. 8 (40.0% decrease on placebo); no. 9 (100% decrease on LTG); no. 12 (56.25% decrease on LTG); no. 15 (68.75% decrease on LTG); no. 16 (20.0% decrease on placebo); no. 17 (17.64% decrease on placebo); no. 19 (40.0% decrease on LTG); no. 21 (63.15% decrease on LTG); no. 22 (62.5% decrease on LTG); no. 33 (32.0% decrease on placebo)</p> <p>2/ SEIZURE DAYS; Reported as the total number of seizure days</p> <p>Intervention 15/23 participants showed an improvement whilst on LTG (n = 3/23 showed at least a 50% decrease in seizure frequency). Placebo vs LTG (p < 0.05)</p> <p>Comparator Data not reported</p> <p>3/ PHYSICIAN/PATIENT GLOBAL EVALUATION OF IMPROVEMENT/EFFICACY/TOLERABILITY; Physician reported global evaluation of improvement</p> <p>Intervention Number of patients considered better on LTG than placebo (10/23) Number of patients where there was no change from baseline for either treatment (8/23)</p> <p>Comparator Number of patients considered better on placebo than LTG (5/23)</p> <p>4/ PERCENTAGE RESPONDERS; >=50% reduction in seizures</p> <p>Intervention First-phase data LTG (n = 11): 2/11</p>

End-phase data (n = 25): 8/25
 Comparator
 First-phase data placebo (n = 14): 1/14
 End-phase data not reported

Safety and adverse effects

Adverse events
 Intervention
 Vertigo (n = 3/23) 13%, nervousness (n = 2/23) 9%, anomaly vascular (n = 1/23) 4%, acne (n = 1/23) 4%, oedema peripheral (n = 1/23) 4%, pain (n = 1/23) 4%, conjunctivitis (n = 1/23) 4%, asthenia (n = 1/23) 4%, dizziness (n = 1/23) 4%
 All events were classified as not serious and there were no withdrawals because of AEs
 Comparator
 Nervousness (n = 1/23) 4%, somnolence (n = 1/23) 4%, stupor (n = 1/23) 4%, dry mouth (n = 1/23) 4%, headache (n = 1/23) 4%
 All events were classified as not serious and there were no withdrawals because of AEs

Does the study answer the question?

Yes. This randomised double-blind placebo-controlled crossover trial assessed the efficacy and safety of LTG in a group of outpatients with therapy-resistant epilepsy. In the very resistant epileptic population represented in this study, the use of LTG for 8 weeks as add-on therapy was effective in reducing total seizure frequencies by more than 50% in 7 out of 23 patients. Fourteen patients experienced fewer simple and complex partial seizures, with 8 patients benefiting by more than a 50% decrease in seizure frequency. The drug was well tolerated over the 2 months treatment period. There were no changes in laboratory safety measures considered to be attributable to Lamotrigine. It did not affect the plasma concentration of concomitant antiepileptic drugs.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Directly applicable to guideline population?

Population, intervention and comparator all relevant to the guideline. Doses used were within the limits of usual doses for the two groups.

Internal Validity

Marson AG;Appleton R;Baker GA;Chadwick DW;Doughty J;Eaton B;Gamble C;Jacoby A;Shackley P;Smith DF;Tudur-Smith C;Vanoli A;Williamson PR;

A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial

Ref ID 1496

2007

Study Type

Randomised Controlled Trial

Funding

Commissioned and sponsored by NHS R&D Health Technology Assessment Programme. Also supported by pharmaceutical companies with drugs in the study (approx 20% of the total costs of study).

Number of participant

Arm A: Total n=1721.
 CBZ n=378; GBP n=377; LTG n=378; OXC n=210; TPM n=378.

Arm B: total n=716.
 VPA n=239; TPM n=239; VPS n=238.

Inclusion/Exclusion Criteria

Inclusion criteria:
 History of 2 or more clinically definite unprovoked epileptic seizures in the previous year and if treatment with a single AED represented the best therapeutic option.
 Patients with newly diagnosed epilepsy, those who had failed previous monotherapy

(providing that did not include one of the drugs present in the randomisation) and patients in remission of epilepsy, who had relapsed after a withdrawal of treatment. Exclusion criteria:

If patient or clinician felt treatment was contraindicated, if all seizures had been acute symptomatic seizures (including febrile seizures), they were aged 4 years or younger or if there was a history of progressive neurological disease.

Patient Characteristics	CBZ vs GBP vs LTG vs OXC vs TPM: Males: 55% vs 55% vs 53% vs 55%
	Treatment history, n(%): Untreated: 309 (81.8) vs 306 (81.2) vs 308 (81.5) vs 181 (86.2) vs 308 (81.5); Monotherapy (not optimally treated): 60 (15.9) vs 60 (15.9) vs 61 (16.1) vs 25 (11.9) vs 60 (15.9); Recent seizures after remission: 9 (2.4) vs 11 (2.9) vs 9 (2.4) vs 4 (1.9) vs 10 (2.7); Epilepsy syndrome, n(%): idiopathic partial 4 (1.1) vs s5 (1.3) vs 6 (1.6) s 3 (1.4) vs 6 (1.6); symptomatic or cryptogenic partial: 338 (89.4) vs 333 (88.6) vs 330 (88) vs 180 (85.7) vs 322 (85.4); idiopathic generalised: 3 (0.8) vs 3 (0.8) vs 4 (1.1) vs 5 (2.4) vs 7 (1.9); other syndrome: 2 (0.5) vs 0 (0) vs 0 (0) vs 1 (0.5) vs 1 (0.3); unclassified: 31 (8.2) vs 35 (9.3) vs 35 (9.3) vs 21 (10) vs 41 (10.9)
Recruitment	Patients presenting to participating clinicians were cued for entry if met inclusion criteria.
Setting	Multicentre study hospital outpatient clinics UK.
Interventions/ Test/ Factor being investigated	At start of study information was recorded including patient demographics, presence of a history of learning disability or developmental delay, prior neurological history including head injury, stroke, intracerebral infection and acute symptomatic seizures, and a history of epilepsy in a first-degree family member. Clinicians were asked to classify seizures and epilepsy syndromes according to ILAE classifications or at least differentiate between focal or generalised onset seizures. Where there was uncertainty patients were recorded as having unclassified convulsive or other unclassified seizures. Any EEG or brain imaging results at time of randomisation were recorded. Clinicians involved in the study were asked to choose either CBZ or VPA as the most appropriate treatment for an individual patient. When CBZ was chosen the patient entered arm A and were then allocated to either CBZ, GBP, LTG, OXC, or TPM in ratio of 1:1:1:1:1 (OXC was included in randomisation only after 1st June 2001). If VPA was chosen patients entered arm B and were randomised to either VPA, LTG or TPM in ratio no 1:1:1. Drug was randomised but drug, dosage and preparation were those used typically by the clinician.
Comparisons	Arm A: carbamazepine versus gabapentin versus Lamotrigine versus oxcarbazepine versus Topiramate.
Length of Study/ Follow-up	Follow-up at 3, 6, 12 months and at successively yearly intervals from randomisation. First randomisation was Jan 1999 and continued to randomise until 31st August 2004. Patients were followed up at least until the end of the study (31st August 2005).
Outcome measures studied	Primary clinical outcomes: Time from randomisation to treatment failure. Time from randomisation to the achievement of a 1-year period of remission of seizures. Quality of life.
Results	Carbamazepine versus Lamotrigine: Seizure freedom: 125/347 vs 103/356 Withdrawal due to adverse events: 96/368 vs 60/370 Withdrawal due to lack of efficacy: 29/368 (7.9%) vs 29/368 (7.9%) Time to exit/withdrawal of allocated treatment due to adverse events: HR 0.62 (0.46 to 0.83) Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 1.17 (0.84 to 1.84) Carbamazepine versus Gabapentin: Seizure freedom: 125/347 (36%) vs 81/337 (24%)

Withdrawal due to adverse events: 114/442 (25.8%) vs 75/512 (14.6%)
Withdrawal due to lack of efficacy: 29/368 (7.9%) vs 91/366 (24.9%)
Time to exit/withdrawal of allocated treatment due to adverse events: HR 0.60 (0.44 to 0.81)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 2.45 (1.81 to 3.32)

Carbamazepine versus Topiramate:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 0.99 (0.77 to 1.30)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 1.43 (1.03 to 1.98)

Carbamazepine versus oxcarbazepine:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 0.85 (0.59 to 1.24)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 1.33 (0.82 to 2.15)

Gabapentin versus Lamotrigine:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 1.04 (0.75 to 1.44)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 0.48 (0.36 to 0.64)

Gabapentin versus Topiramate:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 1.66 (1.24 to 2.24)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 0.58 (0.44 to 0.77)

Lamotrigine versus Topiramate:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 1.60 (1.20 to 2.15)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 1.22 (0.89 to 1.67)

Gabapentin versus oxcarbazepine:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 1.36 (0.90 to 2.05)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 0.43 (0.29 to 0.64)

Lamotrigine versus oxcarbazepine:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 1.21 (0.81 to 1.81)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 0.99 (0.63 to 1.54)

Topiramate versus oxcarbazepine:
Time to exit/withdrawal of allocated treatment due to adverse events: HR 0.98 (0.67 to 1.44)
Time to exit/withdrawal of allocated treatment due to lack of efficacy: HR 0.82 (0.53 to 1.28)

Safety and adverse effects

See results above.

Does the study answer the question?

Yes.

Effect due to factor in study?

Yes. Unblinded but it is a very large pragmatic trial.

Consistency of results with other studies?

Directly applicable to guideline population? Mixed population but over 80% had partial seizures.

Internal Validity

Matsuo F;Bergen D;Faight E;Messenheimer JA;Dren AT;Rudd GD;Lineberry CG;

Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. U.S. Lamotrigine Protocol 0.5 Clinical Trial Group

Ref ID 4739

1993

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant 216 total with 73 placebo, 71 lamotrigine 300mg/day; 72 lamotrigine 500 mg/day

Inclusion/Exclusion Criteria Inclusion: Men or women, aged 18 to 65 years; simple or complex partial seizures refractory to treatment with up to three AEDs. Excluded: newly diagnosed (<32 weeks); primary generalized seizures; seizures due to drugs, alcohol, infection, neoplasia, demyelination, metabolic illness, or progressive neurological disorder; taken VPA.

weeks of

weeks of study entry; drug or alcohol abuse; severe psychiatric condition; IQ<50

weeks of study entry
weeks of study; drug or alcohol abuse; psychiatric condition; IQ <50; medical condition interfering with drug absorption;

Patient Characteristics

	Placebo n=73	300mg/day n=71	500 mg/day n=72
Sex			

Male	22(30%)	30(42%)	15(21%)
Female	51 (70%)	41(58%)	57(79%)
Mean age (yr)	34	33	32
Range	16-63	20-57	18-59
Race			
White	60	66	68
Black	9	3	4
Mean duration (yr)	21.5	22.4	21.8

Recruitment	Unknown
Setting	US multicentre
Interventions/ Test/ Factor being investigated	Long term efficacy and safety of lamotrigine 300mg/day and 500 mg/day
Comparisons	Lamotrigine 300mg/day and 500mg/day and placebo
Length of Study/ Follow-up	39 week study with baseline period 12 weeks, a dose-titration and maintenance treatment period 24 weeks and a taper/follow up period 3 weeks.
Outcome measures studied	Primary: reduction in seizure frequency Secondary: number of days on which a seizure of any type occurred (seizure days) and the investigator's global evaluation of the patients' clinical status
Results	Median seizure frequency decreased by 8% with placebo, 20% with 300 mg lamotrigine and 36% with 500 mg lamotrigine. This decrease was statistically significant only in the 500 group (p=0.004 weeks 1-12; p=0.031 weeks 13-24; p=0.007 weeks 1-24). Seizure frequency decreased by greater than or equal to 50% in one third of the 500 mg group and one fifth of the 300 mg group. The proportion of patients experiencing a greater than or equal to 26% reduction in seizure days was statistically significant (p<0.05) in the 500mg group only.
Safety and adverse effects	9% of patients on lamotrigine withdrew due to adverse events. There was a statistically significant difference in withdrawals due to adverse events between the 300mg group and the 500 mg group value not given). Five adverse events were serious - one in the 300 mg group and four in the 500 mg group.
Does the study answer the question?	Lamotrigine appears to be safe and effective as an adjunct therapy in refractory partial seizure patients.
Effect due to factor in study?	Yes
Consistency of results with other studies?	see GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Multi centre; not ITT analysis

Matsuo F;Gay P;Madsen J;Tolman KG;Rollins DE;Risner ME;Lai AA;

Lamotrigine high-dose tolerability and safety in patients with epilepsy: a double-blind, placebo-controlled, eleven-week study

Ref ID 4769

1996

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=12 (n=8 in lamotrigine group and n=4 in placebo group)

**Inclusion/Exclusion
Criteria** Male or female patients aged 18-65 years with epilepsy but otherwise in general good health with no major organ system dysfunction were eligible for the study. Female patients had to be postmenopausal or surgically sterilized. Patients must have

experienced ≤ 40 seizures (preferably partial seizures) during the month before study entry and must not have experienced status epilepticus for the 6 months before receiving study drug. Patients were allowed as many as three currently marketed AEDs and must have had stable (within 50%) therapeutic plasma AED concentrations, with no dosage or drug regimen changes within 2 weeks (4 weeks for barbiturates) before the baseline phase of this study. They were not allowed VPA for 8 weeks before study entry, any over-the-counter medication or alcohol for 1 week before receiving study drug, or any psychoactive drugs other than those used to treat their epilepsy for 2 weeks before receiving study drug or at any time before completion of the follow-up evaluations. Patients who had a history of hypersensitivity to drugs chemically related to LTG were excluded.

Patient Characteristics Twelve white male patients. Mean age was 32 years (range 24-51 years); mean height was 179 cm (range 168-188 cm), and mean weight was 81 kg (range 50-126 kg). Treatment groups were similar with regard to age, height, and weight. Most patients in both groups had a history of uncontrolled partial seizures. The mean duration of seizure history was slightly longer for the LTG group (22 +/- 8 years) than for the control group (8 +/- 6 years).

Recruitment Not reported.

Setting Drug Research Center, Utah, North America.

Interventions/ Test/ Factor being investigated Lamotrigine up to 700mg per day.

Comparisons The comparison is between lamotrigine (LTG) and placebo as adjunctive therapy

Length of Study/ Follow-up 11 weeks: 2 weeks baseline, 6 weeks titration up to 700mg/day, 2 week tapered dose phase, and 1 week follow up phase.

Outcome measures studied Not specified. Aim of study was to assess dose tolerability and safety of lamotrigine. Also, to determine the pharmacokinetic profile at doses ≥ 500 mg/day.

Results Adverse events

Most commonly reported treatment-emergent AE occurring in at least 50% of patients in either treatment group

Adverse event	LTG (n=8) incidence (%)	Placebo (n=4) incidence (%)
Headache	5(63)	3(75)
Drowsiness	5(63)	2(50)
Faintness	4(50)	2(50)
Diplopia	4(50)	0
Dyspepsia	1(13)	2(50)
Nasal congestion	1(13)	2(50)
Fatigue	0	2(50)
Flushing	0	2(50)

Safety and adverse effects 1 patient withdrawn from LTG treatment because of a skin rash.

Does the study answer the question? Unsure. This was mainly a study to examine the tolerability and safety of lamotrigine in large doses. It did not set out to measure the effectiveness of the drug.

Effect due to factor in study? No. This was mainly a study to examine the tolerability and safety of lamotrigine in large doses. It did not set out to measure the effectiveness of the drug.

Consistency of results with other studies?

Directly applicable to guideline population? Most of the patients enrolled suffered from partial seizures

Internal Validity

Meador KJ;Loring DW;Huh K;Gallagher BB;King DW;

Comparative cognitive effects of anticonvulsants

Ref ID 4653

1990

Study Type	Randomised Controlled Trial	Funding	Ciba-Geigy Corporation
Number of participant	15 patients in three equal groups using a randomised triple crossover design		
Inclusion/Exclusion Criteria	Inclusion: partial complex epilepsy Exclusion: Not described		
Patient Characteristics	9 men and 6 women; mean age of 39 years (range 19 to 62); mean education of 11 years (range 3-16); mean duration of epilepsy was 16 years (range 1 month to 45 years).		
Recruitment	Unknown		
Setting	Augusta, Georgia, USA		
Interventions/ Test/ Factor being investigated	The neuropsychological effects of carbamazepine (CBZ), Phenobarbital (PB) and Phenytoin (PT)		
Comparisons	Comparisons are made re the neuropsychological effects of carbamazepine (CBZ), Phenobarbital (PB) and Phenytoin (PT)		
Length of Study/ Follow-up	9 months; each crossover period was 3 months		
Outcome measures studied	The neuropsychological tests included: Digit Span, Selective Reminding Test, Digit Symbol, Finger Tapping, Grooved Pegboard, Choic Reaction Time, P3 evoked potential and Profile of Mood States.		
Results	Employing anticonvulsant blood levels and seizure frequencies as covariates, the only significant difference was for Digit Symbol. Phenobarbital was worse when co varied for % anticonvulsant blood level (P<0.03) or for seizure frequency (P<0.03).		
Safety and adverse effects	None		
Does the study answer the question?	This study shows that patients receiving CBZ, PB and PT have comparable neuropsychological performance on most measures.		
Effect due to factor in study?	Due to small sample size this study should be repeated. However, the evaluation was very thorough.		
Consistency of results with other studies?	See GRADE		
Directly applicable to guideline population?	See GRADE		
Internal Validity	Small sample size; no control group		

Messenheimer J;Ramsay RE;Willmore LJ;Leroy RF;Zielinski JJ;Mattson R;Pellock JM;Valakas AM;Womble G;Risner M;

Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial

Ref ID 4755

1994

Study Type	Randomised Controlled Trial	Funding	Not mentioned in the study
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but HTA (2005) for adults says this was funded by GlaxoSmithKline.

Number of participant	Total n=98. Ten were excluded from the efficacy analysis as they did not complete 12 weeks of the second leg of the crossover. N=88; n=44 in each arm.
Inclusion/Exclusion Criteria	<p>Inclusion criteria: 18-65 years old. Simple or partial seizures (CPS, with or without secondarily generalised seizures) - ILAE classification 1981.</p> <p>Exclusion criteria: Newly diagnosed epilepsy (<32 weeks). Exhibiting pseudo seizures (non epileptic seizures) or primary generalised seizures. Had seizures secondary to drugs, alcohol, infection, neoplasia, demyelination, metabolic illness, or progressive degenerative disease. Had experienced status epilepticus within 24 weeks of baseline. Had a progressive neurological disorder that was not stable for at least 24 weeks before baseline. Had taken valproate within 2 weeks of baseline. Concomitant VPA treatment during study. Abuse of any prescription or non-prescription drug (including alcohol). Current consumption of any psychoactive drug. A severe psychiatric condition requiring hospitalisation. IQ<50. Any medical condition that would interfere with absorption, distribution, metabolism, or excretion of drugs. A history of non-compliance. A clinically significant chronic medical disorder involving the renal, hepatic, cardiac, vascular, hematopoietic, reticuloendothelial, endocrine, pulmonary, gastrointestinal, genitourinary, or ophthalmic system. Those of childbearing potential had to have a negative pregnancy test before study entry and using an approved contraceptive method and signed a statement of 'intent to avoid pregnancy' before admission.</p>
Patient Characteristics	<p>Total n=88, 47% male and 53% female. Mean age (years/range): 35, 18-64 years. Race white n=79; black n=6; other n=3. Mean duration of epilepsy (years): 23.1. Mean age at onset (years): 12. Median seizure frequency (months): simple partial seizures, complex partial seizures, secondarily generalised seizures (n=88): 12.5 simple partial seizures, complex partial seizures (n=87): 12.5. Secondarily generalised seizures (n=27): 1.5. % of patients receiving 1 concomitant AED: 41. % of patients receiving 2 concomitant AEDs: 57. % of patients receiving 3 concomitant AEDs: 2. CBZ: 76. PHT: 45.</p> <p>By treatment sequence:</p> <p>LTG/PBO n=44; 48% males, 52% females. Mean age (years/range): 35 (18-58). Race: white n=37; black n=4; other n=3. Median seizure frequency (months): simple partial seizures, complex partial seizures, secondarily generalised seizures (n=88): 13.3 simple partial seizures, complex partial seizures (n=87): 12.5. Secondarily generalised seizures (n=27): 2.5. % of patients receiving 1 concomitant AED: 45. % of patients receiving 2 concomitant AEDs: 52. % of patients receiving 3 concomitant AEDs: 2. CBZ: 76. PHT: 45.</p>

PBO/LTG n=44; 45% males, 55% females.
 Mean age (years/range): 35 (18-64).
 Race: white n=42; black n=2; other n=0.
 Median seizure frequency (months):
 simple partial seizures, complex partial seizures, secondarily generalised seizures (n=88): 12.3.
 simple partial seizures, complex partial seizures (n=87): 12.3.
 Secondarily generalised seizures (n=27): 1.0.
 % of patients receiving 1 concomitant AED: 36.
 % of patients receiving 2 concomitant AEDs: 61.
 % of patients receiving 3 concomitant AEDs: 2.
 CBZ: 76.
 PHT: 45.

Recruitment	Not stated.
Setting	US.
Interventions/ Test/ Factor being investigated	Lamotrigine 400mg/day or less as adjunctive treatment in patients with refractory partial seizures. Lamotrigine was taken in capsule form and taken b.i.d at ~12 hour intervals. Starting dosage was 100mg/day (50mg b.i.d) for 3 days; followed by 200mg/day (100mg b.i.d) for the next four days: Dosage was increased by 100mg increments at weekly intervals to a maximum of 400mg/day.
Comparisons	Treatment vs placebo. Cross-over study.
Length of Study/ Follow-up	Total 43 weeks. Baseline period: 8 weeks. First treatment period (treatment A): 14 weeks. Washout period: 4 weeks. Second treatment period (treatment B): 14 weeks. Follow-up period (observed): 3 weeks.
Outcome measures studied	Seizure frequency. Seizure days. Number withdrawn. Adverse events.
Results	<p>Statistical analyses found no evidence of a significant treatment-by-period interaction.</p> <p>Proportion of responders (median seizure frequency reduction of 50% or higher compared to placebo during the lamotrigine maintenance period (percentage/range): 20% (13-27%).</p> <p>ITT analysis of first leg compared LTG and placebo groups: Median 29% reduction in seizures frequency with LTG compared to 4% reduction with placebo (p=0.0248).</p> <p>Proportion of seizure-free participants (percentage of patients (range) experiencing 50% or higher reduction in seizure-free days compared to placebo during the lamotrigine maintenance period): 16%(0-29%).</p> <p>Adverse events occurring in greater than or equal to 10% of participants (n=94): (Lamotrigine versus placebo): Ataxia 32% vs 6% Headache 17% vs 15% Dizziness 31% vs 10% Diplopia 18%vs 3% Somnolence 16% vs 4% Rash 15% vs 6% Rhinitis 13% vs 6% Nausea 17% vs 11% Accidental injury 14% vs 7%</p> <p>Five occurred more frequently - ataxia, dizziness, diplopia, somnolence and rash</p>

	(p</=0.05) with lamotrigine than placebo.
Safety and adverse effects	5% discontinued participation prematurely from the study due to adverse events compared to 1% of participants in the placebo group. One placebo patient and three LTG patients were withdrawn after exhibiting a rash. The other two left during LTG treatment after experiencing mild to moderate CNS-related symptoms (dizziness for one patient and ataxia, nausea, diplopia, dizziness, headache and somnolence for the second patient. All experiences resolved after LTG discontinuation.
	LTG therapy was stopped and the patient withdrawn from the study in three cases (1 with vision abnormality, 2 with rash).
Does the study answer the question?	The author concluded that the addition of twice-daily LTG to an existing AED regimen was safe, effective and well tolerated in these medically refractory partial seizure patient. However the decrease in seizure frequency is only given for all patients and not for lamotrigine and placebo separately.
Effect due to factor in study?	No power calculation was stated. Yes.
Consistency of results with other studies?	Yes.
Directly applicable to guideline population?	Direct. The dose used was within the limits of usual therapeutic dose.
Internal Validity	differences at baseline;

Mikkelsen B;Berggreen P;Joensen P;Kristensen O;Kohler O;Mikkelsen BO;

Clonazepam (Rivotril) and carbamazepine (Tegretol) in psychomotor epilepsy: a randomized multicenter trial

Ref ID 4654

1981

Study Type	Randomised Controlled Trial	Funding	Unknown
Number of participant	36 patients: 19 on carbamazepine and 17 on clonazepam		
Inclusion/Exclusion Criteria	Included: Previously untreated patients with recently diagnosed psychomotor epilepsy, irrespective of age and number of seizures. Excluded: Patients with progressive brain diseases, presenile dementia, liver and kidney disease and pregnant women.		
Patient Characteristics	the median age of 36 patients was 22.3 years (range 6-72 years). The sex ratio of this group was 14/22, 39.61% (M/F).		
Recruitment	Not described		
Setting	Denmark		
Interventions/ Test/ Factor being investigated	Comparison of antiepileptic properties of carbamazepine (CBM or Tegretol) and clonazepam (CLP or Rivotril).		
Comparisons	Number of withdrawals; time of withdrawal; number of seizures until time of withdrawal and side effects.		
Length of Study/ Follow-up	not mentioned.		
Outcome measures studied	Number of withdrawals; time of withdrawal; number of seizures until time of withdrawal and side effects.		

Results	There was no significant difference between the two treatments with regard to Number of withdrawals; time of withdrawal; number of seizures until time of withdrawal and side effects ($p < 0.20$). Irrespective of treatment there was a significant decrease in the median number of seizures per month ($p < 0.01$), a decrease that was not significantly different in the two groups ($p > 0.10$). The estimated percentage of patients without seizures during the 6 months of treatment was 49% on carbamazepine and 46% on clonazepam.
Safety and adverse effects	Except for a single patient on CBM all patients had one or more side effects during treatment. There were no significant differences between the two groups with regard to sedation, headache, dizziness, impaired memory, marital relations, irritability and other complaints ($p < 0.05$)
Does the study answer the question?	This study indicates clonazepam and carbamazepine to be equally effective in the treatment of newly diagnosed and previously untreated patients with psychomotor epilepsy.
Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Small population; multi-centre

Naritoku DK;Warnock CR;Messenheimer JA;Borgohain R;Evers S;Guekht AB;Karlova VA;Lee BI;Pohl LR;

Lamotrigine extended-release as adjunctive therapy for partial seizures

Ref ID 4836

2007 Oct 16

Study Type	Randomised Controlled Trial	Funding	GlaxoSmithKline Research and Development (GSK R&D).
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Number of participant n=243(n=121 in lamotrigine group and n=122 in placebo group)

Inclusion/Exclusion Criteria

Inclusion: age >12 years; confident diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures for >24 weeks before the baseline phase of the study; had at least eight partial seizures during that 8-week baseline phase with at least one partial seizure during each 4-week period; and were treated with a stable regimen of one or two AEDs for at least 4 weeks before starting the baseline phase. Exclusion criteria: presence of primary generalized seizures, status epilepticus during or within 24 weeks before the start of the baseline phase, chronic treatment with three or more AEDs, current or previous use of lamotrigine, current use of felbamate or adherence to the ketogenic diet, and pregnancy.

Patient Characteristics	Lamotrigine extended-release (n = 116)	Placebo (n = 120)
Demographics		
Male, n (%)	54 (47)	63 (53)
Race, n (%)		
African American/African	3 (3)	10 (8)
American Indian/Alaskan Native	4 (3)	3 (3)
Asian: Central/South Asian	16 (14)	9 (8)
Asian: East Asian	15 (13)	14 (12)
Asian: Southeast Asian	0 (0)	2 (2)
White: White/Caucasian/European	77 (67)	83 (69)
Mean age, y (SD)	35.8 (12.7)	37.5 (14.4)
Age stratum, n (%)		
<16 y	5 (4)	4 (3)
16 to 65 y	108 (93)	112 (93)
>65 y	3 (3)	4 (3)

Baseline clinical characteristics		
Mean age at first seizure, y (SD)	14.9 (12.2)	16.4 (13.7)
Mean duration of epilepsy, y (SD)	21.8 (13.2)	22.1 (16.1)
Seizure type, n (%)		
Simple	54 (47)	58 (48)
Complex	83 (72)	91 (76)
Partial with secondary generalization	38 (33)	42 (35)
Median (range) number of partial seizures/wk during baseline phase	2.3 (0.5–59.0)	2.1 (0.9–50.0)
Concomitant AED regimens, n (%)		
Valproate with enzyme-inducing AEDs	7 (6)	24 (20)
Valproate alone or with non-enzyme-inducing AEDs	23 (20)	19 (16)
Enzyme-inducing AEDs alone or with neutral AEDs	59 (51)	43 (36)
Neutral AEDs	27 (23)	34 (28)
Most common concomitant AEDs, n (%)		
Carbamazepine	50 (43)	50 (42)
Valproic acid	27 (23)	42 (35)
Topiramate	18 (16)	17 (14)
Oxcarbazepine	11 (9)	22 (18)
Phenytoin	16 (14)	16 (13)
Levetiracetam	15 (13)	13 (11)

Recruitment

Not reported.

Setting

Study sites in N and S. America, Europe and Asia.

Interventions/ Test/ Factor being investigated

Lamotrigine XR (extended release) in 3 doses (200mg/day, 500mg/day and 300mg/day) depending on type of AED currently used.

Comparisons

Lamotrigine XR is compared with placebo as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up

27 weeks: 12 weeks baseline phase,7 week titration phase and 12 weeks maintenance.

Outcome measures studied

Primary outcome: % change from baseline in weekly partial seizure frequency during maintenance phase. Secondary outcomes:% change during titration phase and maintenance alone, response rate, time to response,% improved.

Results

Primary outcome

All partial seizures.

The median percent reduction from baseline in weekly frequency of partial seizures during double-blind treatment (escalation and maintenance phases) was higher with lamotrigine XR (46.1%) than placebo (24.2%) (median difference: 18.2%; p=0.0004).

Secondary outcomes

Response rate.

The percentage of patients with $\geq 50\%$ reduction in partial seizure frequency during doubleblind treatment (escalation and maintenance phases) was significantly higher in the lamotrigine XR group (42.2%) than the placebo group (24.2%) (p=0.0037).

During

maintenance, the percentage of patients who were seizure free was higher in the lamotrigine XR group (18.9%) than the placebo group (5.1%) (p= 0.0016).

The time to $\geq 50\%$ reduction in partial seizure frequency after 1 week of double-blind treatment was significantly shorter in the lamotrigine XR group than the placebo group (p= 0.0007). This treatment difference reached and subsequently maintained statistical significance at day 18 of the escalation phase (p= 0.0448).

Secondarily generalized seizures.

The median % reduction from baseline in weekly frequency of secondarily generalized seizures during doubleblind treatment was significantly higher in the lamotrigine XR group (55.2%) than the placebo group (3.2%) (median difference between groups: 38.0%; p=0.0036). Similar results were observed for the escalation phase and the maintenance

phase.

The percentage of patients with $\geq 50\%$ reduction in partial seizure frequency during double-blind treatment was significantly higher in the lamotrigine XR group (52.2%) than the placebo group (25.5%) ($p=0.0292$). Similar results were observed for the escalation phase and the maintenance phase.

Investigator assessment of clinical status.

The % of patients with improvement in investigator-rated clinical status during double-blind treatment was higher in the lamotrigine XR group than the placebo group for overall clinical status (60% vs 40%; $p=0.0012$) and for the individual items of seizure frequency. The % of patients with deterioration in investigator-rated clinical status during double-blind treatment was higher in the lamotrigine XR group than the placebo group for adverse events (21% vs 9%; $p=0.03$).

Patient-rated status.

The % of patients reporting improvement in seizure control (mild, moderate, or marked) during double-blind treatment was higher in the lamotrigine XR group (72%) than the placebo group (48%; $p=0.0001$).

Adverse events

Adverse events reported in $>5\%$ of patients in either treatment group (safety population)

Adverse event	Lamotrigine extended-release (n=118)	Placebo (n=121)
Headache	20 (17)	18 (15)
Dizziness	21 (18)	6 (5)
Nasopharyngitis	3 (3)	13 (11)
Diarrhea	8 (7)	5 (4)
Somnolence	8 (7)	5 (4)
Insomnia	4 (3)	7 (6)
Nausea	8 (7)	3 (2)
Asthenia	6 (5)	3 (2)
Tremor	6 (5)	1 (<1)

Safety and adverse effects

The most common adverse events were headache and dizziness.

Does the study answer the question?

Yes. Once-daily adjunctive lamotrigine XR compared with placebo effectively reduced partial seizure frequency.

Effect due to factor in study?

Yes. The study had 90% power to detect a difference between the treatment and placebo groups in the primary outcome.

Consistency of results with other studies?

Directly applicable to guideline population?

The study was comprised of patients with a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures.

Internal Validity

Nieto-Barrera M; Brozmanova M; Capovilla G; Christe W; Pedersen B; Kane K; O'Neill F;

A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy

Ref ID 4723

2001

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant 417 Lamotrigine and 201 carbamazepine

Inclusion/Exclusion Criteria	Inclusion: Newly diagnosed, untreated partial epilepsy ; 2 seizures in preceding 6 months Exclusion: Not discussed
Patient Characteristics	Aged 2-83 years with median age 47 years in both groups and 53% female in both groups. Mean weight 19 kg in Lamotrigine group and 20 kg in carbamazepine group
Recruitment	Unknown
Setting	Spain, Slovakia, Italy, Germany, Denmark, UK
Interventions/ Test/ Factor being investigated	A comparison of monotherapy with Lamotrigine or carbamazepine
Comparisons	Lamotrigine vs. carbamazepine
Length of Study/ Follow-up	24 weeks
Outcome measures studied	Proportion of patients free of seizures during the last 16 weeks of treatment and proportion of patients who did not withdraw before the end of week 18 and were seizure free in the last 16 weeks of the study.
Results	Efficacy was similar with both treatments (65% with Lamotrigine, 73% with carbamazepine, p=0.085), i.e. patients who were seizure free during the last 16 weeks of treatment. More patients receiving Lamotrigine completed the study (81%) compared with those receiving carbamazepine (77%). This was due to adverse events.
Safety and adverse effects	The proportion of patients who experienced adverse events in the Lamotrigine group was lower (218 patients, 52%) compared with the carbamazepine group (120, 60%). Somnolence was the only adverse event reported at an incidence of greater than 5%. Paediatric patients and elderly patients showed better tolerability to Lamotrigine than to carbamazepine (5%vs. 7% and 20% vs. 50% respectively).
Does the study answer the question?	Lamotrigine appears to be as effective as carbamazepine in patients with newly diagnosed partial epilepsy and also appears to be better tolerated.
Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Open label; multi centre

Novotny E;Renfroe B;Yardi N;Nordli D;Ness S;Wang S;Weber T;Kurland CL;Yuen E;Eerdeken M;Venkatraman L;Nye JS;Ford L;

Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures

Ref ID 5087

2010 Mar 2

Study Type Randomised Controlled Trial **Funding** Johnson and Johnson Pharmaceuticals.

Number of participant n=149; placebo n=37, topiramate 5mg/kg/day n=38; topiramate 15mg/kg/day n=37; topiramate 25mg/kg/day n=37.

Inclusion/Exclusion Criteria Inclusion criteria:
aged 1-24 months, inclusive, or at least 41 weeks of gestational age;
weighing \geq 3.5kg and $<$ 15.5kg, length \geq 49cm
receiving regular enteral feeding;
diagnosed with Partial onset seizures with or without secondary generalisation (at

least 1 month before for infants older than 6 months, and at least 2 weeks before for infants aged 6 months or younger)
 CT or MRI scan to confirm absence of a progressive lesion (lesions of tuberous sclerosis and Sturge-Weber syndrome were allowed) and EKG with 'no abnormal, clinically significant' interpretations as made by the central reader;
 must have been receiving at least one concurrent marketed AEE other than topiramate for 1 month or more for infants older than 6 months and for more than 2 weeks for infants aged 6 months or younger;
 existing treatment was concluded by investigator to be inadequate in controlling seizures if infants, at optimised doses of AEDs had at least 1 seizure in the 4 weeks before screening;
 The AED must have been unchanged for at least 5 half-lives before screening.

Exclusion criteria:

If could not take oral medications;
 had a surgically implanted and functioning vagus nerve stimulator;
 had epilepsy surgery within 3 months before screening;
 had febrile seizures, seizures due to an acute medical illness or nonepileptic seizures within 2 weeks before the first day of screening;
 Had progressive neurologic disorders, uncontrolled medical illness, disturbances of autonomic function, inborn errors of metabolism and known hypersensitivity to topiramate.
 Status epilepticus (30 minutes of continuous motor seizures) in the 2 weeks before;
 infants who had received more than 4 courses of rescue treatments (such as diazepam) in the month before the first day of screening;
 infants using 3 or more concurrent AEDs.

Patient Characteristics	Placebo vs 5mg/kg/day vs 15mg/kg/day vs 25mg/kg/day: Age mean (sd) months: 12 (5.9) vs 13 (7.6) vs 12 (6.2) vs 10 (5.2). Males, n(%): 14 (38) vs 22 (58) vs 19 (51) vs 23 (62). Race: white 26 (70) vs 25 (66) vs 19 (51) vs 21 (57); black or african american 1 (3) vs 1 (3) vs 1 (3) vs 2 (5); Asian 9 (24) vs 7 (18) vs 11 (30) vs 7 (19); other: 1 (3) vs 5 (13) vs 6 (16) vs 7 (19).
Recruitment	Not reported.
Setting	19 countries in Asia, EU, Latin America, US.
Interventions/ Test/ Factor being investigated	Topiramate 5mg/kg/day vs 15mg/kg/day vs 25mg/kg/day vs placebo.
Comparisons	Between treatments and between treatments and placebo.
Length of Study/ Follow-up	This study reports only the double-blind treatment phase but there was a 1 year open label extension and follow up visit 30 days after last treatment.
Outcome measures studied	Primary: % reduction in daily partial onset seizures rate.
Results	Placebo vs 5mg/kg/day vs 15mg/kg/day vs 25mg/kg/day: At least 50% reduction in seizure frequency: 10/37 vs 9/38 vs 13/37 vs 15/37. Withdrawal due to treatment emergent adverse events: placebo 5% vs topiramate 4%.
Safety and adverse effects	Incidence of TEAEs higher in the combined topiramate groups (81%) vs placebo group (51%). Incidences of anorexia and weight decrease in topiramate groups were dose related. Status epilepticus in 1 infant each on 5mg/kg/day and placebo. No incidence of death in double-blind phase, but occurred on an unknown date after early discontinuation of topiramate 5mg/kg/day and was considered to have a doubtful relationship with topiramate.
Does the study answer the question?	Yes
Effect due to factor in study?	Yes.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Peltola J;Coetzee C;Jimenez F;Litovchenko T;Ramaratnam S;Zaslavaskiy L;Lu ZS;Sykes DM;Levetiracetam XN;

Once-daily extended-release levetiracetam as adjunctive treatment of partial-onset seizures in patients with epilepsy: a double-blind, randomized, placebo-controlled trial

Ref ID 4837

2009 Mar

Study Type Randomised Controlled Trial **Funding** UCB, Inc and UCB Pharma, SA.

Number of participant n=188 (n=79 in both the placebo and the levetiracetam XR groups)

Inclusion/Exclusion Criteria Inclusion criteria: 12–70 years of age, with recurrent partial-onset seizures despite receiving at least one but no more than three concomitant AEDs, weigh at least 50 kg and have a confirmed diagnosis of POS, whether or not secondarily generalized,for at least 6 months preceding the screening visit and refractory to pharmacotherapy with one to three AEDs. During the 8-week baseline period to have at least eight partial seizures, with or without secondary generalization, and at least two partial seizures in each 4-week interval of the baseline period. Female patients of childbearing potential needed to use a medically accepted contraceptive method.
Exclusion criteria:history of status epilepticus, seizure clusters, flurries of seizures, pseudoseizures, or status epilepticus within 3 months preceding the screening visit. Other exclusion criteria included neoplasia, progressive cerebral or neurodegenerative disease, presence of another clinical condition or clinically significant abnormal laboratory value likely to influence the course of the trial.

Patient Characteristics	Placebo (N = 79)	LEV XR (N = 79)
Agea (years)		
Mean ± SD	32.38 ± 12.60	33.97 ± 13.41
Min–max	13.3–67.9	12.2–67.9
Gender		
Female, n	32	27
Male, n	47	52
Race		
White, n (%)	35 (44.3)	37 (46.8)
Indian/Pakistani, n (%)	27 (34.2)	27 (34.2)
Hispanic, n (%)	15 (19.0)	15 (19.0)
Other, n (%)	2 (2.5)	0
Body weight (kg)		
Mean ± SD	67.80 ± 15.55	70.21 ± 15.66
Min–max	48.0–134.0	50.0–118.0
BMI (kg/m ²)		
Mean ± SD	24.6 ± 4.55	24.76 ± 4.71
Min–max	16.8–38.6	17.6–47.1
Epilepsy duration at randomization (years)		
Mean ± SD	16.43 ± 11.93	13.11 ± 10.87
Min–max	0.7–53.5	0.8–42.6
Age at epilepsy diagnosis (years)		
Mean ± SD	15.95 ± 11.51	20.86 ± 15.18
Min–max	0.1–47.9	0.3–61.5
Seizure count in the 8-week baseline period (mean ± SD)		
Partial-onset seizures	30.3 ± 52.6	39.7 ± 66.3

All seizure types	30.6 ± 52.5	40.7 ± 66.0
Number of concomitant AEDs at baseline, n (%)		
0	1 (1.3)	0
1	17 (21.5)	27 (34.2)
2	38 (48.1)	36 (45.6)
3	22 (27.8)	12 (15.2)
>3	1 (1.3)	4 (5.1)

Recruitment

Not reported.

Setting

34 sites in seven countries.

Interventions/ Test/ Factor being investigated

Extended release levetiracetam (2 x 500mg per day) as adjunctive therapy to currently used AEDs.

Comparisons

Comparison is between levetiracetam XR and placebo as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up

20 weeks: 8 week baseline period and 12 weeks double blind treatment period.

Outcome measures studied

Primary outcome is frequency of partial-onset seizures per week over the treatment period.

Secondary outcomes: responders ($\geq 50\%$ reduction), seizure freedom, adverse events, laboratory tests, physical and neurologic examinations, vital signs

Results

Changes from baseline in partial-onset seizures

Median seizure frequency per week
ITT population (primary efficacy analyses)

	Placebo n=79	LEV XR n=79
Baseline (min–max)	2.11 (1.0–53.5)	1.80 (0.0–47.3)
Treatment period (min–max)	1.36 (0.0–33.9) n = 78	0.99 (0.0–29.1) n = 75
% Reduction from baseline (min–max)	33.40 (-199.0–100.00) n = 78	46.07 (–210.5–100.0) n = 74
Log-transformed value: LSMean ± SE	1.067 ± 0.052 (n = 78)	0.912 ± 0.053 (n = 75)
Two-sided 95% CI (LEV XR–placebo)	0.009–0.301	
Reduction (%): LEV XR over placebo	14.4%	
Two-sided 95% CI (% reduction)	0.9%–26.0%	
p-value	0.038	

Secondary outcomes

Responder rates

In the LEV XR group, 43% of patients (34 of 79) showed a reduction from baseline of at least 50% in partial-onset seizures compared with 29% (23 of 79) in the placebo group (odds ratio 1.84 (0.95–3.55, p = 0.07).

Seizure-free days

LEV XR group had a median of 5.43 (min–max 0.1–6.4) seizure-free days per week at baseline and 6.1 (min–max 0.0–7.0) over the entire treatment period (median change of 13.1%). The placebo group had a median of 5.38 (min–max 0.0–6.5) seizure-free days per week at baseline and 5.83 (min–max 0.0–7.0) over the treatment period (median difference of 8.01%).

Adverse events

Treatment-emergent adverse events reported by $\geq 5\%$ patients in either treatment group (safety population)

Adverse event: MedDRA Preferred Term	Placebo (N = 79)	LEV XR (N = 77)
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Patients with at least one

adverse event, n (%)	43 (54.4)	41 (53.2)
Somnolence, n (%)	2 (2.5)	6 (7.8)
Irritability, n (%)	0	5 (6.5)
Headache, n (%)	11 (13.9)	5 (6.5)
Dizziness, n (%)	2 (2.5)	4 (5.2)
Influenza, n (%)	3 (3.8)	6 (7.8)
Nasopharyngitis, n (%)	4 (5.1)	5 (6.5)
Nausea, n (%)	2 (2.5)	4 (5.2)

Figure 1 showed that 7 patients discontinued (2/79 placebo group and 5/59 in levetiracetam XR group) treatment because of adverse events. However it is stated in the results that:

Five patients (3 on LEV XR and 2 on placebo) discontinued treatment because of adverse events. Six patients in the LEV XR group and two in the placebo group had serious adverse events.

Safety and adverse effects

The intensity of most treatment-emergent adverse events was mild to moderate.

Does the study answer the question?

Yes. This is a well conducted trial which was powered sufficiently to detect differences between the treatment groups. Once daily levetiracetam extended release was effective in patients with partial onset seizures.

Effect due to factor in study?

Yes. The study had 90% power to detect a difference between the groups with regard to seizure frequency.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in the study had a diagnosis of partial-onset seizures.

Internal Validity

Prevey ML;Delaney RC;Cramer JA;Cattanach L;Collins JF;Mattson RH;

Effect of valproate on cognitive functioning. Comparison with carbamazepine. The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group

Ref ID 4817

1996 Oct

Study Type

Randomised Controlled Trial

Funding

Not stated. Main study funded by Department of Veteran Affairs Medical Research Service, with additional support from Abbot Lab and Ciba-Geigy

Number of participant

26 patients from carbamazepine and 39 patients from valproate group

Inclusion/Exclusion Criteria

Main study:
 Inclusion criteria:
 - Adults with well documented recent onset symptomatic localisation related (partial) epilepsy, diagnosed by extensive examination and record reviewed in accordance with ILAE.
 - Newly diagnosed epilepsy (≥2 seizures) or previously diagnosed epilepsy presently untreated with antiepileptic drugs.
 Exclusion criteria:
 Subjects with history of serious medical disorders, progressive neurological diseases, significant psychiatric disturbance or substance abuse.

Special criteria for neurophysical assessment:

Inclusion:
 - received antiepileptic drugs prior to randomisation
 - patients in whom drug treatment failed

Exclusion:

- patients who withdrew prior to the 6-month follow up visit and were unavailable for testing

Patient Characteristics

	CBZ , n=26	Valproate, n=39
Age	43.5±17.1	44.3±14.2
Education	12.2±2.7	12.7±2.0
Full scale IQ score	104.9±22.7	97.4±13.7
Age at onset of seizures	40.4±18.5	39.0±17.0
Seizure frequency, year prior to study (no/year)		
Tonic clonic	1.7±2.0	1.9±2.0
Complex partial	2.2±2.4	1.9±2.4
At the 6 month follow up visit		
Tonic clonic	0.2±0.6	0.0±0.3
Complex partial	0.1±0.3	3.4±20.5

All characteristics not statistically significant different

NO significant difference between groups in all cognitive and behavioural toxicity tests

Recruitment

Participated in the Department of Veteran Affairs Epilepsy Cooperative Study

Setting

A subset of patients from a larger trial

**Interventions/ Test/
Factor being
investigated**

Carbamazepine vs valproate

Comparisons

Carbamazepine vs valproate. Another control group was recruited

**Length of Study/
Follow-up**

Up to 12 months

**Outcome measures
studied**

Not stated

Results

Cognitive tests:

There were no significant difference3s in the effect of carbamazepine vs valproate on motor speed and coordination, memory or concentration and mental flexibility. No significant decline in neuropsychological performance from pre-treatment baseline levels for either drug.

Patients treated with wither CBZ or valproate did not show practice effects experienced by normal controls

**Safety and adverse
effects**

Not reported in this paper

**Does the study
answer the question?**

The impact of carbamazepine and valproate monotherapy on cognitive functioning is similar. Both drugs produce minimal negative effects compared to pre-treatment baseline performance

**Effect due to factor in
study?**

Uncertain. Sample size calculation not discussed

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?**

Uncertain. Selective group of patient. The main study was not included in the review.

Internal Validity

Privitera M;Fincham R;Penry J;Reife R;Kramer L;Pledger G;Karim R;

Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. Topiramate YE Study Group

Ref ID 4700

1996

Study Type Randomised Controlled Trial **Funding** Robert Wood Johnson

Number of participant 190 total: 48 to 600 mg/day; 48 to 800 mg/day; 47 to 1000mg/dau; 47 to placebo

Inclusion/Exclusion Criteria Inclusion: History of partial onset seizures with EEG verification; experienced 12 partial seizures during 12 week baseline period preceding the double blind study phase while maintained on therapeutic AEDs. Age 18-65. Exclusion: Progressive neurological disease. Status, child-bearing potential, alcohol or drug abuse, psychiatric disorder, nephrolithiasis, non-compliance history, abnormal baseline lab tests.

Patient Characteristics Gender: Male 152
Female 38
Race: White 170
Black 16
Other 4
Age (yr)
Mean 35.5
Range 18-68

Recruitment Unknown

Setting Multi-centre

Interventions/ Test/ Factor being investigated Safety and efficacy of three dosages of Topiramate (600, 800, and 1,000 mg/day) as adjunctive therapy

Comparisons Three dosages of Topiramate and placebo

Length of Study/ Follow-up 12 week baseline and 18 week double blind phase divided into 6 week titration segment and a 12 week stabilization period

Outcome measures studied Primary: percent reduction in average monthly seizure rate in the double blind phase relative to the baseline phase.
Secondary: percent treatment responders (those with greater than or equal to 50% reduction in seizure rate);

Results	Placebo	600 mg	800mg	1000mg
% seizure reduction				
Median	1.2	40.7	41.0	37.5
p-value		<0.001	<0.001	<0.001
Treatment responders (>50% reduction in seizure frequency)				
Number	4/47	21/48	19/48	18/47
Percent	8.5	43.8	39.6	38.3
p-value		<0.001	<0.001	<0.001

Safety and adverse effects CNS events were the most common adverse events including dizziness, ataxia, somnolence, nystagmus, diplopia, confusion, thinking abnormal and headache. Discontinuations due to adverse events were: 2% (1/47) placebo; 21% (10/48) - 600mg; 10% (5/48)- 800 mg and 17% (8/47)- 1000 mg. No remarkable abnormal clinical lab findings.

Does the study answer the question? Topiramate may be a promising AED for adjunctive therapy in refractory partial onset seizures and is highly efficacious and well tolerated.

Effect due to factor in study? Yes

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity 26% of total sample

Study Type	Randomised Controlled Trial	Funding	Southern Foundation for Brain Research
Number of participant	Of 87 patients entered into the study, data on 70 patients were complete and used for analysis. Thirty-five patients were treated with each drug.		
Inclusion/Exclusion Criteria	<p>Inclusion: newly diagnosed patients who were previously untreated; over the age of 17 years</p> <p>Exclusion: known hypersensitivity to CBZ tricyclic antidepressants or PHT; history of previous bone marrow depression; pregnancy or a desire to become pregnant and serious diseases that might interfere with the study.</p>		
Patient Characteristics	There were 60 men and 27 women with ages ranging from 18-77 years (mean, 37.4). Twenty seven patients (31%) had generalized convulsive seizures, 18 (20.7%) had partial seizures that secondarily generalized and 37 (42.5%) had partial seizures only.		
Recruitment	Unknown		
Setting	USA and Canada		
Interventions/ Test/ Factor being investigated	Comparison of treatments is studied		
Comparisons	Comparison of Carbamazepine (CBZ) with Phenytoin (PHT)		
Length of Study/ Follow-up	Minimum of 6 months		
Outcome measures studied	<p>Primary: treatment failure defined as the continued occurrence of seizures despite doses of medications that produced toxic symptoms or an increase in seizure frequency with therapeutic plasma levels.</p> <p>Secondary: major and minor side effects</p>		
Results	The incidence of major side effects (8 patients in each group - 22.9%), minor side effects, and complete seizure control (85%) was the same in both groups. A mild but significant elevation of WBC count was found before initiation of drug treatment in the patients presenting with generalized convulsive seizures. Sporadically, elevations in SGOT and LDH were seen; WBC counts below 4,000 were reported, but these were not clinically significant.		
Safety and adverse effects	See trial report. Major adverse effects: erythematous maculopapular rash (4 patients on PHT and one patient taking CBZ); one patient with pruritis on CBZ; cognitive impairment (1 patient) and elevated liver enzymes (1 patient) and generalized headache (1 patient). Minor side effects: nystagmus was most common and a fine tremor seen in both groups.		
Does the study answer the question?	CBZ was as effective as PHT in the control of partial and generalized convulsive seizures. Although the frequency of different side effects varies between the drugs, the overall rate of major and minor side effects was the same for CBZ and PHT.		
Effect due to factor in study?	Small study should be repeated.		
Consistency of results with other studies?	See GRADE		
Directly applicable to guideline population?	See GRADE		
Internal Validity	Small sample size		

Study Type	Randomised Controlled Trial	Funding	Unknown																																																																																										
Number of participant	94 - 49 received sodium valproate and 45 received phenytoin																																																																																												
Inclusion/Exclusion Criteria	Inclusion: Patients with at least 2 fits per month																																																																																												
Patient Characteristics	70 males and 24 females ranging in age from 8-52 years.																																																																																												
Recruitment	Not described																																																																																												
Setting	Epilepsy Clinic at SVBP Hospital, Meerut India																																																																																												
Interventions/ Test/ Factor being investigated	Sodium valproate 15 mg/kg/day in 3 divided doses with increments as needed; Phenytoin in dose of 5 mg/kg/day as a single bedtime dose and increased as needed																																																																																												
Comparisons	Sodium valproate vs. phenytoin for control of seizures																																																																																												
Length of Study/ Follow-up	None reported.																																																																																												
Outcome measures studied	Seizure reduction: excellent (100% reduction), good (75-99% reduction), fair (50-74% reduction) and poor (less than 50% reduction).																																																																																												
Results	<table border="1"> <thead> <tr> <th colspan="6">Sodium Valproate Response</th> </tr> <tr> <th>Seizure Type</th> <th>Patients (49)</th> <th>Excellent</th> <th>Good</th> <th>Fair</th> <th>Poor</th> </tr> </thead> <tbody> <tr> <td>Tonic Clonic</td> <td>28</td> <td>16(57%)</td> <td>8(29%)</td> <td>3(10%)</td> <td>1(4%)</td> </tr> <tr> <td>Tonic</td> <td>5</td> <td>2 (40%)</td> <td>2(40%)</td> <td>1(20%)</td> <td>--</td> </tr> <tr> <td>Myoclonic</td> <td>2</td> <td>--</td> <td>2(100%)</td> <td>--</td> <td>--</td> </tr> <tr> <td>Simple partial</td> <td>8</td> <td>5(62.5%)</td> <td>2(25%)</td> <td>1(12.5%)</td> <td>--</td> </tr> <tr> <td>Complex partial</td> <td>3</td> <td>--</td> <td>1(33.3%)</td> <td>--</td> <td>2(66.7%)</td> </tr> <tr> <td>Sec. gen. of Partial seizures</td> <td>3</td> <td>1(33.3%)</td> <td>2(66.7%)</td> <td></td> <td></td> </tr> </tbody> </table> <table border="1"> <thead> <tr> <th colspan="6">Phenytoin Response</th> </tr> <tr> <th>Seizure Type</th> <th>Patients (49)</th> <th>Excellent</th> <th>Good</th> <th>Fair</th> <th>Poor</th> </tr> </thead> <tbody> <tr> <td>Tonic Clonic</td> <td>27</td> <td>18(67%)</td> <td>7(26%)</td> <td>2(7%)</td> <td>--</td> </tr> <tr> <td>Tonic</td> <td>5</td> <td>3 (60%)</td> <td>1(20%)</td> <td>1(20%)</td> <td>--</td> </tr> <tr> <td>Simple partial</td> <td>8</td> <td>2(25%)</td> <td>4(50%)</td> <td>1(12.5%)</td> <td>1(12.5%)</td> </tr> <tr> <td>Complex partial</td> <td>1</td> <td>--</td> <td>--</td> <td>1(100%)</td> <td>--</td> </tr> <tr> <td>Sec. gen. of Partial seizures</td> <td>4</td> <td>--</td> <td>1(25%)</td> <td>3(75%)</td> <td></td> </tr> </tbody> </table>			Sodium Valproate Response						Seizure Type	Patients (49)	Excellent	Good	Fair	Poor	Tonic Clonic	28	16(57%)	8(29%)	3(10%)	1(4%)	Tonic	5	2 (40%)	2(40%)	1(20%)	--	Myoclonic	2	--	2(100%)	--	--	Simple partial	8	5(62.5%)	2(25%)	1(12.5%)	--	Complex partial	3	--	1(33.3%)	--	2(66.7%)	Sec. gen. of Partial seizures	3	1(33.3%)	2(66.7%)			Phenytoin Response						Seizure Type	Patients (49)	Excellent	Good	Fair	Poor	Tonic Clonic	27	18(67%)	7(26%)	2(7%)	--	Tonic	5	3 (60%)	1(20%)	1(20%)	--	Simple partial	8	2(25%)	4(50%)	1(12.5%)	1(12.5%)	Complex partial	1	--	--	1(100%)	--	Sec. gen. of Partial seizures	4	--	1(25%)	3(75%)	
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Safety and adverse effects	The most common side effects seen with valproate included GI disturbances (12%), drowsiness (6.12%), and weight gain (2.04%). Side effects with phenytoin included gum hyperplasia (17.7%), nystagmus (13.33%), ataxia (2.2%), GI disturbances (4.44%) and drowsiness(4.44%).																																																																																												
Does the study answer the question?	It appears that while sodium valproate and phenytoin were equally effective in controlling generalised epilepsy, valproate was a better drug for controlling partial seizures.																																																																																												
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Directly applicable to guideline population? See GRADE

Internal Validity

Sachdeo RC;Leroy RF;Krauss GL;Drake ME;Green PM;Leppik IE;Shu VS;Ringham GL;Sommerville KW;

Tiagabine therapy for complex partial seizures. A dose-frequency study. The Tiagabine Study Group

Ref ID 4737

1997

Study Type Randomised Controlled Trial **Funding** Abbott Laboratories, North Chicago Ill.

Number of participant n=318 (n=107 in placebo group, n=106 in 16mg x 2 group and n=105 in 8mg x 4 group.)

Inclusion/Exclusion Criteria Inclusion criteria: age 12 to 75 years, min body weight 45kg, not pregnant, diagnosis of a complex partial seizure (CPS) with or without secondary generalization, at least 6 CPSs in the 8 week period before screening, stable regimen of 1 to 3 marketed AEDs.
Exclusion criteria: pseudo seizures, any disease of the CNS, history of drug abuse or addition or severe psychiatric illness.

Patient Characteristics Demographic and clinical characteristics of 318 randomized patients

Characteristic	Placebo n=107	Tiagabine	
		16mg x 2 n=106	8mg x 4 n=105
Sex, F:M, %	50:50	39:61	43:57
Race, white: black; other %	86:7:7	84:9:7	90:5:6
Mean age (range), y	35.3(13-71)	33.4(12-67)	32.6(12-66)
Mean weight (range) kg	71(41-118)	76(37-162)	75(33-133)
Median period with epilepsy (range) y	24(2-62)	18(3-54)	22(1-45)
Mean No. of antiepilepsy drugs ever taken (range)	6.5(2-20)	6.0(1-14)	6.9(2-20)

Recruitment Not reported.

Setting 26 clinical centres in the United States.

Interventions/ Test/ Factor being investigated Tiagabine in two dose regimens 16mg given 2 times per day and 8mg given 4 times per day as adjunctive therapy.

Comparisons The study compares tiagabine with placebo as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up 24 weeks: 8 week baseline period, 12 weeks treatment period and 4 weeks termination period.

Outcome measures studied Primary outcome is the change from the baseline to experimental period in the 4 week frequency of CPSs. Secondary outcomes: same analysis for simple partial and partial seizures with sec. generalization.

Results Primary outcome

Median reduction

In the ITT population patients on 16mg x 2 per day had a median reduction in the 4 week CPS frequency of 1.6 seizure from the baseline of 8.4 (p=0.06 vs P=0.2 with placebo from a baseline of 8.0). In patients who were taking 8mg x 4 per day the median reduction was 1.2 from a baseline of 7.9 (p=0.02 vs the placebo group).

Response rates

A reduction of 50% or more was observed in 33 (31%) of the patients who were taking 16mg x 2, 28(27%) of those who were taking 8mg x 4, and 10(10%) of those

in the placebo group ($p \leq .001$ for each of the tiagabine groups compared to placebo).

Secondary outcomes

Median reduction in simple partial seizures

The 4 week frequency of simple partial seizures decreased by a median of 1.4 and 2.1 seizures in the group of patients who received 16mg x 2 per day and 8mg x 4, respectively, while the 4 week frequency rose by 0.6 seizures in the placebo group ($p=0.008$ for the 8mg x 4 group vs placebo).

Response rates

Significantly more patients in the 16mg x 2 group had 50% or more reductions in the frequency of simple partial seizures than in the placebo group: 37% vs 16% ($p=0.03$). For the 8mg x 4 group there was no significant difference ($p=.21$, 29% vs 16%).

Median reduction in secondarily generalized tonic-clonic (SGTC) seizures

Patients in the 16mg x 2 group, the 8mg x 4 group, and the placebo group experienced median decreases in SGTC seizures of 0.8, 0.7 and 0.3 respectively ($p=0.69$ vs 16mg x 2; $p=0.48$ vs 8mg x 4).

Response rates

The combined partial seizure frequencies declined by 50% or more in 28% of the group that received tiagabine 2 times per day and 23% of the group that was given tiagabine 4 times per day compared with 8% of the placebo group ($p < 0.001$ and $p < 0.002$, respectively).

Adverse events

Adverse events occurring significantly more often in tiagabine-treated patients than in placebo-treated patients*

	Treatment group, % of patients		
	Placebo n=107	16mg x 2 n=106	8mg x 4 n=105
Adverse events			
Nervousness	0.9	9.4*	10.5*
Vomiting	2.8	9.4*	3.8
Abdominal pain	0.9	7.5*	9.5*
Emotional lability	0.9	0.9	7.6*
Amnesia	0.9	6.6*	4.8
Other pain	2.8	9.4*	1.0

* $P \leq 0.05$ vs placebo

28 patients discontinued drug therapy because of adverse events during the titration and fixed-dose periods: 13(12%) in the group that received 16mg x 2, 8(8%) in the group that received 8mg x 4 and 7(7%) in the placebo group. Serious adverse events occurred in 6 patients (2 from each treatment group).

Safety and adverse effects

Does the study answer the question?

Yes. Adjunctive tiagabine therapy given as 32mg/day (16mg x 2 or 8mg x 4) reduced the frequency of partial seizures in patients whose conditions were refractory to treatment with other AEDs.

Effect due to factor in study?

Unsure. This is a relatively large study but no power calculation was performed. It is not clear how much power this study had to detect differences between the treatment groups.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients had to have a diagnosis of complex partial seizures to be included in this study.

Internal Validity

Sackellares JC; Ramsay RE; Wilder BJ; Browne TR; Shellenberger MK;

Study Type Randomised Controlled Trial **Funding** Dainippon Pharmaceutical Company and Elan Pharmaceuticals, Inc.

Number of participant n=152 (n=74 in the placebo group and n=78 in the treatment group)

Inclusion/Exclusion Criteria Inclusion criteria: aged 17 to 65 years, an unequivocal history of partial seizures refractory to current AED therapy; at least four complex partial seizures per month; no more than eight generalized tonic, clonic, or tonic-clonic seizures per month. Receiving at least one, but no more than two standard AEDs. Exclusion criteria: history or evidence of progressive encephalopathy or a progressive structural lesion in the CNS; progressive ophthalmologic disease; or clinically significant cardiac, hematologic, hepatic, or renal disease.

Patient Characteristics Patient demographic characteristics

Characteristic	Placebo n = 74	ZNS n = 78
Sex, no. (%) ^a		
Male	43 (58.1)	58 (74.4)
Female	31 (41.9)	20 (25.6)
Race, no. (%)	n = 74	n = 78
Caucasian	64 (86.5)	68 (87.2)
African American	5 (6.8)	4 (5.1)
Other ^b	5 (6.8)	6 (7.7)
Age (yr)	n = 74	n = 78
Mean ± SD	36.4 ± 11.3	35.6 ± 12.1
Range	17.8–67.5	17.9–64.1
Weight (kg)	n = 74	n = 78
Mean ± SD	72.7 ± 16.1	74.6 ± 15.7
Range	41–120	44–114
Age at seizure onset (yr) ^c	n = 73	n = 77
Mean ± SD	16.5 ± 10.5	15.9 ± 12.5
Range	0.0–43.0	0.0–59.0
Baseline seizure frequency (seizures/mo)		
All partial		
No.	74	78
Mean	20.3	25.6
Median (range)	9.6 (2.0–186.7)	9.1 (1.3–201.0)
Complex partial		
No.	72	78
Mean	15.1	23.6
Median (range)	7.8 (0.3–119.2)	8.0 (0.7–201.0)
All seizures		
No.	74	78
Mean	20.9	25.9
Median (range)	10.6 (2.0–190.7)	9.1 (1.3–201.0)

ZNS, zonisamide.
^aSignificant difference observed between treatment groups (p < 0.05).

^bOther included patients of Hispanic heritage.

^cAge at seizure onset was unavailable for one patient in the placebo group and one patient in the ZNS group.

Recruitment Not reported.

Setting Four locations in the United States.

Interventions/ Test/ Factor being investigated Zonisamide as adjunctive treatment to currently used AEDs.

Comparisons Zonisamide compared to placebo as adjunctive therapy to currently used AEDs.

**Length of Study/
Follow-up**

24 weeks: 8 to 12 weeks baseline and 12 weeks treatment.

**Outcome measures
studied**

Primary outcome: median percentage reduction in frequency in patients with all partial seizures between weeks 5 and 12 of the treatment phase, relative to baseline seizure frequency. Secondary outcomes: responder rate.

Results

Primary outcome

Percentage reduction in seizure frequency and responder rates for the placebo and ZNS groups

seizures	Seizure type		All
	All partial	Complex partial	
Reduction in seizure frequency			
Placebo	n = 74 -4.7%	n = 72 0.5%	n = 74 -6.6%
ZNS	n = 78 28.9%	n = 78 27.4%	n = 78 25.5%
p Value	0.0009	0.0007	0.0005
Responder rate			
Placebo	n = 74 16.2%	n = 72 13.9%	n = 74 16.2%
ZNS	n = 78 26.9%	n = 78 30.8%	n = 78 28.2%
p Value	0.1141	0.0159	0.0796

Adverse events

Overall, treatment-emergent adverse events occurred with significantly greater incidence in the ZNS group compared with the placebo group (p < 0.05). In both treatment groups, adverse events were generally mild (17 of 78, 21.8% ZNS; 20 of 74, 27.0% placebo) or moderate (30 of 78, 38.5% ZNS; 17 of 74, 23.0% placebo) in severity. The most frequently reported adverse events associated with ZNS were somnolence, irritability, dizziness, nausea, and fatigue. 12 patients in the ZNS group and one patient in the placebo group withdrew because of adverse events.

ZNS, zonisamide.

**Safety and adverse
effects**

**Does the study
answer the question?**

Unsure. The study concludes that as adjunctive treatment, ZNS was generally well tolerated and significantly improved seizure control among patients with refractory partial seizures. The study however did not conduct a power calculation so it is not clear how much power the study had to detect a difference between the two groups.

**Effect due to factor in
study?**

No. The study however did not conduct a power calculation so it is not clear how much power the study had to detect a difference between the two groups.

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?**

All patients had an unequivocal history of partial seizures.

Internal Validity

Sander JW;Patsalos PN;Oxley JR;Hamilton MJ;Yuen WC;

A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy

Ref ID 4733

1990

Study Type

Randomised Controlled Trial

Funding

Not reported.

Number of participant n=21 in this cross-over study.

Inclusion/Exclusion Criteria Not reported.

Patient Characteristics Patients were aged 23-42 years (mean = 34 years) and weighed 52-92 kg (mean = 73 kg). The 3 female patients who participated were not considered to be at risk of pregnancy. All patients had severe refractory epilepsy, which was due to a structural lesion in 11; in 10 patients no cause had been found. The duration of epilepsy ranged from 8 to 40 years (mean = 25 years). Eighteen patients had partial and secondarily generalized seizures, and 3 had generalized seizures. All patients had at least 4 seizures/month for the 3 months prior to the study and all had had extensive treatment with carbamazepine (CBZ), phenytoin (PHT), phenobarbitone (or primidone; PRM) and sodium valproate (SVP) in monotherapy or in combinations.

Recruitment All patients were recruited from a residential centre for Epilepsy.

Setting A residential home for patients with epilepsy.

Interventions/ Test/ Factor being investigated Lamotrigine in two doses according to patients' currently used AED.

Comparisons The comparison is between lamotrigine and placebo as adjunctive therapy in patients taking at least one AED.

Length of Study/ Follow-up 44 weeks: an 8-week baseline period, a 12 week treatment period, a 6 week washout period, another 12 week treatment period and a final 6 week washout period.

Outcome measures studied Not specified. Efficacy was evaluated using 2 measures: the overall seizure frequency and the number of seizure days, i.e. days on which at least 1 seizure of any type was reported.

Results Generalized and total of seizures in the 18 patients who completed the trial

	Baseline		Week 0-4		Week 5-8		Week 9-12	
	Gener. Total		Gener. Total		Gener. Total		Gener. Total	
Lamotrigine	76	371	72	450	48	291	33	288
Placebo			66	344	53	298	64	338

Although a comparison between the LTG and placebo periods showed no significant difference in total seizure frequency, there was a marked decrease in the number of generalized seizures observed in the last 4 weeks of the active treatment period, when compared to the placebo treatment period and with baseline.

Adverse events.

Adverse effect	Placebo	Lamotrigine
Ataxia	3	4
Diplopia	2	3
Dizziness	2	3
Drowsiness	3	3
Headache	2	3
Depression	1	0
Nausea	1	2
Vomiting	0	2

Safety and adverse effects There was no significant difference between the adverse experiences during the placebo and active treatment phases.

Does the study answer the question? Unsure. The study sample was small (n=21) and no tests of significance were reported. The study concludes that there appears to be a drug effect as there is a marked reduction in generalized tonic-clonic seizures in favour of lamotrigine in the last 4 weeks of the treatment period.

Effect due to factor in study? No. The study sample is small and no power calculation was performed. It is not clear if the result reported could have been found by chance.

Consistency of results with other studies?

Directly applicable to guideline population?

The study comprised patients with severe epilepsy who all had partial complex seizures with or without generalized seizures.

Internal Validity

Schachter SC;Leppik IE;Matsuo F;Messenheimer JA;Faught E;Moore EL;

Lamotrigine: a six-month, placebo-controlled, safety and tolerance study.

Ref ID 4775

1995

Study Type

Randomised Controlled Trial

Funding

Boroughs Wellcome (one of the companies merged to form GSK)

Number of participant

446, 334 to LTG, 112 to placebo (3:1 ratio)

Inclusion/Exclusion Criteria

Inclusion criteria:

- Men and women 18-65 years old with a history of simple or complex partial seizures (with or without becoming generalised seizures classified according to the International Classification of Epileptic Seizures) that were refractory to treatment with a stable regimen or one to three AEDS (excluding VPA).
- At least one partial seizure in the 12 weeks proceeding to randomisation.
- Women of child bearing age that use and acceptable contraceptive method and not pregnant.

Exclusion criteria:

- Epilepsy is newly diagnosed (>32 weeks)
- Have a diagnoses of primary generalised seizures (including absence seizures) or psychogenic seizures
- Progressive neurologic disorder that was not stable for at least 24 weeks before baseline
- seizures secondary to infection, neoplastic, demyelination, metabolic illness, progressive generative disease, or the active use of drug or alcohol
- Experienced status epilepticus within 24 weeks of baseline
- Received treatment with an investigational drug within 12 weeks of baseline
- Concomitant AED dose adjustments within 2 weeks of baseline (within 4 weeks for phenobarbital)
- Concomitant valproic acid (VPA) within 4 weeks of baseline and during the study period
- Serious side effects from present therapy
- Drug abuse or consumption of any psychoactive drugs
- Severe psychiatric condition requiring hospitalisation
- IQ<50
- A significant concomitant medical disorder, or any condition that interfere with the pharmacokinetics of drugs
- History of non compliance

Patient Characteristics

	Lamotrigine (N=334)	Placebo (N=112)
Male:	173(52%)	63(56%)
Mean age:	35	35
Range:	18-64	18-64
Race		
White	290(87%)	96(86%)
Black	33(10%)	10(9%)
Other	11(3%)	6(5%)
Duration of epilepsy (year)	21	21
Mean age of epilepsy onset (year)	12	11.5
Concomitant therapy		
1 concomitant AED	(43%)	(46%)
2 concomitant AEDs	(50%)	(50%)
3 concomitant AEDs	(7%)	(4%)
Carbamazepine	(75%)	(71%)

Phenytoin	(38%)	(45%)
Primidone	(16%)	(13%)
Phenobarbital	(13%)	(14%)

Recruitment	Patients were recruited from 34 centres
Setting	Multicentre – 34 centres.
Interventions/ Test/ Factor being investigated	Lamotrigine twice daily (to 500 mg/day) Placebo All patients received 1-3 marketed AEDs (except VPA)
Comparisons	Adjunctive: Comparisons between treatment and placebo added on to existing therapy
Length of Study/ Follow-up	Total 27 weeks – 24 weeks for maintenance and titration, 3 weeks for tapering off (over 2 weeks) and follow up
Outcome measures studied	Primary and secondary outcomes not specified. This was described as a “safety and tolerance study”
Results	Subjective Global Investigator Evaluation scale: 65% of patients in the LTG and 35% in the placebo group improved at week 24 as opposed to baseline.

The proportion of participants having treatment withdrawn due to adverse events:
LTG: 28/334 (8%)
Placebo: 9/112 (8%)

Incidence of adverse events >10%		
Adverse events:	LTG	Placebo
Dizziness:	167/334(50%)	20/112(18%) , p≤0.05
Diplopia:	110/334(33%)	12/112(11%), p≤0.05
Ataxia:	80/334(24%)	6/112(5%), p≤0.05
Blurred Vision:	77/334(23%)	10/112(9%) p≤0.05
Nausea:	73/334(22%)	17/112(15%)
Somnolence:...	47/334(14%)	8/112(7%), p≤0.05
Coordination abnormality:	40/334(12%)	7/112(6%)
Rash:	33/334(10%)	6/112(5%)
Dyspepsia: ...	33/334(10%)	6/112(5%)
Respiratory disorder:	23/334(7%)	15/112(13%)

Safety and adverse effects	Most (90%) adverse events are mild or moderate. One patient had Stevens Johnson syndrome while on LTG at 400mg/day. One case of sudden unexplained death in epilepsy in the placebo group during the dose tapering stage. Patients in the LTG group who received CB exhibited more adverse events. ECG, urinalysis, haematology and clinical chemistry: “unremarkable” results
Does the study answer the question?	LTG doses ≤ 500mg/day are well tolerated as an add on therapy for a 6-month treatment period in outpatients with refractory partial seizures.
Effect due to factor in study?	There are no significant factors affecting the overall evaluation. The sample size would be too small to detect significant differences in rarer events.
Consistency of results with other studies?	
Directly applicable to guideline population?	Unsure. No indirectness noticed

Internal Validity

Schapel GJ;Beran RG;Vajda FJ;Berkovic SF;Mashford ML;Dunagan FM;Yuen WC;Davies G;

Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures

Ref ID 4758

1993

Study Type	Randomised Controlled Trial	Funding	GlaxoSmithKline
Number of participant	N=41 n=20 in LTG/Placebo group n=21 in Placebo/LTG group		
Inclusion/Exclusion Criteria	Inclusion: aged 16–65 years; refractory partial seizures; receiving no more than two other standard AEDs; at least 4/month partial seizures in previous 3 months; absence of concomitant medication; no confounding medical or psychiatric disturbances; ability to keep seizure diary; provide informed consent Exclusion: severe organic or psychiatric disease; severe mental subnormality or progressive neurological disease		
Patient Characteristics	<p>Aetiology of seizures: Idiopathic/unknown: total (n=19/41);LTG/placebo: (n=8/20);Placebo/LTG (n=11/21) Symptomatic: total (n=22/41);LTG/placebo (n=12/20);Placebo/LTG (n=10/21)</p> <p>Age at onset (yrs) Mean (SD) : total 10.4 (9.6); LTG/placebo 10.5 (9.5); Placebo /LTG 10.4 (10) Range: total 0-46;LTG/placebo 0-37; Placebo/LTG 0.5-46</p> <p>History of status epilepticus Yes : total n=5/41; LTG/placebo n=2/20; Placebo/LTG n=3/21 No: total n=35/41; LTG/placebo n=18/20; Placebo/LTG n=17/21 Unknown: total n=1/41; LTG/placebo n=0/20; Placebo/LTG n=1/21</p> <p>Number of uncontrolled seizure types: 1: total n=16/41; LTG/placebo n=9/20; Placebo/LTG n=7/21 2: total n=15/41;LTG/placebo n=6/20;Placebo/LTG n=9/21 3: total n=9/41;LTG/placebo n=4/20;Placebo/LTG n=5/21 4: total n=1/41;LTG/placebo n=1/20;Placebo/LTG n=0/21</p> <p>Number of AEDs being taken: One concurrent AED: total (n = 6/41); LTG/placebo: (n = 2/20);placebo/LTG: (n = 4/21). Two concurrent AEDs: total (n = 34/41); LTG/placebo (n = 18/20); placebo/LTG (n = 16/21) Three concurrent AEDs: total (n = 1/41); LTG/placebo (n = 0/20);placebo/LTG: (n = 1/21)</p> <p>Baseline seizure frequency Total baseline seizure frequency (3 months pre-trial): total (n = 41):mean = 84.3 (SD 97.2); LTG/placebo (n = 20): mean = 100.7 (SD 107.3); placebo/LTG (n = 21): mean = 68.8 (SD 86.2)</p>		
Recruitment	Not stated		
Setting	4 centres throughout Australia		
Interventions/ Test/ Factor being investigated	Lamotrigine (150mg or 300mg) as add-on therapy in patients with partial seizures poorly controlled by established AEDs. There was a 3-month retrospective baseline period to establish seizure frequency. Patients were given full dose of LTG by week 2 of the 12-week treatment period. Patients on enzyme-inducing concomitant AEDs only received 300 mg/day (Group 1), patients on enzyme-inducing concomitant AEDs and VPA received 150 mg/day (Group 2). This was followed by a 4-week washout period with dosage tapered in the first week and placebo given in the remaining 3 weeks. The same procedure was followed for phase 2 of the study		
Comparisons	Lamotrigine (150mg or300mg daily) compared to placebo		
Length of Study/ Follow-up	12 weeks		

Outcome measures studied	Total seizure count; number of participants experiencing specified percentage reductions in total seizure counts; seizure days; Change in seizure frequency; Physician/patient global evaluation of improvement/efficacy/tolerability
Results	<p>There was a highly significant ($p < 0.001$) decrease in total seizure counts on LTG compared with placebo. Overall, 22% of patients experienced at least a 50% reduction in the total numbers of all seizure types on LTG compared with none on placebo.</p> <p>There was a significant ($p < 0.05$) reduction in partial seizure counts on LTG compared with placebo. When total numbers of secondarily generalised seizures were compared the trend for a reduction in this seizure type did not reach significance ($0.05 < p < 0.1$).</p> <p>Concomitant AED plasma concentrations were virtually unchanged.</p> <p>There was a significant reduction in the number of seizure days on LTG ($p < 0.001$)</p> <p>Adverse events: All patients reported at least 1 adverse event, all but one of the 321 reports were classified as "not serious". Confidence intervals indicate that patients on LTG more frequently reported dizziness than on placebo. There were also trends for diplopia and vision abnormality to be reported more frequently on LTG than placebo, but the CI included zero. One serious adverse event was reported for a patient who developed CSF leak after a skull fracture due to seizure which required surgical repair. This occurred when the patient was receiving placebo. There was no evidence of any effect of LTG on blood pressure, heart rate or body weight.</p> <p>Results from Banks and Beran (RMId 4715) - cognitive outcomes in sub sample of 10 patients: Neuropsychological assessment including the following tests (National Adult Reading Test for intellectual level, Stroop Colour Word Test for concentration and attention, Trail Making Tests A and B and Digit Symbol for General Cerebral Efficiency, Digit Span and Rey Complex Figure Test for Mnestic functions) Parametric statistical methods were impossible to use because of differing format of scores across cells (scaled scores, percentiles, IQ scores...)</p> <p>While the neuropsychological data collection for LTG is still in infancy, it was readily apparent that this medication has few, if any, of the sedating properties previously associated with the older generation AEDs, particularly phenobarbitone and phenytoin.</p>
Safety and adverse effects	see results section
Does the study answer the question?	This study concludes that lamotrigine is an effective AED in the treatment of therapy-resistant partial seizures and is well tolerated when given in addition to up to 2 other established AEDs
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	Population, intervention, comparator and outcomes relevant. Dosages used were within the usual dose range.

Internal Validity

Sethi A;Chandra D;Puri V;Mallika V;

Gabapentin and lamotrigine in Indian patients of partial epilepsy refractory to carbamazepine

Ref ID 903

2002 Sep

Study Type	Randomised Controlled Trial	Funding	Unknown.
Number of participant	n=52 (25 in lamotrigine group and 27 in gabapentin)		
Inclusion/Exclusion Criteria	Inclusion criteria: suffering from partial seizures of not more than 2 years duration and on carbamazepine (CBZ) monotherapy, at least 4 seizures before being enrolled.		
Patient Characteristics	<p>For the group as a whole (n=52) characteristics were as follows: simple partial seizures n=17, complex partial seizures n=15 and secondarily generalized seizures n=20; age group 10 to 60 years; female n=27 and male n=25.</p> <p>In the gabapentin group the average frequency of seizures at baseline was 6.26+/-3.86 and 5.04+/-2.47 in the lamotrigine group. The time period was not reported nor was length of baseline reported.</p>		
Recruitment	Not reported.		
Setting	India.		
Interventions/ Test/ Factor being investigated	Gabapentin and lamotrigine as adjunctive therapy to carbamazepine.		
Comparisons	Comparisons are made between gabapentin and lamotrigine as adjunctive therapy to carbamazepine.		
Length of Study/ Follow-up	Unknown. Length of baseline period and titration period not reported. It is unclear whether the add-on period included a titration phase.		
Outcome measures studied	The primary efficacy criteria for efficacy were PCB (percentage change in seizure frequency from baseline), responder rate and response ratio. Subgroup analysis of seizures was performed by type of seizures.		
Results	<p>Primary outcome.</p> <p>The average frequency of seizures at baseline was 6.26+3.86 and 5.04+2.47 in the gabapentin group and lamotrigine group, respectively. This frequency decreased significantly ($p < .001$) after 12 weeks of add on therapy to 1.75+2.16 and 1.68+2.94. The PCB value was -72+34.92 and -76.22+29.68 in the gabapentin group and lamotrigine group, respectively. However, no significant difference was seen in seizure frequency and PCB values between these two groups after 12 weeks of add on therapy. An inadequate response i.e. less than 50% reduction in number of seizures was observed in 4 out of 27 cases (14.8%) in group I, while, one out of 25 cases (4.0%) in group II, after 12 weeks of add on therapy. The responder rates in the gabapentin group and lamotrigine group were 77.7% and 92%, respectively.</p> <p>Subgroup analysis</p> <p>The responder rate for SPS, CPS and partial seizures with secondarily generalization was 90.9% (10 of 11 cases), 75% (3 of 4 cases), 66.6% (8 of 12 cases) respectively in the gabapentin group, while corresponding value in the lamotrigine group was 100%(6 of 6 cases), 90.9% (10 of 11 cases), 87.5% (7 of 8 cases) .</p> <p>Adverse events</p> <p>The most commonly occurring adverse events were dizziness, headache and drowsiness in both groups. However, skin hypersensitivity reaction only occurred in the lamotrigine group.</p>		
Safety and adverse effects	Skin rashes appear to be related to lamotrigine use only.		
Does the study answer the question?	Unsure. The paper is not well written in that it is not clear how long treatment and titration were for, or what the target dose of medication was. Both the lamotrigine and gabapentin groups saw a significant reduction in seizure frequency after 12 weeks adjunctive therapy, but there was no significant difference between the groups in seizure reduction.		

Effect due to factor in study? No. No statistical power calculations were conducted.

Consistency of results with other studies?

Directly applicable to guideline population? The study population consisted of patients with partial seizures whose seizures were refractory to carbamazepine.

Internal Validity

Sharief M;Viteri C;Ben-Menachem E;Weber M;Reife R;Pledger G;Karim R;

Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy

Ref ID 4745

1996

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant 24 patients placebo; 23 patients topiramate

Inclusion/Exclusion Criteria
Inclusion: 18-65 years; hx of partial seizures by EEG and good mental and physical health without progressive lesion; refractory on one or two AEDs; women of childbearing age using birth control
Exclusion: Seizure free three weeks during baseline period; hx of nephrolithiasis or allergy to carbonic anhydrase inhibitors or sulfonamide.

Patient Characteristics

	Placebo n=24	Topiramate n=23	Total n=47
Gender			
Men	19	21	40
Women	5	2	7
Age, y			
Mean (SD)	32.6(11.1)	35.4(14.0)	34(12.6)
Race			
Caucasian	24	23	47
Weight (kg)			
Mean (SD)	73.1+/-12.3	74.9+/-12.4	74+/-12.2

Recruitment Unknown

Setting Sweden, Spain, UK and France

Interventions/ Test/ Factor being investigated Safety and efficacy of topiramate as adjunctive therapy

Comparisons Topiramate vs. placebo

Length of Study/ Follow-up 3 week titration and 8 week stabilization

Outcome measures studied Seizure type and frequency data and global evaluations of investigators and patients.

Results
Median percent reduction from baseline in monthly seizure frequency during the double-blind phase was not significantly greater in the topiramate group than in the placebo group (41% vs. 1%; P = 0.065).
There were a greater number of treatment responders in the topiramate groups (> or = 50% reduction in seizures; 35% vs. 8%; P = 0.033); better investigator (P = 0.002) and patient (P = 0.021) global assessments; and greater reductions in secondarily generalized seizures compared to placebo (P = 0.002).

Premature withdrawals from study due to adverse events: 1/24 in placebo group and 6/34 in topiramate group.

Safety and adverse effects	The most commonly reported topiramate treatment-emergent adverse events were somnolence, fatigue, abnormal vision, weight decrease, and anxiety. Most adverse events were mild or moderate in severity. Among 7 withdrawals due to limiting adverse events, 6 were CNS-related (in 5 topiramate-treated patients).
Does the study answer the question?	Results of this trial strongly suggest that topiramate 400 mg/day is effective and well tolerated in the treatment of refractory partial epilepsy
Effect due to factor in study?	This is a small study and should be repeated
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Multicentre and small sample

Shorvon SD;Lowenthal A;Janz D;Bielen E;Loiseau P;

Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group

Ref ID 4742

2000

Study Type	Randomised Controlled Trial	Funding	UCB Pharma funded. Statistical analysis support from UCB.
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Number of participant N=324, n=112 placebo, 106 in LEV1000mg/day and LEV2000mg/day

Inclusion/Exclusion Criteria

Inclusion criteria:

- Men and women with refractory epilepsy who had seizure that were only or predominantly partial, with or without secondary generalisation.
- 16-65 years old
- Seizures persisted at least the previous 2 years despite treatment with ≥ 2 other AEDs
- maintain a stable dose of up to 2 AEDs for at least 4 weeks before selection visit and throughout the study
- AT least 4 partial seizures during each 4 week intervals in the 8-or 12-week baseline period.
- Women of childbearing age with medically accepted contraception method or sterilised

Exclusion criteria:

Renal insufficiency, progressive neurological disorders, serious psychiatric disorders Clinically significantly baseline laboratory abnormalities , current or recent history of substance abuse, questionable compliance with drug treatment or concomitant disorders that could hinder evaluation of efficacy or tolerability
Severe or progressive disease excluded with EEG, 12 lead ECG and either cranial CT or MRI scan.

Patient Characteristics	Placebo N=112	LEV1000mg/d N=106	LEV2000mg/d N=106
Age, mean \pm SD (yrs):	37 \pm 12	36 \pm 10	37 \pm 12
Males:	55(49%)	51(48%)	51(48%)
Weight \pm SD:	71 \pm 15	72 \pm 17	72 \pm 17
Duration of epilepsy (yrs):	23.2 \pm 11.0	23.8 \pm 12.3	23.6 \pm 13.3
Idiopathic/cryptogenic:	64(57.1%)	59(55.7%)	60(56.6%)
Seizure type:			
Simple partial:	40(36%)	31(29%)	30(28%)
Complex partial:	93(83%)	84(79%)	93(88%)
Secondary generalised:	26(23%)	28(26%)	29(27%)
Others:	8(7%)	4(4%)	10(9%)
Median baseline seizures:	2.50	2.82	2.58

Number of concomitant AEDs:			
1:	18(16%)	23(22%)	19(18%)
2:	88(79%)	76(72%)	83(78%)
≥3:	6(5%)	7(7%)	4(4%)

Recruitment	324 patients recruited from 61 European centres from 392 screened																				
Setting	61 European centres																				
Interventions/ Test/ Factor being investigated	LEV 1000mg/day vs, LEV 2000mg/day vs Placebo																				
Comparisons	Adjunctive therapy: LEV 100mg/day vs LEV 2000mg/day vs placebo added on to 1-2 stabilised AEDs																				
Length of Study/ Follow-up	8-12 weeks baseline, 4 weeks titration plus 16 weeks double blinded maintenance doses (Total 28 weeks)																				
Outcome measures studied	Primary: Mean number of seizure per week Secondary: Seizure type or subtype , proportion of patients experiencing ≥50% reduction in partial seizure frequency compared to baseline, number of seizure free patients																				
Results	<p>Proportion of patients experiencing ≥50% reduction in partial seizure frequency (responder rate):</p> <p>LEV 1000mg/day: 23/101 (22.8%) p=0.019 vs placebo LEV 2000mg/day: 30/95 (31.6%) p=<0.001 vs placebo Placebo: 11/106 (10.4%) p=0.004 vs treatment groups</p> <p>Proportion of seizure free patients:</p> <p>LEV 1000mg/day: 5/101 (5.0%) LEV 2000mg/day: 2/95 (2.0%) Placebo: 1/106 (0.9%)</p> <p>Withdrawal due to adverse events:</p> <p>LEV 1000mg/day: 8/106 (7.5%) LEV 2000mg/day: 15/106 (14.2%) Placebo: 6/112 (5.4%)</p> <p>Incidence of adverse events≥10%</p> <table> <thead> <tr> <th></th> <th>Placebo N=112</th> <th>LEV1000mg/day N=106</th> <th>LEV2000mg/day N=106</th> </tr> </thead> <tbody> <tr> <td>Accidental injury:</td> <td>17(15.2%)</td> <td>13(12.3%)</td> <td>14(13.2%)</td> </tr> <tr> <td>Headache*:</td> <td>10(8.9%)</td> <td>14(13.2%)</td> <td>17(16.0%)</td> </tr> <tr> <td>Asthenia*:</td> <td>9(8.0%)</td> <td>8(7.5%)</td> <td>14(13.2%)</td> </tr> <tr> <td>Somnolence*:</td> <td>5(4.5%)</td> <td>10(9.4%)</td> <td>12(11.3%)</td> </tr> </tbody> </table> <p>* "more commonly reported" in LEV groups</p>		Placebo N=112	LEV1000mg/day N=106	LEV2000mg/day N=106	Accidental injury:	17(15.2%)	13(12.3%)	14(13.2%)	Headache*:	10(8.9%)	14(13.2%)	17(16.0%)	Asthenia*:	9(8.0%)	8(7.5%)	14(13.2%)	Somnolence*:	5(4.5%)	10(9.4%)	12(11.3%)
	Placebo N=112	LEV1000mg/day N=106	LEV2000mg/day N=106																		
Accidental injury:	17(15.2%)	13(12.3%)	14(13.2%)																		
Headache*:	10(8.9%)	14(13.2%)	17(16.0%)																		
Asthenia*:	9(8.0%)	8(7.5%)	14(13.2%)																		
Somnolence*:	5(4.5%)	10(9.4%)	12(11.3%)																		
Safety and adverse effects	<p>Serious adverse events with probable relationship to drug was recorded in 13 patients, 3 in placebo, 2 in LEV1000mg/day and 15 in 2000mg/day groups. Somnolence, asthenia and headache are more commonly reported among patients receiving LEV.</p> <p>No clinically relevant changes in laboratory values</p>																				
Does the study answer the question?	Treatment by LEV is superior compared to placebo as an add on therapy in patients with refractory seizures in terms of efficacy at 1000mg/day and 2000mg/day, without interactions with other AEDs. Adverse events were profile comparable to placebo																				
Effect due to factor in study?	Industry sponsored double blinded study. Randomisation allocation, concealment and blinding methods not clearly reported.																				
Consistency of results with other studies?																					
Directly applicable to guideline population?	No indirectness observed. Baseline frequency of 4 seizures/4 week typical?																				

Internal Validity

11 January 2011

Study Type Randomised Controlled Trial **Funding** Parke Davis/Warner Lambert

Number of participant 43 total: 16 Gabapentin (GBP) 900 mg; 9 GBP 1200 mg; 18 placebo.

Inclusion/Exclusion Criteria Inclusion: Severe epilepsy, experiencing four or more seizures a month despite one or two AEDs. The dosage of AED therapy stable for 3 months.

Patient Characteristics The 43 patients (20 men and 23 women) had a mean age of 39 years (range 16-59) and mean duration range from 1 to 49 years (median 23 years). CBZ was received by 39 patients, clonazepam by 14, valproate by 8 and phenytoin by 3.

Recruitment Unknown

Setting Finland

Interventions/ Test/ Factor being investigated GBP as add on therapy

Comparisons Placebo or 900 mg GBP or 1200 mg GBP per day

Length of Study/ Follow-up Initial 3 month baseline; treatment for 3 months.

Outcome measures studied Percentage of change of seizure frequency in the treatment group as compared with baseline

Results	Seizure reduction %	GBP 900 n(%)	GPB 1200 n(%)	Placebo n(%)
Worse		6(38)	0	5(27)
0-24		4(25)	2(22)	7(39)
25-49		4(25)	4(45)	3(17)
50-74		2(12)	0	0
>75		0	3(33)	0
Total		16	9	18

A statistically significant difference in seizure frequency from the baseline to the treatment phase was noted between patients receiving placebo and GBP 1,200 mg (p=0.016). The difference between GBP dosage of 900 mg and placebo was not statistically significant. The difference between doses of 900mg and 1200mg were significant (p=0.032).

Safety and adverse effects The adverse effects were minor and consisted mainly of transient drowsiness.

Does the study answer the question? GBP appears to be effective in the treatment of partial epileptic seizures in a dosage-related manner

Effect due to factor in study? This is a small study and should be repeated.

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity Small study

Study Type	Randomised Controlled Trial	Funding	Industry: GlaxoSmithKline.
Number of participant	N=81. Intervention group: 41. Comparator group: 40.		
Inclusion/Exclusion Criteria	Inclusion: Aged 12–70 years; A clinical and neurophysiological diagnosis of epilepsy uncomplicated by pseudoseizures; A history of partial seizures that did or did not become secondarily generalised, recognisable by patients or relatives, at least once weekly; Resistant to current AEDs; Concomitant AEDs unchanged for the previous 2 months. Exclusion: severe organic or psychiatric disease; Mental subnormality; Progressive neurological disease; A history of status epilepticus in the previous 6 months; The receipt of concomitant medication for other indications was discouraged but this criterion was not strictly adhered to if the other drugs were likely to remain unchanged throughout the trial; A history of non-compliance, non-attendance at clinics or unreliable recording of seizures; Pregnancy, lactation or current risk of pregnancy.		
Patient Characteristics	Type of epilepsy: Refractory. Type of seizures: Partial onset. Mean age: 33.7 years; age range: 15–67 years. Gender: men = 33, women = 48. Age at onset of seizures: Mean duration of epilepsy: total: 21 years (range 4–45 years). Mean age at onset: total: 11.8 years (range <1–52 years).		
Recruitment	Attendees at a regional neurology outpatient department.		
Setting	UK.		
Interventions/ Test/ Factor being investigated	Lamotrigine 200 or 400 mg/day for 18 weeks. 400 mg/day for patients receiving enzyme-inducing drugs only; 200 mg/day for patients receiving a combination of enzyme-inducing drugs and VPA. Dosage could be reduced to a minimum of 50% of the intended maximum dosage but it is not clear how many patients this applied to.		
Comparisons	Lamotrigine versus placebo.		
Length of Study/ Follow-up	Total: 46 weeks. Baseline 4 weeks. Treatment period 1: 18 weeks. Washout: 6 weeks. Treatment period 2: 18 weeks. Washout: 4 weeks.		
Outcome measures studied	Seizure frequency; seizure severity; health-related quality of life; neuropsychological tests; number of patients responding.		
Results	Proportion of responders; reported as number of patients in the given response categories with LTG compared with placebo: Intervention 1: First-phase data LTG (n = 41): 4/41 End-phase data:		

Total seizures (n = 62):
Worse (>26% increase): n = 7
No change (\pm 25%): n = 26
Mild improvement (26–49% decrease): n = 18
Marked improvement (\geq 50% decrease): n = 11

Partial seizures (n = 62):
Worse (>26% increase): n = 10
No change (\pm 25%): n = 23
Mild improvement (26–49% decrease): n = 17
Marked improvement (\geq 50% decrease): n = 12

Secondarily generalised seizures (n = 36):
Worse (>26% increase): n = 4
No change (\pm 25%): n = 17
Mild improvement (26–49% decrease): n = 5
Marked improvement (\geq 50% decrease): n = 10

Comparator
First-phase data placebo (n = 40): 1/40
End-phase data: not reported

Change in seizure frequency; percentage seizure reduction comparing LTG with placebo:

Intervention 1 (n = 62):
Total seizures: 29.7% (95% CI: 17.8 to 39.9)
Total partial seizures: 25.2% (95% CI: 10.7 to 37.4)
Secondarily generalised seizures: 20.3% (95% CI: 0.3 to 36.2)
CPSs: 33.4 (95% CI: 14.8 to 47.9)

Comparator: see above.

Change in seizure severity; assessed by patient using a 16-item questionnaire divided into two subscales [perception and control (PERCEPT) and ictal and postictal (ICTAL)], and by the carer using an 8-item questionnaire. Mean scores are reported

Intervention 1:
LTG (n = 53)
PERCEPT: mean = 25.19
ICTAL: mean = 19.47
Carer view: mean = 20.35

Difference between means for LTG and placebo (95% CI)
PERCEPT: -0.28 (95% CI: -1.00 to 0.43)

ICTAL: -1.06 (95% CI: -1.90 to -0.22) (p = 0.017)
Carer view: -1.45 (95% CI: -2.77 to -0.14) (p = 0.035)

Comparator
Placebo (n = 53)
PERCEPT: mean = 25.47
ICTAL: mean = 20.53
Carer view: mean = 21.80

Change in patient-related QoL; assessed using Nottingham Health Profile (6 subscales). Mean scores reported:

Intervention 1:
LTG (n = 53)
Energy: mean = 0.68
Pain: mean = 0.60
Emotional reaction: mean = 1.96
Sleep: mean = 0.89
Social isolation: mean = 0.92
Physical mobility: mean = 0.96

Difference between means for LTG and placebo (95% CI):
Energy = 0.00 (95% CI: -0.26 to 0.26).
Pain = -0.09 (95% CI: -0.39 to 0.21)
Emotional reaction = 0.00 (95% CI: -0.43 to 0.43)
Sleep = 0.13 (95% CI: -0.11 to 0.37)
Social isolation = -0.02 (95% CI: -0.31 to 0.27)
Physical mobility = 0.05 (95% CI: -0.24 to 0.35)
All p-values non-significant

Comparator
Placebo (n = 53)
Energy: mean = 0.68
Pain: mean = 0.69
Emotional reaction: mean = 1.96
Sleep: mean = 0.76
Social isolation; mean = 0.94
Physical mobility: mean = 0.91

HRQoL – psychological variables:

Intervention 1:
LTG
Depression (The Hospital Anxiety and Depression Scale, n = 54): mean = 4.24
Anxiety (The Hospital Anxiety and Depression Scale, n = 54): mean = 6.87
Happiness (Affect Balance Scale, n = 51): mean = 3.80
Mood (Profile of Moods States, n = 50): mean = 24.36
Self-esteem (Rosenberg Self-esteem Scale, n = 50): mean = 30.06
Mastery (Pearlin and Schooler Scale 1978, n = 50): mean = 20.02
Difference between the means for LTG vs placebo (95% CI):
Depression = -0.02 (95% CI: -0.76 to 0.40)
Anxiety = 0.04 (95% CI: -0.56 to 1.31)
Happiness = 1.84 (95% CI: 0.70 to 2.99), p = 0.003
Mood = -2.44 (95% CI: -8.64 to 3.76)
Self-esteem = 0.90 (95% CI: -0.21 to 2.00)
Mastery = 1.24 (95% CI: 0.47 to 2.01), p = 0.003

Comparator:
Placebo
Depression (n = 54): mean = 4.26
Anxiety (n = 54): mean = 6.83
Happiness (n = 51): mean = 1.96
Mood (n = 50): mean = 26.80
Self-esteem (n = 50): mean = 29.16
Mastery (n = 50): mean = 18.78

Neuropsychological tests

Intervention 1
LTG
Number Cancellation (this is used to assess repetitive mental activity)
Task AC (n = 44): mean = 51.36
Task AE (n = 43): mean = 3.60
Task BC (n = 42): mean = 48.21
Task BE (n = 43): mean = 1.14
Task C (n = 42): mean = 38.19
Stroop Test (this is used as a measure of concentration)
Time (n = 41): mean = 93.98
Error (n = 44): mean = 2.18
Critical Flicker Fusion Test (n = 40):
mean = 30.44
Choice Reaction Time (n = 40):
mean = 0.675
Difference between means for LTG vs placebo (95% CI):
Number cancellation

Task AC = 1.66 (95% CI: -0.58 to 3.90)
Task AE = 0.56 (95% CI: -0.09 to 1.21)
Task BC = -0.33 (95% CI: -3.04 to 2.48)
Task BE = 0.16 (95% CI: -0.50 to 0.82)
Task C = -1.10 (95% CI: -2.84 to 0.65)
Stroop Test
Time = -4.41 (95% CI: -12.25 to 3.43)
Error = -0.23 (95% CI: -1.10 to 0.65)
Critical Flicker Fusion = 0.07 (-0.57 to 0.70)
Choice Reaction Time = 0.0006 (95% CI: -0.026 to 0.037)

Comparator:

Placebo
Number Cancellation
Task AC (n = 44): mean = 49.70
Task AE (n = 43): mean = 3.04
Task BC (n = 42): mean = 48.54
Task BE (n = 43): mean = 0.98
Task C (n = 42): mean = 39.29
Stroop Test
Time (n = 41): mean = 98.39
Error (n = 44): mean = 2.41
Critical Flicker Fusion Test (n = 40):
mean = 30.37
Choice Reaction Time (n = 40):
mean = 0.669

Adverse events

Intervention 1

Ataxia (36%), diplopia (33%), dizziness (29%), nausea (29%), respiratory disorder (23%), vomiting (17%), headache (16%), somnolence (16%), blurred vision (14%), pain (13%), pharyngitis (11%), asthenia (10%), accommodation abnormality (9%), insomnia (9%), rash (9%), depression (7%), paraesthesia (7%), non-specific symptoms (7%), agitation (6%), amnesia (6%), fever (6%), tremor (6%), emotional lability (4%), menstrual disorder (4%), abdominal pain (4%), back pain (4%), bronchitis (3%), constipation (3%), convulsion (3%), cough (3%)

Comparator

Ataxia (9%), diplopia (6%), dizziness (19%), nausea (11%), respiratory disorder (23%), vomiting (3%), headache (13%), somnolence (10%), blurred vision (4%), pain (9%), pharyngitis (1%), asthenia (17%), insomnia (1%), rash (7%), depression (7%), paraesthesia (1%), non-specific symptoms (7%), agitation (1%), amnesia (7%), tremor (3%), emotional lability (4%), menstrual disorder (3%), abdominal pain (3%), back pain (4%), bronchitis (1%), constipation (1%), convulsion (1%), cough (7%)

Time to exit/withdrawal of allocated treatment: n=19 in first treatment period.

Reasons: adverse events: 11; believed treatment ineffective: 4; withdrew consent: 2; protocol violation: 1; moved from the area: 1.

Treatment failures: 16. Reason: adverse experience while receiving LTG or discontinued prematurely after treatment with LTG, for whatever reason.

Withdrawals

post randomisation
LTG (n = 41): AEs (n = 6),
patient believed treatment was
ineffective (n = 1), withdrew
consent (n = 1)
Placebo (n = 40): AEs (n = 4),
patient believed treatment was
ineffective (n = 3), withdrew
consent (n = 1), protocol
violation (n = 1), lost to follow-up
(n = 1)

Safety and adverse effects 73 different adverse events were reported by patients receiving Lamotrigine and 69 were reported by patients receiving placebo, but many were clearly unrelated to medication. Yet patients reported ataxia, diplopia, nausea, vomiting, blurred vision, pharyngitis, accommodation abnormality, and insomnia significantly less frequently when they received placebo rather than Lamotrigine.

11 reactions in 8 patients were considered 'serious' and none were 'life-threatening'. Four patients while on LTG developed a severe rash: generalised maculopapular in 3 patients, with oral mucous membrane involvement in 2. Severe fever occurred in 3 patients. 2 patients were admitted to hospital, and 1 required high-dose oral prednisolone because of persistent fever.

Does the study answer the question? Author's conclusions: this study indicates that LTG is effective in reducing seizure frequency and has additional favourable effects on seizure severity, mood and perceived internal control. Some of the scales used indicate the potential of secondary measures of efficacy to enhance the sensitivity of trials of new AEDs.

Effect due to factor in study? No prior calculation of sample size based on statistical power was made. Uncertain.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Steiner TJ;Dellaportas CI;Findley LJ;Gross M;Gibberd FB;Perkin GD;Park DM;Abbott R;

Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin

Ref ID 4705

1999

Study Type Randomised Controlled Trial **Funding** Wellcome Foundation Ltd.

Number of participant 181 patients with newly diagnosed untreated partial seizures or secondarily or primary generalised tonic-clonic seizures were randomised to two treatment groups. One group (n = 86) received LTG titrated over 6 weeks from a starting dose of 100 mg/day. The other (n = 95) received PHT titrated from 200 mg/day.

Inclusion/Exclusion Criteria Inclusion: ages 14-75 after two or more partial, secondarily generalised or primary generalised tonic-clonic seizures in the previous 6 months
Exclusion: absence seizures; previous AEDs; clinically significant abnormal lab values; other chronic medical disorders, severe mental subnormality; abuse of alcohol and pregnancy or risk of pregnancy.

Patient Characteristics	LTG, n=86	PHT, n=95	All, n=181
Male/female (%)	55/45	57/43	56/44
Age (yr)			
Median	28 (13-70)	27 (13-74)	28(13-74)
Weight (kg)			
Median	68	68	68
Age at first seizure (yr)			
Median	25	25	25

Recruitment Unknown

Setting UK (authors from 6 settings)

Interventions/ Test/ Factor being investigated Comparison of LTG with PHT monotherapy for efficacy and tolerability in previously untreated patients with newly diagnosed epilepsy

Comparisons Comparison between lamotrigine and phenytoin.

Length of Study/ Follow-up	6 week titration and a treatment phase for less than or equal to 48 weeks.
Outcome measures studied	Primary: Percentages of patients remaining on treatment and seizure free and the numbers of seizures with each treatment during the last 24 and 40 weeks of the study. Secondary: time to first seizure and time to discontinuation.
Results	<p>The percentages of patients remaining on each treatment and seizure free during the last 24 and 40 weeks of the study, and times to first seizure after the first 6 weeks of treatment (dose-titration period), did not differ significantly between the treatment groups. Time to discontinuation, a composite index of efficacy and safety, likewise did not distinguish between treatments.</p> <p>In last 24 weeks: for primary generalised tonic-clonic the proportion of seizure-free participants was 19 (44%) in the lamotrigine group vs 17 (34%) in the phenytoin group. 95% CI for difference was -10.30%.</p> <p>In last 40 weeks: for primary generalised tonic-clonic the proportion of seizure-free participants was 13 (30%) in the lamotrigine group vs 16 (32%). 95% CI for difference was -21.17%.</p> <p>For primary generalised tonic-clonic the time to first seizure after the first 6 weeks of treatment was 1.5 (95% CI 0.7-3.2).</p> <p>Adverse events led to discontinuation of 13 (15%) patients from LTG and 18 (19%) from PHT.</p> <p>Adverse events affected more than 10% of patients: LTG : Asthenia 14/86* Rash 12/86 Headache: 9/86 Dizziness: 8/86 Somnolence: 6/86* Ataxia: 0/86</p> <p>PHT Asthenia 28/95* Rash 12/95 Headache: 9/95 Dizziness: 8/95 Somnolence: 6/95* Ataxia: 0/95</p> <p>* P<0.05</p> <p>A quality-of-life instrument, the SEALS inventory, favoured LTG. Patients taking PHT showed the biochemical changes expected of an enzyme-inducing drug, whereas those taking LTG did not.</p>
Safety and adverse effects	Adverse events led to discontinuation of 13 (15%) patients from LTG and 18 (19%) from PHT. The adverse-event profile for LTG was dominated by skin rash [discontinuation of 10 (11.6%) patients compared with five (5.3%) from PHT] rather than central nervous system side effects: asthenia, somnolence, and ataxia were each significantly more frequent in the PHT group. The high rate of rash with LTG was probably due to the high starting dose and may be avoidable.
Does the study answer the question?	LTG and PHT monotherapy were similarly effective against these seizure types in patients with newly diagnosed epilepsy. LTG was better tolerated, more frequently causing rash, but with a lower incidence of central nervous system side effects
Effect due to factor in study?	Yes
Consistency of results with other studies?	
Directly applicable to guideline population?	See GRADE

Internal Validity

Stolarek I;Blacklaw J;Forrest G;Brodie MJ;

Vigabatrin and lamotrigine in refractory epilepsy

Ref ID 4759

1994

Study Type	Randomised Controlled Trial	Funding	Funding was not stated. The lamotrigine and placebo tablets were supplied by Wellcome Trust.
Number of participant	22 patients were recruited, and 20 completed this cross over trial.		
Inclusion/Exclusion Criteria	Patients with refractory complex partial seizures with or without secondary generalisation despite treatment with anticonvulsants containing vigabatrin.		
Patient Characteristics	All reported a minimum of three seizures a month despite stable regimen of anticonvulsant treatment. 9 and 13 patients took VIG and one or two other antiepileptic drugs respectively.		
Recruitment	Not stated		
Setting	Glasgow		
Interventions/ Test/ Factor being investigated	Addition of placebo, lamotrigine 25mg, 50 mg and 100 mg to stabilised treatment regimen containing vigabatrin		
Comparisons	Comparison was made between the treatment and active treatment (matched pairs used)		
Length of Study/ Follow-up	The patients were followed up during treatments (week 0, 4, 8 and 12).		
Outcome measures studied	This was not stated		
Results	<p>Proportion of patients with at least 50% reduction in seizure:</p> <p>Phase I: 25 mg twice daily : 3/20(15%)</p> <p>Phase II: 50 mg twice daily : 7/20(35%)</p> <p>Phase III: 100mg twice daily : 9/20 (45%)</p> <p>Overall - 12 weeks: 4/20 (20%)</p> <p>(p values not reported in paper)</p> <p>Number of seizure free patients: 3, while on 100 mg twice daily lamotrigine. This was not reported for placebo or other treatment doses.</p> <p>Withdrawal from study : 1/22 on placebo arm (due to adverse events)</p> <p>Outcomes related to cognitive effects:</p> <p>Mean VAS score for sedation, concentration, memory, and depression did not differ significantly after a month's treatment of lamotrigine 100 mg twice daily vs placebo. (data not shown)</p> <p>16/20 patients preferred the LTG treatment</p> <p>There were no significant difference in the total number of requested or spontaneously reported side effects 6 for lamotrigine and 7 for placebo.</p>		
Safety and adverse effects	There were no difference in number of reported adverse events between the placebo and treatment arms.		
Does the study answer the question?	There was no statistically difference in number of adverse events between the two treatment arms for this very small cross over RCT		

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Tanganelli P;Regesta G;

Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study

Ref ID 4692

1996

Study Type	Randomised Controlled Trial	Funding	Unknown
Number of participant	26 patients assigned to vigabatrin (VGB) and 25 patients assigned to carbamazepine (CBZ)		
Inclusion/Exclusion Criteria	Inclusion: Age between 18 and 65 years; at least two untreated and unprovoked seizures, complex partial type in the previous 8 weeks. Exclusion: history of alcohol or drug abuse; the presence of a brain tumour or progressive neurological disease; an IQ <90; the presence or history of psychiatric, cardiac, renal, hepatic or metabolic disease; pregnancy or the risk of pregnancy.		
Patient Characteristics		VGB	CBZ
	Mean age (y)	37.9	34.8
	Male/female ratio	1.5	1.4
	Seizure frequency	9.1	7.4
Recruitment	Unknown		
Setting	Italy		
Interventions/ Test/ Factor being investigated	The effects of VGB in the monotherapy of newly diagnosed subjects		
Comparisons	Vigabatrin vs. carbamazepine		
Length of Study/ Follow-up	Initially for 4 months; crossover to the alternative drug was carried out for 4 months only in cases with persisting seizures or in the presence of intolerable side effects		
Outcome measures studied	Primary: seizure frequency Secondary: side effects, EEG, lab tests for serum levels and routine WBC and chemistries		
Results	No significant difference (p values not given) between VGB and CBZ in control of seizures: 17/37 (45.9%) with VBZ and 20/39 (51.3%) with CBZ. Side effects were more frequent and severe with CBZ (41% vs. 21.6% in VGB).		
Safety and adverse effects	Side effects were generally slight - drowsiness was the most common side effect but was not significantly different in the two groups (p=0.079). One patient in CBZ group dropped out due to a generalised rash.		
Does the study answer the question?	VGB may be considered as a first line drug for epilepsy with CP seizures and as a valid alternative when other monotherapies are ineffective or poorly tolerated.		
Effect due to factor in study?	The study should be repeated with a larger sample and with appropriate blinding and concealment.		
Consistency of results with other studies?	See GRADE		

Directly applicable to guideline population? See GRADE

Internal Validity No blinding or allocation concealment

Tartara A;Manni R;Galimberti CA;Hardenberg J;Orwin J;Perucca E;

Vigabatrin in the treatment of epilepsy: a double-blind, placebo-controlled study

Ref ID 4713

1986

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=23 including 3 patients who dropped out before study end..

Inclusion/Exclusion Criteria Inclusion criteria: (a) age 16-65 years; (b) epilepsy uncontrolled by conventional treatment, irrespective of seizure type; (c) minimum seizure frequency of one seizure a week, with a stable seizure frequency during the previous 6 months; (d) treatment with no more than two antiepileptic drugs, without major changes in drug therapy during the 2 months prior to entry; (e) routine hematology, blood chemistry, and urinalysis values within the expected ranges; (f) absence of psychiatric, cardiac, renal, hepatic, metabolic, or progressive neurological diseases; (g) no pregnancy or risk of pregnancy; (h) no history of poor compliance; and (i) written informed consent (patient or guardian). Exclusion criteria: none listed.

Patient Characteristics Mean age = 31, mean number of years duration of epilepsy = 18, females n=10, males n=13, All patients on two concurrent AEDs the majority receiving carbamazepine and Phenobarbital.

Recruitment Not reported.

Setting Outpatients at an epilepsy clinic in Italy..

Interventions/ Test/ Factor being investigated Vigabatrin as add-on therapy.

Comparisons The comparison is between Vigabatrin as add-on therapy and placebo.

Length of Study/ Follow-up 14 weeks: two periods of 7 weeks, one period on placebo and the other on Vigabatrin.

Outcome measures studied Primary outcome: number of seizures a week in each 7-week period. Secondary outcomes: neurological outcomes and adverse events.

Results Primary outcome
On average, the total number of seizures a week was significantly lower during the Vigabatrin period than during the placebo period (2.2 +/- 2.6 vs. 3.8 +/- 3.7, respectively, means +/- SD, p < 0.01).

In terms of individual responses, 12 of the 20 patients (60%) experienced a decrease in seizure frequency of >50%, with 4 of the 12 showing a >75% decrease. For the remaining 8 patients, 3 showed a decrease between 25 and 50%, 1 showed a decrease of 0-25%, and 4 showed an increase in seizure frequency.

To evaluate the effect of treatment on seizure type, the data from the 17 patients with partial seizures were analyzed separately. Weekly seizure numbers in these patients were significantly lower during the Vigabatrin period (2.0 +/- 2.4) than during the placebo period (3.7 +/- 3.8) (p < 0.01), with 10 of the 17 patients (62%) showing a >50% improvement in seizure control.

Adverse events

The most frequent emergent event was drowsiness, which developed in 7 patients on Vigabatrin and in 1 patient on placebo. Nausea and vomiting were reported by 2

patients on Vigabatrin; in at least 1 of them, in whom vomiting occurred after 28 days of 2 g/day Vigabatrin and lasted for 3-4 days, the relationship to drug intake is uncertain.

Withdrawal due to adverse events:
Vigabatrin :1/21
Placebo: 0/21

Safety and adverse effects

No serious adverse events.

Does the study answer the question?

Unsure. The study concludes that add-on treatment with Vigabatrin is effective and well tolerated in adult patients with drug resistant epilepsy. However, the study sample size is small (n=20) and results can only be considered exploratory since no power calculation was performed.

Effect due to factor in study?

Unsure. The study concludes that add-on treatment with Vigabatrin is effective and well tolerated in adult patients with drug resistant epilepsy. However, the study sample size is small (n=20) and results can only be considered exploratory since no power calculation was performed.

Consistency of results with other studies?

Directly applicable to guideline population?

17 of the 20 patients who completed the study suffered from partial seizures and three had generalized seizures.

Internal Validity

Tassinari CA;Michelucci R;Chauvel P;Chodkiewicz J;Shorvon S;Henriksen O;Dam M;Reife R;Pledger G;Karim R;

Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy

Ref ID 4688

1996

Study Type Randomised Controlled Trial **Funding** Johnson Pharmaceutical

Number of participant 60- 30 in each arm

Inclusion/Exclusion Criteria

Inclusion criteria:
18-65 years with good mental and physical health and a documented history of partial seizures.
EEG in the preceding 5 years to verify presence of lateralised epileptic form consistent with a diagnosis of partial epilepsy
CT or MRI scan in the preceding 2 years to exclude potentially progressive neurologic diseases
Received fixed regimen of one of two of the following AEDs: PHT, CBZ, VPA, PB, PRM. Clobazam or clonazepam permitted only in combination with either PHT, CBZ, PN pr PRM.
Women of child bearing age who are not nursing or pregnant and using birth control measures

Exclusion :
Known to be allergic or hyper sensitive to carbonic anhydrase inhibitors or sulphonamides, or contraindicated to these
History of nephrolithiasis
At least 8 partial seizures while being maintained with therapeutic plasma levels of AED concentrations

Patient Characteristics

Men: 47/60 (68%)
White: 57/60(95%)
Mean age: 32.9 years
Mean weight: 69.4kg
Mean height: 172.1cm
Median seizure rate: 16.8(4-230) for TPM group, and 15.0 (4-925) for placebo group.
63% received CBZ in combination with PB, PHT, PRM or VPA.
Study reported that the demographics were comparable between the two groups

Recruitment	Recruited from 6 study sites																																																				
Setting	UK, Italy France, Norway Denmark																																																				
Interventions/ Test/ Factor being investigated	TPM600mg or placebo																																																				
Comparisons	Adjunctive: TPM vs placebo																																																				
Length of Study/ Follow-up	8 weeks baseline, plus 12 weeks treatment (including 4 week of titration)																																																				
Outcome measures studied	Not stated																																																				
Results	<p>Proportion of seizure free participants TPM: 0/30 Placebo: 0/30 P value: NS</p> <p>Proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders) TPM: 11/30(47%) Placebo: 3/30(10%) P value: 0.001</p> <p>The proportion of participants having treatment withdrawn due to adverse events: TPM: 4/30 Placebo: 1/30</p> <p>Incidence of adverse events</p> <table border="0"> <thead> <tr> <th></th> <th>Placebo n=30, [%]</th> <th>TPM n=30, [%]</th> </tr> </thead> <tbody> <tr><td>Headache:</td><td>3[10]</td><td>8[27]</td></tr> <tr><td>Somnolence:</td><td>4[13]</td><td>7[23]</td></tr> <tr><td>Dizziness:</td><td>3[10]</td><td>7[23]</td></tr> <tr><td>Fatigue:</td><td>3[10]</td><td>7[23]</td></tr> <tr><td>Thinking abnormal:</td><td>0[0]</td><td>6[20]</td></tr> <tr><td>Depression:</td><td>2[7]</td><td>5[17]</td></tr> <tr><td>Weight decrease:</td><td>2[7]</td><td>5[17]</td></tr> <tr><td>Nausea:</td><td>2[7]</td><td>4[13]</td></tr> <tr><td>Emotional liability:</td><td>1[3]</td><td>4[13]</td></tr> <tr><td>Confusion:</td><td>0[0]</td><td>4[13]</td></tr> <tr><td>Anxiety:</td><td>3[10]</td><td>3[10]</td></tr> <tr><td>Convulsions aggravated:</td><td>2[7]</td><td>3[10]</td></tr> <tr><td>Concentration impaired:</td><td>1[3]</td><td>3[10]</td></tr> <tr><td>Diarrhoea:</td><td>1[3]</td><td>3[10]</td></tr> <tr><td>URTI:</td><td>1[3]</td><td>3[10]</td></tr> <tr><td>Amnesia:</td><td>3[10]</td><td>2[7]</td></tr> </tbody> </table> <p>URTI= upper respiratory tract infections</p>			Placebo n=30, [%]	TPM n=30, [%]	Headache:	3[10]	8[27]	Somnolence:	4[13]	7[23]	Dizziness:	3[10]	7[23]	Fatigue:	3[10]	7[23]	Thinking abnormal:	0[0]	6[20]	Depression:	2[7]	5[17]	Weight decrease:	2[7]	5[17]	Nausea:	2[7]	4[13]	Emotional liability:	1[3]	4[13]	Confusion:	0[0]	4[13]	Anxiety:	3[10]	3[10]	Convulsions aggravated:	2[7]	3[10]	Concentration impaired:	1[3]	3[10]	Diarrhoea:	1[3]	3[10]	URTI:	1[3]	3[10]	Amnesia:	3[10]	2[7]
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Safety and adverse effects	There were no noteworthy laboratory value changes. The most frequently reported adverse events were CNS related. Most AEs were classified as mild or moderate severity																																																				
Does the study answer the question?	TPM600mg/day effective in the treatment of refractory partial onset seizures with or without secondarily generalised seizures																																																				
Effect due to factor in study?	The sample size is too small to detect significant differences for smaller differences																																																				
Consistency of results with other studies?																																																					
Directly applicable to guideline population?	No indirectness ascertained.																																																				

Internal Validity

Tsai JJ;Yen DJ;Hsieh MS;Chen SS;Hirsemenzel R;Edrich P;Lai CW;

Efficacy and safety of levetiracetam (up to 2000 mg/day) in Taiwanese patients with refractory partial seizures: a multicenter, randomized, double-blind, placebo-controlled study

Ref ID 437

2006 Jan

Study Type	Randomised Controlled Trial	Funding	Not reported.																																																																																																						
Number of participant	n=94 (n=47 in LEV group and n=47 in placebo group)																																																																																																								
Inclusion/Exclusion Criteria	<p>Inclusion criteria: diagnosed as having epilepsy for ≥ 6 months before the study. Partial seizures were treatment resistant in all cases, and, during an 8-week baseline period, all patients had at least four complex or secondarily generalized partial seizures (type IB or IC). For ≥ 2 weeks before the study, patients had received a stable dosage of one to three AEDs (including benzodiazepines) other than LEV; all patients had been treated with at least two classic AEDs, either simultaneously or consecutively, before the study. Exclusion criteria: status epilepticus in the 3 months before the study, or if they had clusters of seizures that could not be reliably and regularly counted. A history or presence of pseudoseizures; a history of recurrent psychotic or major affective disorder; the presence of clinically significant acute or chronic illness.</p>																																																																																																								
Patient Characteristics	<p>Summary of baseline demographic characteristics for the intention-to-treat population of 94 randomized patients</p> <table border="1"> <thead> <tr> <th>Demographic characteristic vs. PLA)</th> <th>LEV (n = 47)</th> <th>PLA (n = 47)</th> <th>p Value (LEV vs. PLA)</th> </tr> </thead> <tbody> <tr> <td>Age (yr)</td> <td>32.8 (± 10.5)</td> <td>31.7 (± 8.2)</td> <td>0.564 c</td> </tr> <tr> <td>Sex</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Number of males (%)</td> <td>17 (36.2%)</td> <td>25 (53.2%)</td> <td rowspan="2">0.146 d</td> </tr> <tr> <td>Number of females (%)</td> <td>30 (63.8%)</td> <td>22 (46.8%)</td> </tr> <tr> <td>Race</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Asian/Pacific Islander [no. of patients (%)]</td> <td>47 (100%)</td> <td>47 (100%)</td> <td></td> </tr> <tr> <td>Body weight (kg)</td> <td>63.3 (± 14.1)</td> <td>64.7 (± 12.6)</td> <td>0.596 c</td> </tr> <tr> <td>Height (cm)</td> <td>160.7 (± 8.5)</td> <td>164.1 (± 7.9)</td> <td>0.051 c</td> </tr> <tr> <td>Body mass index (kg/m²)</td> <td>24.4 (± 5.0)</td> <td>24.0 (± 4.0)</td> <td>0.620 c</td> </tr> <tr> <td>Epilepsy history</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Duration of illness (yr)</td> <td>18.6 (± 8.5)</td> <td>18.7 (± 10.7)</td> <td>0.968 c</td> </tr> <tr> <td>Age at onset (yr)</td> <td>14.3 (± 8.5)</td> <td>13.1 (± 8.7)</td> <td>0.499 c</td> </tr> <tr> <td>Cause unknown [number (%) of patients]</td> <td>13 (27.7%)</td> <td>20 (42.6%)</td> <td>0.194 d</td> </tr> <tr> <td>Withdrawal seizures [number (%) of patients]</td> <td>4 (8.5%)</td> <td>7 (14.9%)</td> <td>0.523 d</td> </tr> <tr> <td>Status epilepticus [number (%) of patients]</td> <td>6 (12.8%)</td> <td>10 (21.3%)</td> <td>0.411 d</td> </tr> <tr> <td>Documentation of spikes or Spike-waves on EEG [number (%) of patients]</td> <td>41 (87.2%)</td> <td>45 (95.7%)</td> <td>0.267 d</td> </tr> <tr> <td>Baseline seizure frequency per week</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Partial seizures Mean (SD)</td> <td>4.0 (± 14.1)</td> <td>4.0 (± 5.6)</td> <td rowspan="2">0.378 e</td> </tr> <tr> <td>Median (interquartile range)</td> <td>1.6 (1.2–2.5)</td> <td>2.0 (1.1–3.9)</td> </tr> <tr> <td>Total seizures Mean (SD)</td> <td>4.0 (± 14.1)</td> <td>4.3 (± 7.0)</td> <td rowspan="2">0.378 e</td> </tr> <tr> <td>Median (interquartile range)</td> <td>1.6 (1.2–2.5)</td> <td>2.0 (1.1–3.9)</td> </tr> <tr> <td>Number of concomitant AEDs taken by patients (overall study) [number (%) of patients]</td> <td></td> <td></td> <td></td> </tr> <tr> <td>One</td> <td>7 (14.9%)</td> <td>11 (23.4%)</td> <td rowspan="4">0.314 f</td> </tr> <tr> <td>Two</td> <td>19 (40.4%)</td> <td>18 (38.3%)</td> </tr> <tr> <td>Three</td> <td>21 (44.7%)</td> <td>16 (34.0%)</td> </tr> <tr> <td>Four or more</td> <td>0 (0.0)</td> <td>2 (4.3%)</td> </tr> </tbody> </table>			Demographic characteristic vs. PLA)	LEV (n = 47)	PLA (n = 47)	p Value (LEV vs. PLA)	Age (yr)	32.8 (± 10.5)	31.7 (± 8.2)	0.564 c	Sex				Number of males (%)	17 (36.2%)	25 (53.2%)	0.146 d	Number of females (%)	30 (63.8%)	22 (46.8%)	Race				Asian/Pacific Islander [no. of patients (%)]	47 (100%)	47 (100%)		Body weight (kg)	63.3 (± 14.1)	64.7 (± 12.6)	0.596 c	Height (cm)	160.7 (± 8.5)	164.1 (± 7.9)	0.051 c	Body mass index (kg/m ²)	24.4 (± 5.0)	24.0 (± 4.0)	0.620 c	Epilepsy history				Duration of illness (yr)	18.6 (± 8.5)	18.7 (± 10.7)	0.968 c	Age at onset (yr)	14.3 (± 8.5)	13.1 (± 8.7)	0.499 c	Cause unknown [number (%) of patients]	13 (27.7%)	20 (42.6%)	0.194 d	Withdrawal seizures [number (%) of patients]	4 (8.5%)	7 (14.9%)	0.523 d	Status epilepticus [number (%) of patients]	6 (12.8%)	10 (21.3%)	0.411 d	Documentation of spikes or Spike-waves on EEG [number (%) of patients]	41 (87.2%)	45 (95.7%)	0.267 d	Baseline seizure frequency per week				Partial seizures Mean (SD)	4.0 (± 14.1)	4.0 (± 5.6)	0.378 e	Median (interquartile range)	1.6 (1.2–2.5)	2.0 (1.1–3.9)	Total seizures Mean (SD)	4.0 (± 14.1)	4.3 (± 7.0)	0.378 e	Median (interquartile range)	1.6 (1.2–2.5)	2.0 (1.1–3.9)	Number of concomitant AEDs taken by patients (overall study) [number (%) of patients]				One	7 (14.9%)	11 (23.4%)	0.314 f	Two	19 (40.4%)	18 (38.3%)	Three	21 (44.7%)	16 (34.0%)	Four or more	0 (0.0)	2 (4.3%)
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Setting Five centres in Taiwan.

Interventions/ Test/ Factor being investigated Levetiracetam up to 2000mg per day as adjunctive therapy with currently used AEDs.

Comparisons The comparison is between levetiracetam (up to 2000mg per day) and placebo as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up 22 weeks: 8 week baseline period, 2 weeks titration and 12 week maintenance.

Outcome measures studied Primary outcome: the logarithmically transformed weekly frequency of partial-onset seizures over the 14-week treatment phase. Secondary outcomes: % reduction in weekly frequency of partial-onset seizures and total seizures. Responder rates, seizure free

Results

Summary of results for primary and secondary efficacy variables in the intention-to-treat population

Variable	LEV (n = 47) ^a	PLA (n = 47) ^a	p value
Partial seizures:			
Primary efficacy variable			
Least square mean	0.813	1.085	
0.001			
% reduction over placebo	23.8% (95% CI: 10.4% to 35.2%)		
Secondary efficacy variables			
Weekly seizure frequency (absolute decrease from baseline) ^b	0.6 (-0.1 to 1.4)	0.3 (-0.2 to 0.7)	0.129
Weekly seizure frequency (percentage decrease from baseline) ^c	45.4 (-13.1 to 76.9)	15.6 (-5.7 to 41.4)	0.010
Responder rated	20/46 (43.5%)	5/47 (10.6%)	< 0.001
Number (%) of patients free of seizures	4 (8.5%); [47]	0 (0.0%); [47]	0.117
Number of seizure-free days per 4 wke	24.2 (±3.3); [46]	21.4 (±6.3); [46]	
Number (%) of patients in six ranked categories of % change from baseline in weekly seizure frequency:			
>25% increase	7 (15.2%); [46]	8 (17.0%); [47]	
25% increase to <25% decrease	9 (19.6%); [46]	19 (40.4%); [47]	
25% decrease to <50% decrease	10 (21.7%); [46]	15 (31.9%); [47]	
50% decrease to <75% decrease	7 (15.2%); [46]	4 (8.5%); [47]	
75% decrease to <100% decrease	9 (19.6%); [46]	1 (2.1%); [47]	
100% decrease	4 (8.7%); [46]	0 (0.0%); [47]	
0.008			
(for the six ranks)			
Total seizures			
Least square mean	0.819	1.095	
0.001			
% reduction over placebo	24.1% (95% CI, 10.6%–35.6%)		
Weekly seizure frequency (absolute decrease from baseline) ^b	0.6 (-0.1–1.4)	0.3 (-0.2–0.7)	0.129
Weekly seizure frequency (percent decrease from baseline) ^c	45.4 (-13.1–76.9)	15.6 (-5.7–39.1)	0.009
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Number of seizure-free days per 4 wke	24.2 (±3.3); [46]	21.3 (±6.4); [46]	

LEV, levetiracetam; NA, not applicable; PLA, placebo.

^aValues in square brackets indicate numbers of evaluable patients.

^bAbsolute decrease from baseline over the evaluation period; median and interquartile range.

^cPercentage decrease from baseline over the evaluation period; median and

interquartile range.
 dProportion of patients with a $\geq 50\%$ decrease from baseline in weekly seizure frequency.
 eMean (\pm standard deviation).

Adverse events

Number (%) of patients with adverse events observed with an incidence of $\geq 5\%$ during the evaluation period (data for the intention-to-treat population)

Adverse event	All adverse events		Adverse events considered at least possibly related to study medication by the investigator	
	LEV (n = 47)	PLA (n = 47)	LEV (n = 47)	PLA (n = 47)
Somnolence (14.9%)	19a (40.4%)	7 (14.9%)	19a (40.4%)	7
Dizziness (excluding vertigo)	7 (14.9%)	4 (8.5%)	5 (10.6%)	2 (4.3%)
Headache (2.1%)	5 (10.6%)	4 (8.5%)	3 (6.4%)	1
ECG abnormalities	4 (8.5%)	2 (4.3%)		
Diplopia	3 (6.4%)	0		
Pruritus	3 (6.4%)	0		
Nasopharyngitis	2 (4.3%)	6 (12.8%)		
Dissociation (psychiatric)	0	3 (6.4%)		
Memory impairment	0	3 (6.4%)		

ECG, electrocardiogram; LEV, levetiracetam; PLA, placebo.
 a $p < 0.05$, Fisher's exact test.

Four patients (three LEV and one placebo patient) were withdrawn from the study because of AEs. During the evaluation period, five patients (two LEV and three placebo patients) reported a total of seven serious AEs (SAEs).

Safety and adverse effects

Does the study answer the question? Yes. Adjunctive LEV therapy, $\leq 1000\text{mg}$ twice daily, was significantly more effective than placebo in Taiwanese adults with treatment-resistant partial-onset seizures.

Effect due to factor in study? Yes. The study had a power of 80% to detect 20% superiority for LEV over placebo regarding logarithmically transformed weekly seizure frequency.

Consistency of results with other studies?

Directly applicable to guideline population? All patients had a diagnosis of partial-onset seizures with or without secondary generalization.

Internal Validity

Turnbull DM;Howel D;Rawlins MD;Chadwick DW;

Which drug for the adult epileptic patient: phenytoin or valproate?

Ref ID 4672

1985

Study Type Randomised Controlled Trial **Funding** Sanofi

Number of participant 140 in total sample with 70 in each arm, valproate and phenytoin respectively.

Inclusion/Exclusion Criteria Inclusion: a history of two or more seizures in the previous three years; over age 16 and had received no previous anticonvulsant.

Patient Characteristics	Valproate (70 patients) 16-69 (30 median)	Phenytoin (70 patients) 16-70 (30 median)
Age (years)		
Gender		
Female	36	31
Male	34	39
Recruitment	Unknown.	
Setting	Dept of Neurology, Royal Victoria Infirmary.	
Interventions/ Test/ Factor being investigated	Valproate vs. phenytoin in newly diagnosed adult patients with epilepsy. PHT 100mg 3 times a day; VPA 200mg 3 times a day; if further seizures occurred medication was increased PHT depending on plasma concentration if less than 10mg/l the dose was increased by 50mg/day and if greater than 10mg/l it was increased by 25mg/day, doses were further increased until seizures stopped or adverse effects seen; valproate was increment of 1200mg/2100mg and 3000mg/day given in 3 divided doses regardless of serum concentration.	
Comparisons	Comparison is made between two treatments< valproate vs. phenytoin	
Length of Study/ Follow-up	48 months.	
Outcome measures studied	Achievement of a two year remission and 'time to first seizure'.	
Results	Valproate	Phenytoin
No. of patients	70	70
No achieving 2 year remission	36	31
No controlled for <2 years	12	11
No continuing to have seizures	10	11
Idiosyncratic adverse effect requiring drug withdrawal	0	5
Death	3	3
Non-compliant or lost to follow-up	9	9
	In patients with tonic clonic seizures 27 of 37 patients on valproate and 22 of 39 on phenytoin achieved 2 year remission. In patients with partial seizures 9 of 31 patients on valproate and 9 of 31 on phenytoin achieved 2 year remission. Sodium valproate and phenytoin in the treatment of tonic clonic or partial seizures showed no significant difference in the efficacy as regards time to two year remission. However patients with a clinical history of partial seizures did significantly less well than those with a history of tonic clonic seizures only ($p<0.025$) and to time to first seizure ($p<0.001$). There were not figures to report time to first seizure in evidence review.	
Safety and adverse effects	Valproate dose related adverse effects: tremor, irritability and restlessness and alopecia. Phenytoin dose related adverse effects: nystagmus, ataxia, tremor, diplopia and mental change. Idiosyncratic effects of phenytoin: skin eruption, erythoderma and jaundice.	
Does the study answer the question?	This study showed no major difference in efficacy between sodium valproate and phenytoin in adults with recent onset of epilepsy.	
Effect due to factor in study?	Yes	
Consistency of results with other studies?		
Directly applicable to guideline population?	See GRADE	
Internal Validity		

Study Type	Randomised Controlled Trial	Funding	Unknown
Number of participant	127 total; 61 Gabapentin and 66 placebo		
Inclusion/Exclusion Criteria	Inclusion: 1 partial seizure per week despite adequate medication with one or two standard anticonvulsants Exclusion: Less than one seizure per week baseline		
Patient Characteristics	Age (yr): 30 (15-62) in GABA group and 31 (14-73) in placebo group. Sex (M/F): 39%/61% in GABA group and 44%/56% in placebo group.		
Recruitment	Not discussed		
Setting	UK and West Germany		
Interventions/ Test/ Factor being investigated	Gabapentin as additional therapy in patients with drug resistant partial epilepsy		
Comparisons	Gabapentin vs. placebo		
Length of Study/ Follow-up	12 weeks		
Outcome measures studied	Responder rate: percentage of patients in whom the number of partial seizures fell by at least 50% from baseline. Response ratio: a calculation of percent change		
Results	Frequency of partial seizures was at least halved in 25% of patients treated with gabapentin compared with 9.8% treated with placebo ($p=0.043$). The median reduction in partial seizure frequency during 12 weeks treatment was 29.2% with gabapentin compared with 12.5% with placebo. The mean adjusted response ratio for gabapentin (-0.192) was significantly better than the ratio of -0.060 for placebo ($p=0.0056$) by analysis of variance.		
Safety and adverse effects	Gabapentin: 62% of patients reported mostly mild or moderate adverse effects Placebo: 41% of patients reported mostly mild or moderate adverse effects Haematological and biochemical parameters monitored during treatment showed no significant trends for any parameter, compared with baseline for either gabapentin or placebo.		
Does the study answer the question?	Gabapentin is an effective additional treatment for patients with partial epilepsy refractor to standard therapy.		
Effect due to factor in study?	Yes		
Consistency of results with other studies?	See GRADE		
Directly applicable to guideline population?	See GRADE		
Internal Validity	Multicentre study		

US Gabapentin Study group no.5

Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study.

Study Type	Randomised Controlled Trial	Funding	Park-Davis		
Number of participant	306 patients total: 98 placebo, 53 received 600 mg gabapentin, 101 received 1200 mg gabapentin, 54 received 1800 mg gabapentin.				
Inclusion/Exclusion Criteria	<p>Inclusion: Patients with documented partial seizures refractory to treatment with at least 4 partial seizures per month for 3 months prior to baseline while taking one or two AEDs at stable dosages. Age over 16 years. Use of reliable contraception if female in childbearing years.</p> <p>Excluded: Patients with atypical absence seizures or nonepileptic seizures, progressive structural lesion in the CNS; severe liver or kidney insufficiency; neutropenia; previous investigational drug use in the past 3-12 months.</p>				
Patient Characteristics	Total N=306				
	Gender				
	Male	202 (66%)			
	Female	104 (34%)			
	Age				
	Mean	35 yr			
	Range	16-70 yr			
	Partial seizure frequency/ 28 days during baseline				
	Mean	36.3			
Recruitment	Not described				
Setting	15 centres in the US between May 1987 and November				
Interventions/ Test/ Factor being investigated	To define the safety, efficacy and dose response characteristics of gabapentin administered as an add on therapy in patients with refractory partial seizures				
Comparisons	Comparison is made between three doses of gabapentin (600 mg, 1200 mg and 1800 mg) and placebo.				
Length of Study/ Follow-up	12 week baseline period;12 week double blind phase				
Outcome measures studied	<p>Primary outcome: Number of seizures per 28 days</p> <p>Secondary outcomes: Response ratio (RRatio); percent change in seizure frequency and responder rate.</p>				
Results	Variable	Placebo	600 mg GBP	1200 mg GBP	1800 mg
	Response ratio	-0.025	-0.151	-0.118	-0.233
	Adjusted mean	0.022	0.037	0.027	0.034
	SEM				
	p value compared to placebo		0.007	0.023	<0.001
	Responder rate	8.4%	18.4%	17.6%	26.4%
	(percent of patients with at least 50% reduction in seizure frequency from baseline to treatment)				
	p value compared to placebo		0.103	0.080	0.007
	Median percent change in seizure frequency	-5.9	-24.3	-20.0	-31.9
Safety and adverse effects	The three most frequently occurring adverse events were somnolence, dizziness and ataxia, were not dose related and usually occurred within the first 15 to 20 days of therapy and resolved in 2 weeks or less for most patients				
Does the study answer the question?	Gabapentin's low inherent toxicity and its lack of drug interactions make it an ideal candidate for use as add on therapy in patients with refractory partial epilepsy.				
Effect due to factor in study?	Yes				

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity Multi-centre study

Uthman BM;Rowan AJ;Ahmann PA;Leppik IE;Schachter SC;Sommerville KW;Shu V;

Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial

Ref ID 4760

1998

Study Type Randomised Controlled Trial **Funding** Abbott Laboratories; the study drugs were also provided by Abbott Laboratories.

Number of participant n=297 (n=91 in placebo group, n=61 in TGB 16mg/d, n=88 in 32mg/d, and n=57 in 56mg/d groups)

Inclusion/Exclusion Criteria Inclusion criteria: (1) age between 12 and 77 years; (2) good health except for epilepsy; (3) occurrence of at least 6 CPS alone or in combination with any other seizure type in the 8 weeks preceding the screening visit (with each of the two 4-week segments containing at least 1 CPS); (4) electroencephalographic evidence of a unilateral or bilateral abnormality consistent with CPS; and (5) availability of at least 1 neuroimaging study of the brain to rule out the presence of any progressive lesions. Female patients could not be pregnant or lactating. The patient had to be receiving a stable regimen of 1 to 3 hepatic enzyme-inducing AEDs: phenytoin, carbamazepine, phenobarbital, or primidone.

Patient Characteristics Demographic and Medical Characteristics of Patients With Complex Partial Seizures Randomized to Treatment (N=297)*

F/M ratio, %	42:58
Mean age, y (range)	34.0 (12.0-77.0)†
Medical history, median (range)	
History of epilepsy, y	22.9 (1.4-65.8)
No. of different AEDs ever taken	7.0 (2.0-20.0)
Concomitant AEDs,‡ No. (%)	
Carbamazepine	
As monotherapy	77 (26)
Combined with other AED	128 (43)
Phenytoin sodium	
As monotherapy	25 (8)
Combined with other AED	69 (23)
Divalproex sodium§	79 (27)
Primidone	40 (13)
Phenobarbital	76 (26)

*There were no significant differences between treatment groups on any demographic or medical variable.

†One patient in the study was 77 years old, 2 years over the protocol limit; he was enrolled because his health was excellent in other respects.

‡Patients had to be receiving a stable regimen of concomitant antiepileptic drugs (AEDs) for at least 8 weeks preceding the baseline phase.

§Patients taking divalproex sodium could enter the study only if taking it in combination with another enzyme-inducing drug.

Recruitment Unknown.

Setting 21 treatment sites in the United States.

Interventions/ Test/ Factor being investigated Tiagabine in four daily doses: 16mg, 32mg or 56mg as adjunctive therapy to currently used AEDs.

Comparisons

The comparison is between the 3 doses of tiagabine and placebo as adjunctive therapy.

**Length of Study/
Follow-up**

32 weeks: a 12 week baseline phase, a four week titration phase and a 16 week maintenance period.

**Outcome measures
studied**

Primary outcome: change in 4-week median complex partial seizures frequency from baseline phase to double-blind treatment phase. Secondary outcomes: proportions of patients having a 50% or greater reduction in CPS frequency. Also SPS and SGTCS.

Results

Change in Frequency of Complex Partial Seizures From Baseline to Double-blind Treatment Phase in Placebo- and Tiagabine-Treated Patients*

Treatment Phase: Change in Seizure Frequency

Reduction	Median Change	P vs Placebo	Median % Change	>=50% Seizure	
				No. (%)	P vs
Placebo					
Placebo	-0.7	...	-11	4 (4)	...
Tiagabine					
16 mg/d	-0.8	.44	-13	5 (8)	.42
32 mg/d	-2.2	.03	-25†	17 (20)	
.002					
56 mg/d	-2.8	.03	-33‡	16 (29)	
<.001					

*Counts include complex partial seizures occurring alone or in combination with other seizure types. Values for P vs placebo were calculated by weighted pair wise comparison, nonparametric. P values comparing the proportions of tiagabine-treated patients and placebo-treated patients experiencing 50% or greater reduction in seizure frequency were calculated using the Cochran-Mantel-Haenszel statistic. Median percent change was based on the percentages of seizure reduction from baseline in individual patients.

†P=.02.

‡P=.009.

Secondary outcomes

Change in frequency of simple partial seizures between baseline and double-blind treatment phase in placebo and tiagabine treated patients *

Treatment Phase: Change in Seizure Frequency

Reduction	Median Change	P vs Placebo	Median % Change	>=50% Seizure	
				No. (%)	P vs
Placebo					
Placebo	0.9	...	10.5	5 (9.8)	.
..					
Tiagabine					
16 mg/d	-2.3	.001	-23.7	11(28.2)	.03
32 mg/d	-1.7	.04	-12.4	17 (34.7)	
.003					
56 mg/d	-3.3	.003	-36.3	12 (36.4)	
.005					
32 and 56 mg/d, combined	-2.6	.004	-25.0	29(35.4)	
.001					

Adverse events

Adverse Events for Which Significant Differences Between Tiagabine and Placebo Groups Were Observed*

mg/d	Placebo Group	Tiagabine Group		56
		16 mg/d	32 mg/d	
Adverse Event†	(n=91)	(n=61)	(n=88)	(n=57)
Dizziness [.07]	15 (16)	18 (30) [.71]	29 (33) [.02]	17 (30)
Tremor [.001]	3 (3)	6 (10) [.16]	13 (15) [.008]	12 (21)
Abnormal thinking‡	3 (3)	2 (3) [.99]	7 (8) [.21]	8 (14)
Depression [.02]	0	4 (7) [.02]	2 (2) [.24]	4 (7)

*Data are given as number (percentage) of patients, with P vs placebo indicated in brackets. P values for comparison with placebo were determined using the Fisher exact test.

†Terms used to describe adverse events are from the COSTART system (US Department of Health and Human Services, 1989).

‡Abnormal thinking was usually described as difficulty concentrating or mental lethargy.

8% of patients in the placebo terminated study prematurely because of adverse events. Percentages in other drug groups were 7% in 16mg/d group, 15% in 32mg/d group and 16% in 56mg/d group. Adverse events were serious in 6 patients (7%) in the placebo group, 2 (3%) in the tiagabine 16-mg group, 4 (4%) in the 32-mg group, and 4 (7%) in the 56-mg group.

Safety and adverse effects

Does the study answer the question?

Yes. A clear dose-response relationship was observed between tiagabine dose levels and reduction in CPS frequency, with higher doses of tiagabine (32 and 56 mg/d) resulting in a significantly greater decrease in 4-week seizure frequency than that observed in the placebo group.

Effect due to factor in study?

Yes. The study was sufficiently well powered to detect differences in seizure frequency between the groups.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients had had at least 6 complex partial seizures in the 8 weeks preceding study enrolment.

Internal Validity

Wu XY;Hong Z;Wu X;Wu LW;Wang XF;Zhou D;Zhao ZX;Lv CZ;

Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in Chinese patients with refractory partial-onset seizures

Ref ID 4841

2009 Mar

Study Type Randomised Controlled Trial

Funding UCB Pharma SA.

Number of participant n=206 (n=103 in the placebo group and n=103 in the LEV group)

Inclusion/Exclusion Criteria

Inclusion criteria: Chinese subjects aged 16 to 70 years with partial-onset seizures, with or without secondary generalization, diagnosed at least 6 months prior to the selection visit, present with treatment-resistant partial onset seizures and had to have experienced at least eight partial-onset seizures during the 8-week historical baseline period. Exclusion criteria: history of pseudoseizures or if they had status epilepticus in the 3

months before the study or clusters of seizures that could not be reliably and regularly counted, a history of recurrent psychotic or major affective disorder; alcohol or drug abuse within the previous year; or current cardiac, renal, hepatic dysfunction; questionable compliance with drug treatment; laboratory test abnormalities; and the use of central nervous system (CNS)-influencing medication (other than concomitant AED therapy), unless patients had been stabilized on such medication for more than 1 month before the trial.

Patient Characteristics	Baseline demographic characteristics and history of epilepsy (intent-to-treat population)																																																															
	<table border="0"> <thead> <tr> <th></th> <th>Placebo (n=100)</th> <th>LEV (n=102)</th> </tr> </thead> <tbody> <tr> <td>Age (years), mean (SD)</td> <td>32.8 (11.9)</td> <td>32.7 (13.4)</td> </tr> <tr> <td>Range</td> <td>16–64</td> <td>15–70</td> </tr> <tr> <td>Gender, male, n (%)</td> <td>54 (54.0)</td> <td>51 (50.0)</td> </tr> <tr> <td>Weight (kg), mean (SD)</td> <td>63.2 (13.6)</td> <td>60.7 (11.6)</td> </tr> <tr> <td>Age at onset of epilepsy (years), mean (SD)</td> <td>15.2 (10.9)^a</td> <td>16.0 (11.0)</td> </tr> <tr> <td>Duration of epilepsy (years), mean (SD)</td> <td>17.3 (12.1)^a</td> <td>16.5 (12.7)</td> </tr> <tr> <td>Seizure type at baseline, n (%)</td> <td></td> <td></td> </tr> <tr> <td>Simple partial</td> <td>30 (30.0)</td> <td>30 (29.4)</td> </tr> <tr> <td>Complex partial</td> <td>61 (61.0)</td> <td>57 (55.9)</td> </tr> <tr> <td>Secondarily generalized</td> <td>48 (48.0)</td> <td>56 (54.9)</td> </tr> <tr> <td>Primary generalized</td> <td>2 (2.0)</td> <td>1 (1.0)</td> </tr> <tr> <td>Concomitant AEDs,^b n (%)</td> <td></td> <td></td> </tr> <tr> <td>Carbamazepine</td> <td>52 (52.0)</td> <td>59 (57.8)</td> </tr> <tr> <td>Valproate</td> <td>30 (30.0)</td> <td>31 (30.4)</td> </tr> <tr> <td>Topiramate</td> <td>25 (25.0)</td> <td>29 (28.4)</td> </tr> <tr> <td>Gabapentin</td> <td>16 (16.0)</td> <td>12 (11.8)</td> </tr> <tr> <td>Phenytoin</td> <td>9 (9.0)</td> <td>9 (8.8)</td> </tr> <tr> <td>Clonazepam</td> <td>9 (9.0)</td> <td>7 (6.9)</td> </tr> <tr> <td>Phenobarbital</td> <td>9 (9.0)</td> <td>6 (5.9)</td> </tr> <tr> <td>Lamotrigine</td> <td>5 (5.0)</td> <td>3 (2.9)</td> </tr> </tbody> </table>		Placebo (n=100)	LEV (n=102)	Age (years), mean (SD)	32.8 (11.9)	32.7 (13.4)	Range	16–64	15–70	Gender, male, n (%)	54 (54.0)	51 (50.0)	Weight (kg), mean (SD)	63.2 (13.6)	60.7 (11.6)	Age at onset of epilepsy (years), mean (SD)	15.2 (10.9) ^a	16.0 (11.0)	Duration of epilepsy (years), mean (SD)	17.3 (12.1) ^a	16.5 (12.7)	Seizure type at baseline, n (%)			Simple partial	30 (30.0)	30 (29.4)	Complex partial	61 (61.0)	57 (55.9)	Secondarily generalized	48 (48.0)	56 (54.9)	Primary generalized	2 (2.0)	1 (1.0)	Concomitant AEDs, ^b n (%)			Carbamazepine	52 (52.0)	59 (57.8)	Valproate	30 (30.0)	31 (30.4)	Topiramate	25 (25.0)	29 (28.4)	Gabapentin	16 (16.0)	12 (11.8)	Phenytoin	9 (9.0)	9 (8.8)	Clonazepam	9 (9.0)	7 (6.9)	Phenobarbital	9 (9.0)	6 (5.9)	Lamotrigine	5 (5.0)	3 (2.9)
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Recruitment	Not reported.																																																															
Setting	Six centres in China.																																																															
Interventions/ Test/ Factor being investigated	Levetiracetam up to 3000mg per day as adjunctive therapy.																																																															
Comparisons	The comparison is between levetiracetam up to 3000mg per day and placebo as adjunctive therapy to currently used AEDs.																																																															
Length of Study/ Follow-up	24 weeks: 8 week baseline, 4 week titration and 12 week maintenance.																																																															
Outcome measures studied	Primary outcome: weekly frequency of partial-onset seizures over the 16 week treatment period. Secondary outcomes: weekly freq of all seizures, % reduction of in weekly freq partial onset and all seizures, responder rate, seizure freedom rates.																																																															
Results	Weekly frequency of partial-onset seizures during historical baseline and 16-week treatment periods, and absolute and percentage reduction from historical baseline in partial-onset seizure frequency over 16-week treatment period (intent-to-treat population)																																																															

	Placebo (n=100)	LEV (n=102)	p-
value			
Historical baseline weekly seizure frequency			
Median (Q1–Q3)	1.75 (1.13–4.00)	1.81 (1.13–3.38)	
Treatment period weekly seizure frequency			
Median (Q1–Q3)	1.74 (0.90–3.67)	0.85 (0.25–2.54)	
Transformed LSmean 1.23 0.92			
Percentage reduction over placebo (95% CI) —		26.8% (14.0–37.7)	
<0.001			

Absolute reduction in weekly seizure frequency from historical baseline		
Median (Q1–Q3)	0.29 (-1.25–0.81)	0.91 (0.02–1.75)
<0.001		
Percentage reduction in weekly seizure frequency from historical baseline		
Median (Q1–Q3)	13.7 (-38.8–50.4)	55.9 (0.9–87.6)
<0.001		

CI, confidence interval; LEV, levetiracetam; LSmean, least-squares mean.

Responder rates

Significantly more LEV than placebo patients (57 of 102, 55.9% versus 26 of 100, 26.0%) experienced a $\geq 50\%$ reduction from historical baseline in the weekly frequency of partial-onset seizures (odds ratio 3.6; 95% CI, 2.0–6.5; $p < 0.001$).

Seizure free

In the LEV group, 11 of 102 patients (10.8%) were free from partial-onset seizures during the 16-week treatment period, compared with 2 of 100 placebo patients (2.0%, $p = 0.012$).

Global evaluation scale

According to the investigator-completed GES, 84 patients (82.4%) in the LEV group were rated as improved compared with 51 patients (51.0%) in the placebo group. Of these, marked improvement was observed in 36 patients (35.3%) in the LEV group and 12 (12.0%) in the placebo group. The differences between the LEV and placebo groups were statistically significant ($p < 0.001$).

Adverse events

Treatment-emergent adverse events reported by at least 5% of patients in either treatment group (safety population)

	Number (%) of patients	
	Placebo (n=103)	LEV (n=103)
At least one TEAE	62 (60.2)	65 (63.1)
Somnolence	18 (17.5)	18 (17.5)
Decreased platelet count	10 (9.7)	10 (9.7)
Dizziness	14 (13.6)	8 (7.8)
Headache	9 (8.7)	4 (3.9)

LEV, levetiracetam; TEAE, treatment-emergent adverse event.

None of the patients in the LEV group discontinued medication due to an adverse event, compared with two patients (1.9%) in the placebo group. Serious adverse events were reported by three patients (2.9%) in LEV group (appendicitis, pregnancy, fracture) and two (1.9%) in the placebo group (schizophrenia, overdose). None of the serious adverse events was considered to be related to the study drug.

Safety and adverse effects

Does the study answer the question?

LEV was effective in Chinese patients with refractory partial onset seizures. The study appeared to be well conducted but no power calculation was performed. Cannot be confident about the effectiveness of LEV compared to placebo.

Effect due to factor in study?

No. No power calculation was performed. Therefore, it is not clear if the difference in seizure reduction between LEV and placebo occurred by chance.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients had a diagnosis of partial-onset seizures.

Internal Validity

Study Type Randomised Controlled Trial **Funding** UCB pharmacy, Netherlands

Number of participant 56 patients. 28 in each arm.

Inclusion/Exclusion Criteria

Inclusion criteria:

- o16 to 70 years old
- oUnequivocal history of partial seizures, with or without secondary generalisation
- oRefractory to current antiepileptic therapy
- oExperienced at least 4 seizures per month (averaged within the two preceding month) while on AEDs
- oReceived 1-2 of the following AEDs: phenytoin, carbamazepine, phenobarbital or primidone, valproate Topiramate, gabapentin, clonazepam, or lamotrigine for at least 10 weeks.
- oGood physical health and capable of counting seizures
- oFemale patients should be post-menopause, had surgical sterilisation or an approved method of birth control
- oPrior (if any) surgery for epilepsy failed to reduce frequency (≥ 6 months ago).

Exclusion criteria:

- oPrevious exposure to LEV
- oHistory or evidence of progressive encephalopathy or structural lesion in the CNS, progressive degenerative neurological disorder, serious psychiatric disorder or mental retardation within the past 5 years.
- oPseudoseizures within the past year
- oUncountable seizures or history of convulsive status epilepticus within the past 5 years
- oClinically significant cardiac, haematologic hepatic, or renal disease or any conditions that might interfere with the pharmacokinetics of the drugs
- oSerum creatinine >177 micromol/l or neutrophil counts < 2800 /ml or platelet counts $<1000,000$ /ml

Patient Characteristics	LEV, n=28	Placebo, n=28
Demographics		
Gender (male):	12 (42.9%)	12(45.9%)
Age, years, mean \pm SD	32.8 \pm 11.2(17-60)	32.5 \pm 11.2 (12-58)
Weigh, kg, mean \pm SD	58.4 \pm 9.5 (43-82)	58.1 \pm 14.6 (41-102)
Asian	28(100%)	28(100%)
Epilepsy aetiology		
Cause unknown	23(82.1%)	17(60.7%)
Age at onset:	18.6 \pm 9.4 (2-40)	16.3 \pm 11.2 (1-41)
Duration of epilepsy:	14.1 \pm 9.4 (2-40)	16.1 \pm 12.5 (2-48)
Baseline frequency of seizure:	4.9 \pm 7.3 (1-23.6)	5.6 \pm 5.4 (1-50)
Seizure type:		
Simple partial	3(10.7)	8(28.6)
Complex partial	18(64.3)	19(67.9)
Secondary generalised	14(50)	15(53.6)
Concomitant AED		
Topiramate	11(39.3)	10(35.7)
Carbamazepine	11(39.3)	9(32.1)
Valproic acid	9(32.1)	9(32.1)
gabapentin	5(17.9)	9(32.1)
barbiturates	1(3.6)	2(7.1)
lamotrigine	1(3.6)	2(7.1)
clonazepam	3(13.8)	1(3.6)

Recruitment Enrolled by the Epilepsy Centre over a period of 4 months. All patients screened were eligible.

Setting China – Chongqing Medical University

Interventions/ Test/ Factor being investigated	Levetiracetam vs placebo																								
Comparisons	Adjunctive therapy: Levetiracetam vs placebo added on to existing therapy																								
Length of Study/ Follow-up	8 weeks baseline period. Treatment: 16 weeks – 4 week titration and 8 week maintenance Withdrawal: 4 weeks study of medication withdrawal																								
Outcome measures studied	Primary outcome: weekly frequency of partial seizures (logarithmically transformed) Secondary: o Absolute and % reduction in frequency/week o 50% responder rate o Number and % of seizure free patients and number of seizure free days/4 weeks.																								
Results	<p>Proportion of seizure free participants: LEV: 3/28 (10.7%) Placebo: 2/28 (7.1%) P= NS</p> <p>Proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders) LEV: 13/28 (46.4%) Placebo: 11/28 (39.3%) P= NS</p> <p>The proportion of participants having treatment withdrawn because of adverse events: LEV: 0/28 (0%) Placebo: 0/28 (0%) P= NS</p> <p>The proportion of participants having treatment withdrawn because of lack of efficacy: LEV: 0/28 (0%) Placebo: 0/28 (0%) P= NS</p> <p>Incidence of adverse events more than 10% in each arm:</p> <table border="0"> <thead> <tr> <th></th> <th>LEV</th> <th>PLA</th> </tr> </thead> <tbody> <tr> <td>Increases in ALT:</td> <td>4(14.3%)</td> <td>3(10.7%)</td> </tr> <tr> <td>Increases in AST:</td> <td>3(10.7%)</td> <td>2(7.1%)</td> </tr> <tr> <td>Decreases in Platelets:</td> <td>10(35.7%)</td> <td>10(35.7%)</td> </tr> <tr> <td>Decreases in WBC:</td> <td>3(10.7%)</td> <td>0(0%)</td> </tr> <tr> <td>Somnolence:</td> <td>3(10.7%)</td> <td>5(17.9%)</td> </tr> <tr> <td>Dizziness (except vertigo):</td> <td>3(10.7%)</td> <td>0(0%)</td> </tr> <tr> <td>Agitation:</td> <td>3(10.7%)</td> <td>0(0%)</td> </tr> </tbody> </table>		LEV	PLA	Increases in ALT:	4(14.3%)	3(10.7%)	Increases in AST:	3(10.7%)	2(7.1%)	Decreases in Platelets:	10(35.7%)	10(35.7%)	Decreases in WBC:	3(10.7%)	0(0%)	Somnolence:	3(10.7%)	5(17.9%)	Dizziness (except vertigo):	3(10.7%)	0(0%)	Agitation:	3(10.7%)	0(0%)
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Safety and adverse effects	The most common treatment emergent adverse events were mild to moderate in severity.																								
Does the study answer the question?	Adjunctive therapy with LEV 3000 mg daily was well tolerated but not as effective as expected in controlling partial seizures. Considering the lower mean weight of the study population, the dosage of LEV3000 mg may contribute to the results.																								
Effect due to factor in study?	The sample size was not powered to detect a significant difference in the outcomes measured.																								
Consistency of results with other studies?																									
Directly applicable to guideline population?	Uncertain – baseline frequency of epileptic episodes is a minimum of 4 /month. Is this the typical frequency(severity)?																								

Internal Validity

Yamauchi T;Kaneko S;Yagi K;Sase S;

Treatment of partial seizures with gabapentin: double-blind, placebo-controlled, parallel-group study

Ref ID 362

2006 Aug

Study Type	Randomised Controlled Trial	Funding	Not reported.	
Number of participant	n=209 (n=86 in gabapentin 1200mg/day, n=41 in gabapentin 1800mg/day and n=82 in placebo group)			
Inclusion/Exclusion Criteria	<p>Inclusion criteria: men and non-pregnant women, at least 16 years of age with partial seizures, inpatients or outpatients, weight 40–110 kg, on a stable dose of no more than two AED.</p> <p>Exclusion criteria: evidence of unstable diseases, such as progressive lesions in the central nervous system, encephalopathy, or histological lesions as detected by magnetic resonance imaging or computed tomography scan conducted in the previous 2 years.</p>			
Patient Characteristics	Demographic and baseline disease characteristics†			
			Gabapentin (mg/day)	
		Placebo	1200	
	1800			
Enrolled patients		82	86	
41				
Gender, n (%)				
Male		42 (51.2)	37 (43.0)	22
(53.7)				
Female		40 (48.8)	49 (57.0)	19
(46.3)				
Age (years)				
<18		9	4	2
18–44		55	70	31
45–64		18	11	5
≥65		0	1	3
Mean ± SD		31.8 ± 11.3	31.3 ± 10.6	32.7 ±
13.7				
Bodyweight (kg) (mean ± SD)		59.3 ± 11.5	59.4 ± 11.1	62.1 ±
11.4				
Type of seizure (n/%):				
SP		44 (58.7)	44 (55.0)	18
(51.4)				
CP		67 (89.3)	66 (82.5)	30
(85.7)				
SG		25 (33.3)	21 (26.3)	13
(37.1)				
Duration of epilepsy† (years)				
Mean		19.5	19.8	
21.2				
Range		2.1–47.0	4.0–42.0	
5.2–43.3				
Baseline seizure (per 28 days)				
Mean		19.9	31.6	
24.4				
Median		9.7	11.2	
12.3				
Range		3.3–289.7	2.7–564.3	
2.9–101.4				
Concomitant AED, n (%)				
One		16 (19.5)	12 (14.0)	2
(4.9)				
Two		66 (80.5)	74 (86.0)	39
(95.1)				
Recruitment	Not reported.			
Setting	54 sites in Japan.			
Interventions/ Test/ Factor being investigated	Gabapentin 1200mg per day and 1800mg per day as adjunctive therapy to currently used AEDs.			

Comparisons

The comparisons are between the two doses of gabapentin (1200mg and 1800mg) and placebo.

**Length of Study/
Follow-up**

32 weeks: 12 weeks baseline, 12 weeks treatment, 4 weeks phased withdrawal and 4 weeks observation period.

**Outcome measures
studied**

Primary outcome: response ratio (RRatio). $RRatio = (T - B)/(T + B)$, where T and B are the seizure frequencies during treatment and during baseline. RRatio = -1 (reduction) to +1.

Secondary outcomes: % change from baseline in seizure frequency.

Results

Primary and secondary outcomes

Efficacy results for the per-protocol set population

Efficacy parameters mg/day	Gabapentin		
	Placebo (n = 75)	1200 mg/day (n = 80)	1800 (n = 35)
% change in partial seizures†			
Mean	2.6	-17.8	
-22.2			
Median	-9.7	-21.2	
-27.9			
Responder rate‡, n (%)	5 (6.7)	13 (16.3)	7 (20.0)
Improvement in seizure frequency§, n (%)			
Completely resolved	0	0	0
Markedly improved (2.9)	0	2 (2.5)	1
Moderately improved (17.1)	5 (6.7)	11 (13.8)	6
Slightly improved (37.1)	17 (22.7)	22 (27.5)	13
No change (20.0)	23 (30.7)	29 (36.3)	7
Worse (22.9)	30 (40.0)	16 (20.0)	8
Improvement in seizure intensity/duration¶, n (%)			
Better (45.7)	25 (33.3)	36 (45.0)	16
No change (48.6)	40 (53.3)	39 (48.8)	17
Worse	7 (9.3)	5 (6.3)	2 (5.7)

† Percent change in partial seizures (PCH) was calculated by the formula: $PCH (\%) = 100(T-B)/B$, where T and B are the seizure frequencies during treatment and during baseline, respectively.

‡ The responder was defined as a patient with reduction in PCH >50%, meaning summed patients categorized into completely resolved, markedly improved and moderately improved with regard to improvement in seizure frequency rating.

§ Improvement in seizure frequency was classified into six categories by PCH: completely resolved (-100%), markedly improved (-99.9 to -75.0%), moderately improved (-74.9 to -50%), slightly improved (-49.9 to -25%), no change (-24.9 to 0%), and aggravated (>+0.1%).

¶ Improvement in seizure intensity/duration was rated by summed scores at weeks 4, 8, and 12 compared to baseline (better,+1; no change, 0; worse, -1).

**Safety and adverse
effects**

Adverse events

Treatment-related adverse events† (>10%)

Efficacy parameters mg/day	Gabapentin		
	Placebo n (%)	1200 mg/day n(%)	1800 n(%)
Evaluated subjects	82	86	41
No. events	65	108	50
No. patients with events (%)	38 (46.3)	55 (64.0)	27 (65.9)
Somnolence	17 (20.7)	44 (51.2)	18 (43.9)

Dizziness 4 (4.9) 16 (18.6) 8 (19.5)

15 patients withdrew prematurely due to aggravation of seizures (3 in placebo), safety reasons (one placebo, four gabapentin 1200mg/day, 3 gabapentin 1800mg/day).

Discontinuation rates due to adverse events or laboratory test abnormalities were 5.5% for gabapentin-treated patients (7/127) compared to 1.2% for placebo-treated patients (1/82). Serious treatment-related adverse events were reported for two gabapentin patients: ataxic gait, nystagmus, dizziness, ataxia and leg pains appeared in one patient receiving gabapentin 1200 mg/day, and seizures and dizziness appeared in another patient receiving gabapentin 1800 mg/day.

Does the study answer the question?

Yes. The study demonstrated that 1200 mg/day and 1800 mg/day gabapentin significantly reduced the frequency of refractory partial seizures compared to placebo and that there was a definite dose-response relationship for this effect.

Effect due to factor in study?

Yes. The sample size for the study was determined from the RRatio obtained in previous studies.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients enrolled in this study had refractory epilepsy with partial seizures.

Internal Validity

Yen DJ;Yu HY;Guo YC;Chen C;Yiu CH;Su MS;

A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy

Ref ID 4762

2000

Study Type

Randomised Controlled Trial

Funding

Grant from Taipei Veterans General Hospital and Yen Tjing Ling Medical Foundation. Topiramate and placebo tablets provided by Jassen Cilag Taiwan.

Number of participant

Total : 46; 23 in each arm

Inclusion/Exclusion Criteria

Chinese adults aged 18 to 65 with a history of partial seizure that has not responded to adequate doses of AED treatment for 2 or more years. Diagnosis were supported with scalp electroencephalograms with nasopharyngeal electrode and MRI or CT scans of the head. The seizure patterns and rates were recorded in diaries.

Exclusion criteria: intracranial tumour, severe hepatic or renal dysfunction, history of nephrolithiasis; pregnancy or breast feeding.

Patients who did not benefit from previous temporal lobotomy did were not excluded.

To quality for randomisation, patients should have 4 or more complex partial seizures with or without secondary generalisation during the 8-week baseline period.

Patient Characteristics

Gender(male/female): topiramate: 6/17, placebo: 13/10
 Age (years), mean, sd (range): topiramate : 31.4 sd 10.1(18-54), placebo: 32.0 sd 8.7 (22-48)
 Weight (kg), mean, sad (range): topiramate : 58.2 sd 12.7(39.5 to 85), placebo: 60.4 sd 12.6 (34 to 83)
 Seizure history (years, mean, sd (range): topiramate : 14.9 sd 10.9(5 to 45), placebo: 18.9 sd 11.1 (2 to 39)
 Seizure focus (temporal /non temporal lobe): topiramate : 21/2, placebo:21/2
 (Among the non temporal lobe origin, 2 were frontal , 1 centroparietal and 1 occipital)
 Number of AEDs (1/2/3/4 or more): topiramate: 4/6/11/2, mean 2.48 sd 0.90, placebo : 1/7/11/4, mean 2.78 sd 0.80.

	Specific AEDs used (carbamazepine/valproate/lamotrigine/phenytoin): topiramate: 19/11/5/2, placebo: 17/10/8/5. The other concomitant AEDs were phenobarbital (7 patients), clonazepam (4), vigabatrin (4), primidone (3), acetolamide (1)
Recruitment	Patients were recruited from the epilepsy outpatient clinic at Taipei Veterans General Hospital, Taiwan
Setting	Taipei, Taiwan from October 1997 to 1998
Interventions/ Test/ Factor being investigated	Topiramate vs placebo as adjuvant therapy to patients with at least one other stabilised AED
Comparisons	Treatment vs placebo
Length of Study/ Follow-up	14 weeks of treatment, plus 8 weeks of baseline follow up
Outcome measures studied	These were not clearly specified
Results	<p>Proportion of patients experiencing at least 50% reduction in complex partial seizures: 11/23 in topiramate, 3/23 in placebo group (auras or simple partial seizures were not included in analysis)</p> <p>Proportion of patient shaving treatment withdrawn due to adverse events : 2/23 in topiramate and 2/23 in placebo. Note: In the topiramate group, one patient had intolerable somnolence and the other had severe secondary generalised seizures. In the placebo group, one had intolerable headache, the other had skin rashes. One other patient dropped out from the topiramate group due to protocol violation (refused blood sampling).</p> <p>Incidence of adverse events (>10% per treatment arm): Dizziness/somnolence: topiramate 4/23, placebo: 2/23 Headache: topiramate 1/23, placebo 3/23</p>
Safety and adverse effects	<p>There were no significant changes in laboratory values during the study.</p> <p>Paper noted that most of the adverse events reported were mild and transient, occurring predominantly during the titration phase.</p>
Does the study answer the question?	Topiramate (at 300mg) was more effective than placebo as an adjunct therapy in reducing complex partial seizures among patients refractory to stabilised AED treatments
Effect due to factor in study?	The treatment effect was large (RR 3.67, 95% CI 1.32 to 11.34) but the confidence interval was wide due to the small sample size and there were uncertainty about the blinding of the analysis.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct
Internal Validity	

Grading: 1-**Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias***

Aldenkamp AP;Baker G;Mulder OG;Chadwick D;Cooper P;Doelman J;Duncan R;Gassmann-Mayer C;de Haan GJ;Hughson C;Hulsman J;Overweg J;Pledger G;Rentmeester TW;Riaz H;Wroe S;

A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures

Ref ID 4728

2000

Study Type Randomised Controlled Trial **Funding** Not reported.**Number of participant** n=59(n=29 in Topiramate and n=30 in the valproate group)**Inclusion/Exclusion Criteria** Inclusion criteria: age between 18 and 60 years, minimum weight of 45 kg; localization-related epilepsy with partial-onset seizures, with or without secondary generalization; steady-state treatment with CBZ monotherapy for at least 28 days; and epilepsy uncontrolled on CBZ or requiring another AED for other reasons. Exclusion criteria: progressive cerebral lesion, degenerative disorder, malignancy, or history of malignancy in the past 5 years; cognitive impairment; females who do not practice reliable contraception; nonepileptic seizures; documented history with generalized status epilepticus in the past 3 months; unstable medical or psychiatric disease.

Patient Characteristics	Demographic and clinical characteristics of the intent-to-treat population	
	Topiramate (n = 24)	Valproate (n = 29)
Age (years)	34.7 (10.2)	39.4 (11.4)
Gender (% male)	63	52
Weight (kg)	75.9 (17.5)	76.2 (18.0)
Height (cm)	174.2 (13.0)	172.1 (10.4)
Duration of epilepsy time since first seizure (years)	18.3 (12.4)	22.7 (16.0)
Median baseline seizure rate (all seizures)	5.9 per month	5.8 per month
CBZ average daily dose (baseline medication) (mg/d)	1070.8 (411.23)	1231 .0 (409.79)
Study medication average dose during maintenance (ug/d	251.1 TPM (101.8)	1384 VPA (377.0)

Data shown are means (SD) unless specified otherwise.

Recruitment Not reported.**Setting** Multicentre study in Netherlands.**Interventions/ Test/ Factor being investigated** Topiramate as add-on therapy**Comparisons** The comparison is between topiramate and valproate up to their maximum tolerated doses as adjunctive therapy to carbamazepine.**Length of Study/ Follow-up** 22 weeks: 2 week baseline phase, 12 week titration phase and 8 week maintenance phase.**Outcome measures studied** The primary outcome measure is the difference between the treatments (TPM versus VPA) in change from baseline to end point and change from baseline to titration. That is, in cognitive tests: motor speed, mental speed, memory, and mood and well-being.

Results

Cognitive test results

Comparisons between baseline and end point for the two treatments.

In the memory tasks (4 tasks) there is a worsening of scores for topiramate in all tasks and improvement for valproate in all but one task. Only one of these tasks shows a statistically significant difference between the treatments (The Rey Auditory Verbal Learning Task, (p=0.02)).

Comparisons between baseline to titration for the two treatments

There was a tendency for worsening of memory performance for topiramate, with again one memory test, Recognition of Words, showing worsening of performance for both treatments, but significantly more for topiramate (p = 0.04).

Seizure reduction

The mean percentage reduction in the average monthly seizure rate for all seizure types during maintenance was 29.6% for topiramate and 22.1 % for valproate; thus, the percentage reductions were comparable.

Safety and adverse effects

No adverse events data reported.

Does the study answer the question?

Yes. Although, it is of concern that only those administering the cognitive tests were blind to patient treatment: clinicians and patients were not.

Effect due to factor in study?

No. The sample size was chosen based on sample sizes from other studies which had used an information-processing task. This study assumed therefore that such a sample size would be sufficient to detect statistically significant differences of a magnitude that is generally reported in cognitive function studies.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients who were enrolled had localization-related epilepsy with partial-onset seizures.

Internal Validity

Ben-Menachem E;Gabbai AA;Hufnagel A;Maia J;Almeida L;Soares-da-Silva P;

Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy

Ref ID 5077

2010 May

Study Type

Randomised Controlled Trial

Funding

BIAL - Portela & Co, SA.

Number of participant

n=395. Placebo n=100; esl 400mg n=96; esl 800mg n=101; esl 1200mg n=98.

Inclusion/Exclusion Criteria

aged 18 years or over;
assessed in general good health;
diagnosed with simple or complex partial-onset seizures (with or without secondary generalisation) for minimum of 12 months prior to screening;
experienced at least 4 partial-onset seizures in the two 4-week periods before screening as well as during each of the two 4-week periods of the 8-week baseline period;
treated with 1 to 3 concomitant AEDs in a stable dose regimen for at least 2 months prior to screening (vagus nerve stimulation considered an AED);
Exclusion criteria:
If at time specified they had:
an uncontrolled, relevant medical disorder;
visual field loss caused by vigabatrin use (at least 1 year);
simple partial-onset seizures without motor symptoms;
primary generalised epilepsy;
rapidly progressive neurological disorder;

status epilepticus;
 cluster seizures (within 3 months)
 history of seizures of psychogenic origin (within 2 years)
 a history of schizophrenia or suicide attempts;
 a known hypersensitivity to carbamazepine or oxcarbazepine or chemically related substances.

Patient Characteristics	Placebo vs 400mg vs 800mg vs 1200mg Mean age (s.d): 36.7 (12.2) vs 37.6 (11.2) vs 36.4 (12.6) vs 36.9 (11.6) Males n (%): 52 (52) vs 39 (40.6) vs 51 (50.5) vs 52 (53.1) Ethnic group: caucasian 84 (87) vs 87 (90.6) vs 91 (90.1) vs 81 (82.7); black 6 (6) vs 2 (2.1) vs 6 (5.9) vs 9 (9.2); Asian 0 vs 2 (2.1) vs 0 vs 5 (5.1); other 7 (7) vs 5 (5.2) vs 4 (4.0) vs 3 (3.1); Seizure types at baseline: simple partial, complex partial, secondarily generalised and unclassified. No. Of concomitant AEDs - up to 4. Types of AEDs: carbamazepine, valproic acid, lamotrigine, clobazam, levetiracetam, phenytoin, phenobarbital, topiramate, clonazepam.
Recruitment	Not reported.
Setting	45 sites in 13 countries across world.
Interventions/ Test/ Factor being investigated	Eslicarbazepine 400mg, 800mg 1200mg.
Comparisons	Comparisons between dosages and placebo.
Length of Study/ Follow-up	Those who completed 14-week double-blind could enter an open-label extension treatment with ESL - not reported here.
Outcome measures studied	Primary efficacy: Seizure frequency.
Results	placebo vs 400mg vs 800mg vs 1200mg: 50% reduction in seizure frequency: 13% vs 17% vs 40% vs 37.1%. Seizure freedom: 1% vs 1% vs 8% vs 4.1%. Exacerbation of seizures (>25%): 30% vs 14% vs 18.6% - no details given for 400mg. Incidence of adverse events n(%): dizziness 10 (10%) vs 22 (22.9%) vs 30 (29.7%) vs 43 (43.9%); somnolence 17 (17%) vs 15 (15.6%) vs 17 (16.8%) vs 21 (21.4); headache 9 (9%) vs 12 (12.5%) vs 15 (14.9%) vs 19 (19.4%); nausea 4 (4%) vs 8 (8.3%) vs 12 (11.9%) vs 15 (15.3%); diplopia 4 (4%) vs 8 (8.3%) vs 15 (14.9%) vs 10 (10.2%); TEAEs leading to discontinuation: 3 (3%) vs 12 (12.5%) vs 19 (18.8%) vs 26 (26.5%).
Safety and adverse effects	Serious TEAE 0% vs 4.2% vs 5.9% vs 2%, no deaths occurred.
Does the study answer the question?	Yes.
Effect due to factor in study?	Allocation and blinding methods unclear. Power calculation: 80% - sample size of 86 per treatment group and drop-out assumed at 15% so 400 required for enrollment. Drop-out was considerably higher than assumed and 400 were not enrolled.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	

Study Type	Randomised Controlled Trial	Funding	GlaxoSmithKline
Number of participant	193: 192 (96 patients randomised to each treatment group) were randomised and received at least one dose of study drug.		
Inclusion/Exclusion Criteria	Inclusion criteria: Aged >= 18, confident diagnosis of epilepsy for >= 6mths, >= 1 and <=8 partial or secondary gen. tonic-clonic seizures in past month, currently receiving carbamazepine or phenytoin as monotherapy or one additional AED , no change of AED dose > 10% for at least 1 month before enrolment. Exclusion criteria: none listed.		
Patient Characteristics	Lamotrigine N=96	Topiramate n=96	
Male, n (%)	59 (61)	53 (55)	
Race, n (%)			
White	72 (75)	67 (70)	
Black	12 (13)	19 (20)	
Hispanic	11 (11)	8 (8)	
Other	1 (1)	2 (2)	
Mean age, y (SD)	39.2 (14.1)	40.5 (12.5)	
Mean age at first seizure, y (SD)	23.9 (15.6)	22.6 (14.9)	
Seizure classification, n (%)			
Simple partial	40 (42)	40 (42)	
Complex partial	82 (85)	80 (83)	
Partial evolving to			
secondarily generalized	52 (54)	47 (49)	
Absence	1 (1)	0 (0)	
Myoclonic	0 (0)	1 (1)	
Tonic	1 (1)	0 (0)	
Generalized tonic-clonic	9 (9)	10 (10)	
Atonic	0 (0)	2 (2)	
Unclassified	1 (1)	1 (1)	
Mean number of seizures/month (SD)	4.3 (4.2)	3.7 (2.9)	
Antiepileptic medication, n (%)			
Carbamazepine	43 (45)	54 (56)	
Recruitment	Unknown.		
Setting	Study sites in the United States and Canada.		
Interventions/ Test/ Factor being investigated	Lamotrigine is compared with topiramate as adjunctive therapy in adult patients with partial seizures.		
Comparisons	Comparison between lamotrigine and active comparator topiramate as adjunctive therapy.		
Length of Study/ Follow-up	18 weeks: 2 weeks screening,8 weeks titration and 8 weeks maintenance phase.		
Outcome measures studied	Primary endpoint: change in a combined analysis of the standardized measures of cognition (COWA; Stroop Color-Word Interference; Digit Cancellation; Lafayette Grooved Pegboard, dominant hand; RAVLT, delayed recall; and symbol-Digit modalities test.)		
Results	Primary outcome		
	Lamotrigine, n= 67		Topiramate, n = 57
Value	n	Mean (SD)	n Mean (SD) p

Combined cognitive scores
 Combined score using the sum of the rank
 of changes for all cognitive tests
 65 415.3 (104.4) 54 315.1 (109.9)
 <0.001

In the intent-to-treat population the % of patients seizure-free was lower with lamotrigine than topiramate during the escalation phase (42% vs 60%; p=0.019). This trend became no significant during the maintenance phase (41% vs. 57%; p=0.054).

The percentage of patients with at least one adverse event during the study was 74% in the lamotrigine group and 83% in the topiramate group. The most common adverse events were headache (13% lamotrigine, 24% topiramate), dizziness (19% lamotrigine, 9% topiramate), fatigue (8% lamotrigine, 13% topiramate), and nausea (11% lamotrigine, 6% topiramate).

Adverse events led to premature withdrawal from the study in 21% of patients in the lamotrigine group and 25% in the topiramate group. The adverse events most frequently leading to premature withdrawal were vomiting (4% lamotrigine, 2% topiramate), dizziness (5% lamotrigine, 0% topiramate), nausea (3% lamotrigine, 0% topiramate), and memory impairment (0% lamotrigine, 3% topiramate).

Safety and adverse effects

Although adverse events were not serious, a fifth of patients in the lamotrigine group and a quarter of patients in the topiramate group discontinued treatment because of adverse events.

Does the study answer the question?

Yes. The study concludes that the frequencies of cognitive adverse events and of premature withdrawals related to cognitive decline were higher with topiramate than with lamotrigine.

Effect due to factor in study?

No. The study was powered (80%) to detect a significant difference of a 12-point reduction from baseline in the Stroop Color-Word Interference measure. The primary outcome however, was a combined score of six different measures including the Stroop measure.

Consistency of results with other studies?

Directly applicable to guideline population?

The study population included patients suffering from mostly partial seizures. High maintenance dose of lamotrigine compared to medium dose in topiramate - indirectness of comparison.

Internal Validity

Bourgeois B;Leppik IE;Sackellares JC;Laxer K;Lesser R;Messenheimer JA;Kramer LD;Kamin M;Rosenberg A;

Felbamate: a double-blind controlled trial in patients undergoing presurgical evaluation of partial seizures

Ref ID 4627

1993

Study Type Randomised Controlled Trial

Funding Wallace Laboratories

Number of participant 30 patients in FBM arm and 34 in placebo arm

Inclusion/Exclusion Criteria

Inclusion: video/EEG confirmed partial onset seizures; frequency not exceeding an average of four complex partial onset seizures per day or more than one secondarily generalized seizure per day during the last 3 days of the surgical evaluation; interictal duration of greater than 2 hours; minimum average of one seizure per day for the last 3 days of the surgical evaluation; previous CT or MRI to confirm the absence of progressive lesion; age at least 18 and body weight at least 40 kg and ECG and CXR normal in previous year. Women of childbearing age were to be non-gravid, non-nursing and either incapable of conception or practicing birth control. Exclusion: status epilepticus in last 3 months, significant medical disorder with recent history of psychiatric disorder, poor compliance with prior AED therapy, serious AED complication in the past, change in benzodiazepine dosing during the surgical evaluation, drug or alcohol abuse.

Patient Characteristics	Felbamate n=30	Placebo n=34
Age (yr)		
Mean	33.3	33.3
Weight (kg)		
Mean	78.9	71.6
Sex		
Male	18	20
Female	12	14
Race		
White	30	32
Black	0	1
Other	0	1
Recruitment	During 4 week outpatient baseline period, patients were identified who were appropriate for study participation.	
Setting	USA	
Interventions/ Test/ Factor being investigated	The efficacy and safety of felbamate in patients with refractory partial onset seizures with or without generalization who had completed a hospital evaluation for epilepsy surgery	
Comparisons	Felbamate and placebo as an add on therapy to the AED regimen existing at the completion of the surgical evaluation	
Length of Study/ Follow-up	8 hospital days and 21 outpatient days	
Outcome measures studied	The efficacy variable was the time to the fourth seizure. Secondly the number of patients having a fourth seizure was reported.	
Results	<p>Thirty patients were randomized to felbamate; of these, 13 completed the trial by having a fourth seizure, 15 completed 28 study days without a fourth seizure, and two dropped out due to adverse clinical events. Thirty four patients were randomized to placebo; of these, 29 completed the trial by having a fourth seizure, four completed 28 study days without a fourth seizure and one withdrew consent. The primary efficacy analysis included 61 patients . The mean rank according to seizure frequency for placebo treated patients was 35.4 compared with 25.8 for the felbamate treated patients ($p=0.028$). In the secondary analysis, 13 (46.4%) of 28 patients in the felbamate group experienced a fourth seizure compared with 29 (87.9%) of 33 patients in the placebo group ($p<0.001$). In a "worst-case" analysis, with the two felbamate patients who dropped out classified as having experienced a fourth seizure and the one placebo patient who dropped out classified as a completer, 15 (50%) of 30 patients in the felbamate group experienced a fourth seizure compared with 29 (85.3%) of 34 patients in the placebo group ($p=0.003$).</p>	
Safety and adverse effects	<p>The most commonly occurring adverse experience in both groups was headache reported in 12 (40%) of FBM group and in 4 (12%) of the placebo group. The other commonly occurring adverse experiences in the felbamate group were insomnia and nausea (11 patients - 37%), dizziness (7 patients - 23%), fatigue, constipation and anorexia each in six (20%) of patients. Only one patient in the FBM group had adverse experiences (stupor and confusion) reported as severe; however these resolved without intervention and the patient continued in the study. Two patients in the felbamate group failed to complete the trial due to adverse experiences: one patient on the second treatment day due to agitation, insomnia and psychosis and the second patient on the third treatment day due to dizziness, unsteadiness, numb feet and hands, sleeplessness, upset stomach, nausea and general malaise. In both patients the adverse experiences were mild or moderate in severity and were not considered related to felbamate.</p>	
Does the study answer the question?	The results confirmed the anticonvulsant activity of felbamate and its ability to quickly and safely reduce the occurrence of frequent partial onset seizures .	
Effect due to factor in study?	Yes	

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity Small study with short time period

Brodie MJ;Richens A;Yuen AW;

Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group

Ref ID 4808

1995 Feb 25

Study Type Randomised Controlled Trial **Funding** Supported by the Wellcome foundation.

Number of participant N= 260; n=131 lamotrigine and n=129 carbamazepine.

Inclusion/Exclusion Criteria No specific inclusion and/or exclusion criteria.

Patient Characteristics Patients 13 years and older with newly diagnosed epilepsy with partial seizures without secondary generalisation, and primary or secondary generalised tonic-clonic seizures. No patient had received previous treatment with an AED. Lamotrigine group had a median baseline seizure count of 4 (mean 36) versus 3 mean (mean 22) for the carbamazepine group.

Recruitment Not reported.

Setting 8 centres in the UK.

Interventions/ Test/ Factor being investigated Pharmacological interventions. Patients received increasing doses of identical 50mg lamotrigine or 200mg carbamazepine tablets. At the end of 4 weeks, all patients were taking 150mg lamotrigine or 600mg carbamazepine daily. During weeks 6-24 the daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant adverse events had been reported provided the drug concentration was in the lower half of the target range or lower.

Comparisons Lamotrigine versus carbamazepine.

Length of Study/ Follow-up For 48 weeks.

Outcome measures studied time to first seizure and adverse events.

Results No significant difference between the drugs in time to first seizure after 6 weeks treatment for the whole study population (hazard ratio 0.8, 95% CI 0.6-1.2), or for the subgroup with partial seizures with or without secondary generalisation or the subgroup with primary tonic-clonic seizures.

Percentage seizure-free (for primary generalised tonic-clonic seizures) at last 40 weeks:
LTG: 37% - calculated as 22/60
CBZ: 35% - calculated as 22/62

Percentage seizure-free (for primary generalised tonic-clonic seizures) at last 24 weeks:
LTG: 47% - calculated as 28/60
CBZ: 47% - calculated as 29/62

Percentage seizure-free (for partial seizures with or without generalisation) at last 40 weeks:
LTG: 22%

CBZ: 31%

Percentage seizure-free (for partial seizures with or without generalisation) at last 24 weeks:

LTG: 35%

CBZ: 37%

Percentage seizure-free (all seizures) at last 40 weeks:

LTG: 26%

CBZ: 29%

Percentage seizure-free (all seizures) at last 24 weeks:

LTG: 39%

CBZ: 38%

A greater proportion of the LTG group completed the study compared to the CBZ group (65 vs. 51%, $p=0.018$).

Safety and adverse effects

Adverse events: Headache 30% LTG group vs. 25% CBZ group (95% CI -6 to 16); Asthenia 21% LTG group vs. 29% CBZ group (95% -18 to 3); rash 19% LTG vs. 19% CBZ group (95% CI -10 to 9); nausea 15% LTG group vs. 12% CBZ group (95% CI -3 to 14); dizziness 12% LTG vs. 17% CBZ (95% CI -13 to 4); sleepiness 12% LTG group vs. 22% CBZ group (95% CI -19 to -1); and flu-like symptoms 11% LTG group vs. 8% for the CBZ group (95% CI -3 to 11). The only significant adverse event is sleepiness.

Nineteen patients withdrew from the LTG group ($n=131$) and 35 withdrew from the CBZ group ($n=129$).

Does the study answer the question?

Similar efficacy for both LTG and CBZ. LTG seems to be better tolerated.

Effect due to factor in study?

No.

Consistency of results with other studies?

Directly applicable to guideline population?

Yes.

Internal Validity

Chmielewska B;Stelmasiak Z;

Clinical evaluation of Gabitril and Lamictal for drug-resistant epilepsy in adults

Ref ID 4731

2001

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant LTG $n=22$ vs TGB $n=26$.

Inclusion/Exclusion Criteria

Inclusion criteria:
adults, aged 16-60 years;
CPS in accordance with ILAE classification;
Refractory epilepsy during at least 1 year and 4 or above CPS/ 4 weeks during the last 3 months;
Intake of max 2 concomitant AEDs;
Able to record all seizures in a seizure diary throughout trial;

Exclusion criteria:
Data of status epilepticus in last year;
Any signs of serious somatic or psychiatric pathologies;
Data of non-compliance during previous treatment.

Patient Characteristics	LTG vs TGB: male %: 59.01 vs 53.85; AGE 25 (6.7) vs 27 (8.2) Epilepsy duration year mean (sd): 10 (7.1) vs 11 (8.2); Aetiology - unknown (%) : 81 vs 85;	
Recruitment	Not reported.	
Setting	Not reported.	
Interventions/ Test/ Factor being investigated	Lamotrigine versus tiagabine adjunctive treatment.	
Comparisons	Between treatments.	
Length of Study/ Follow-up	See above.	
Outcome measures studied	Efficacy: >50% reduction of seizure frequency; Tolerability: % of patients with at least one treatment emergent AE; Quality of life.	
Results	LTG vs TGB: At least 50% reduction in seizure frequency:11/22 (50%):11/26 (42.3%) Seizure freedom:2/22 (9.1%):2/26 (7.7%) Incidence of headache:6/22 (27.3%):8/26 (30.8%) Incidence of fatigue:5/22 (22.7%):9/22 (40.9%) Incidence of disturbed sleep:4/22 (18.2%):7/26 (26.9%) Incidence of dizziness:4/22 (18.2%):6/26 (23.1%) Incidence of nervousness:5/22 (22.7%):1/26 (3.8%) Incidence of paresthesia:3/22 (13.6%):3/26 (11.5%) Incidence of nausea:2/22 (9.1%):4/26 (15.4%)	
Safety and adverse effects	See results above.	
Does the study answer the question?	Yes.	
Effect due to factor in study?	No details of randomisation, allocation concealment and no blinding and small sample size so uncertainty in the overall effect due to intervention.	
Consistency of results with other studies?		
Directly applicable to guideline population?	Direct.	
Internal Validity		
	Cramer J;Ryan J;Chang J;Sommerville K;	
	The short-term impact of adjunctive tiagabine on health-related quality of life	
	Ref ID 4697	2001
Study Type	Randomised Controlled Trial	Funding Abbott Laboratories.
Number of participant	CBZ+PHT n=101 vs CBZ+TGB n=105; PHT+CBZ n=76 vs PHT+TGB n=67.	
Inclusion/Exclusion Criteria	Inclusion criteria: Seizures poorly controlled with the baseline AED defined as four or more CPS per month.	

Patient Characteristics	CBZ+PHT vs CBZ+TGB; PHT+CBZ vs PHT+TGB: Males (%): 35 vs 45; 55 vs 46; Age: 33 vs 37; 41 vs 41;
Recruitment	Not reported.
Setting	Not reported.
Interventions/ Test/ Factor being investigated	Tiagabine, Phenytoin and carbamazepine. Randomised to adjunctive therapy.
Comparisons	Between treatments. CBZ+PHT vs CBZ+TGB or PHT+CBZ vs PHT+TGB.
Length of Study/ Follow-up	3-4 months.
Outcome measures studied	QOL outcomes.
Results	TGB vs PHT: At least 50% reduction in seizure frequency: 23/105 (21.9%) vs 28/101 (27.7%). TGB vs CBZ: At least 50% reduction in seizure frequency: 14/67 (20.9%) vs 33/76 (43.4%).

QOLIE was the health related quality of life tested in the study that included the SF-36 as a generic core with four additional domains; the epilepsy targeted domain (seizure worry, medication effects, health discouragement, and work/driving/ social function subscales), the cognitive domain (language, attention, concentration and memory subscales), the mental health domain (overall quality of life, emotional, well being, role limitation-emotional, social isolation, social support and energy/fatigue subscales) and the physical health domain (health perceptions, physical function role limitation-physical and pain subscales).

There was no significant difference on mean scores of any of the subscales between tiagabine and Phenytoin adjunctive to Phenytoin groups.

There was no significant difference on mean scores of none of these subscales between tiagabine and carbamazepine adjunctive to Phenytoin groups

Safety and adverse effects Not reported.

Does the study answer the question? Yes.

Effect due to factor in study? Study not powered for HRQOL but for the primary safety outcome. No details of methodology.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Dean C;Mosier M;Penry K;

Dose-Response Study of Vigabatrin as add-on therapy in patients with uncontrolled complex partial seizures

Ref ID 4751

1999

Study Type Randomised Controlled Trial

Funding Marion Merrell Dow.

Number of participant	174 patients: randomized to placebo= 45 pts, 1g/day= 45 pts, 3g/day= 43 pts, 6g/day= 41 pts.				
Inclusion/Exclusion Criteria	<p>Inclusion criteria: age 18 to 60, uncontrolled complex partial seizures or partial seizures with secondary generalization, receiving at least one but not more than two concomitant AEDs. Lack of adequate seizure control was defined as at least six seizures plus a seizure-free interval of <28 days during the last 8 weeks of the pre-treatment evaluation period. Previous adequate therapeutic trials with phenytoin (PHT) or carbamazepine (CBZ) were required. In addition, patients had a history of an abnormal EEG documenting focal abnormalities, including focal rhythmic, slow, sharps, or spikes.</p> <p>Exclusion criteria: treatable causes of seizures, such as metabolic or neoplastic causes or active infection; history of more than one episode of status epilepticus within the previous 6 months; progressive neurologic disorders, such as multiple sclerosis or brain tumors; surgery for epilepsy or brain tumor within the previous 6 or 12 months, respectively; history of alcoholism, drug addiction, major depression, or other serious psychiatric disorders; and clinically significant hepatic, renal, hematologic, endocrine, or gastrointestinal disease. Patients with a Verbal or Performance Intelligence Quotient (IQ) 4 5 on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) also were excluded.</p>				
Patient Characteristics		placebo	1g VGB	3g VGB	6g
VGB					
n=41		n =45	n=45	n=43	
Sex					
Male n(%)		17(38)	19(42)	24(56)	
23(56)					
Age (yr)					
Mean (SD)		35(11)	34(9)	34(9)	
35(11)					
Weight (kg)					
Mean (SD)		69(15)	76(19)	72(17)	
75(18)					
Number (%) of concurrent AEDs					
One		19(42)	24(53)	23(53)	
15(37)					
Two		26(58)	20(44)	20(47)	
26(63)					
Three		0(0)	1(2)	0(0)	
0(0)					
Onset age (yr)					
Mean (SD)		13(10)	10(8)	14(10)	
15(10)					
Duration of epilepsy (yr)					
Mean (SD)		22(11)	24(9)	20(9)	
21(11)					
Seizure frequency					
Median (range)		9(3-71)	8.5(3-786)	8(1-228)	9(2-45)
Recruitment	Unknown.				
Setting	14 investigative sites in the United States.				
Interventions/ Test/ Factor being investigated	Comparison is between 3 doses of vigabatrin (VGB) (1, 3 or 6 g per day) and placebo as adjunctive therapy to currently used AEDs.				
Comparisons	The comparisons are between three doses of VGB and placebo, on top of currently used AEDs.				
Length of Study/ Follow-up	30 weeks: 12 weeks pre-treatment period,6 weeks titration and 12 weeks maintenance phase.				

Outcome measures studied

Primary outcome: mean monthly frequency of complex partial seizures (1B) plus partial seizures secondarily generalized (1C) during the last 8 weeks of the study as compared with the last 8 weeks of the baseline phase. Secondary outcomes: response rates,

Results

Primary outcome

		Seizure frequency (no/28 days)	
		Baseline median	End study median
Treatment	No.	(95% CI)	(95% CI)
Placebo	45	9.0 (7.0, 10.5)	8.8 (6.0, 12.1)
1 g VGB	45	8.5 (6.0, 12.3)	7.7 (4.1, 11.5)
3 g VGB	43	8.0 (7.0, 10.5)	3.7 (2.5, 6.0)
6 g VGB	41	9.0 (7.0, 14.5)	4.5 (3.3, 6.0)

Treatment comparisons

	p-value
Linear trend	0.0001
Placebo versus 1 g VGB	0.1263
Placebo versus 3 g VGB	0.0001
Placebo versus 6 g VGB	0.0001
3 g VGB versus 6 g VGB	0.8140
(Placebo and 1 g VGB) versus (3 g VGB and 6 g VGB)	0.0001

p Values from ANCOVA of the ranked end-study seizure frequencies using model that adjusted for treatment, investigative site, ranked baseline seizure frequency, and investigative Site-by-Treatment interaction. VGB, vigabatrin.

Secondary outcome: therapeutic success (>=50% reduction in seizure freq)

The percentages of therapeutic successes were 7% for placebo and 24, 51, and 54% for VGB daily doses of 1, 3, and 6 g, respectively.

The difference from placebo was significant for all VGB groups; however, the 6-g dose was not significantly different from the 3-g dose of VGB.

Adverse events

Treatment-related adverse events were reported by 77.8% of patients in the placebo group and by 82.6, 88.6, and 90.9% of patients taking VGB daily doses of 1, 3, and 6 g, respectively. Fatigue, drowsiness, and dizziness were the most common treatment-related adverse events. The incidence of severe adverse events increased with increasing dose of VGB, ranging from 2.2% for the placebo group to 8.7, 11.4, and 15.9% for patients taking 1, 3, and 6 g, respectively.

Safety and adverse effects

The incidence of severe adverse events increased with increasing dose of VGB.

Does the study answer the question?

Yes. VGB was significantly more effective than placebo as add-on therapy in reducing seizure frequency. VGB at 3 and 6 g/day produced the best efficacy; however, adverse events may limit the use of the 6-g/day dose in some patients.

Effect due to factor in study?

No. The study did not perform any power calculations to help determine sample size.

Consistency of results with other studies?

Directly applicable to guideline population?

The population is relevant because only patients with partial seizures were recruited.

Internal Validity

Dodrill CB;Arnett JL;Deaton R;Lenz GT;Sommerville KW;

Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood

Ref ID 4695

2000

Study Type Randomised Controlled Trial **Funding** Sponsored by Abbott Laboratories.

Number of participant n=277 in this analysis (n=349 in the original RCT).

Inclusion/Exclusion Criteria Inclusion criteria: adults with uncontrolled partial seizures who at study entry were on Phenytoin (PHT) or carbamazepine (CBZ) alone. At least four complex partial seizures had to have occurred alone or in combination with other seizure types while receiving either CBZ or PHT monotherapy in the baseline period.

Patient Characteristics	Variable	Baseline CBZ group		Baseline PHT group	
		PHT added (n=71)	TGB added (n=82)	CBZ added (n=66)	TGB added (n=58)
	Years of age Mean	33.34	37.07	40.42	39.41
	S.D.	13.11	11.13	12.19	13.48
	Age at seizure onset Mean	12.73	12.23	20.45	16.38
	S.D.	10.78	10.40	15.84	12.93
	Gender F	47	45	29	31
	Baseline complex partial seizure frequency (seizures 28 days)				
	N	70	81	66	57
	Median	7	6	6	7
	Baseline total partial seizure frequency (seizures 28 days)				
	N	70	81	66	58
	Median	10	7	8	9
	Baseline generalized tonic-clonic seizures (seizures 28 days)				
	N	23	24	20	22
	Median	2	2	2	1

Recruitment Not reported.

Setting Not reported.

Interventions/ Test/ Factor being investigated In one part of the study tiagabine (TGB) was compared with Phenytoin (PHT) in patients who were currently receiving carbamazepine (CBZ) at baseline. In the second part of the study TGB was compared to CBZ in patients who were currently receiving PHT.

Comparisons In part 1 of the study TGB is compared with PHT as add-on therapy to CBZ. In part 2 of the study CBZ is compared with TGB as add-on therapy to PHT.

Length of Study/ Follow-up 24 weeks: 8-week baseline period and 16-week double blind treatment period.

Outcome measures studied Primary outcomes in original trial not known. This investigation reports on the neuropsychological portion of the study. All the patients were administered a battery of tests midway through the baseline period and again after 12 weeks of treatment.

Results The study presents 4 large tables of results. 2 report scores for tests of abilities and scores for tests of adjustment and mood, for add-on therapies PHT and TGB in patients currently receiving CBZ. The other two tables report the same scores for add-on therapies CBZ and TGB in patients currently receiving PHT.

PHT vs TGB as add-on therapy in patients receiving CBZ

A statistical test comparing the average difference scores of the two add-on treatment groups was performed with each of the 37 variables related to tests of ability. No statistically significant differences between the add-on treatment groups were found. The same was true for the tests of adjustment and mood.

CBZ vs TGB as add-on therapy in patients receiving PHT

Two statistically significant differences were found in the measures of abilities with

improvements with TGB versus worsening with CBZ on tests of verbal fluency and perceptual: motor speed. For measures of adjustment and mood, treatment with TGB resulted in poorer scores on measures of overall mood (Mood Rating Scale, total) and financial concern (WPSI Financial Status Scale) compared to treatment with CBZ.

Safety and adverse effects

None reported.

Does the study answer the question?

No. The study concludes that overall, add-on tiagabine showed few or no differences in comparison with Add-on carbamazepine and add-on Phenytoin. However, this analysis was based on only 79% of the original RCT sample. And it is not clear from which groups the data is missing. Also, we must presume that these variables were secondary outcomes. The original study would have been powered to detect differences in different efficacy variables). Therefore this analysis can only be exploratory.

Effect due to factor in study?

No. It can only be presumed that the variables described in this study are secondary outcomes. The original study would have been powered to detect differences in different efficacy variables). Therefore this analysis can only be exploratory.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients in this study were included because they suffered from partial seizures.

Internal Validity

Dodrill CB;Arnett JL;Sommerville KW;Shu V;

Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy

Ref ID 4764

1997

Study Type

Randomised Controlled Trial

Funding

Supported by Abbot Laboratories.

Number of participant

In the main RCT 297 were randomised to placebo (n=91), tiagabine (TCB) 16mg/d (n=61), TCB 32mg/d (n=88) and TCB 56mg/d (n=57). Those included in this study were those who had had neuropsychological testing: placebo (n=57), TCB 16mg/d (n=34), TCB 32mg/d (n=88) and TCB 56mg/d (n=26).

Inclusion/Exclusion Criteria

In the main RCT the inclusion criteria were: at least six complex partial seizures during the prior 8 weeks.

Patient Characteristics

Mean (SD) age 35.62 (11.44)
Mean years of education 12.02 (2.92)
There were more men in the placebo group and 56mg TCB group (p<0.05)

Recruitment

Unknown.

Setting

21 centres in the United States.

Interventions/ Test/ Factor being investigated

This study compares placebo with 3 doses of tiagabine (16mg/d, 32mg/d and 56mg/d) as adjunctive treatment for complex partial seizures.

Comparisons

Comparisons are between placebo and 3 doses of TCB as adjunctive therapy to currently used AEDs.

Length of Study/ Follow-up

24 weeks: baseline period of 8 weeks and 4 week titration phase, followed by 12 week fixed dose phase.

Outcome measures studied

Not clearly stated. This study compared changes from baseline testing with the testing at the end of the drug treatment period o f the combined higher dose (32 and 56mg) tiagabine groups compared with placebo group for all psychological tests (n=11).

Results	From 37 statistical comparisons, only 1 was statistically significant at the 0.05 level of confidence, and none was significant at the 0.01 level. The one statistically significant finding was on form F of the Benton Visual Retention Test where the placebo group improved somewhat (average change +0.78 items correct) and where the 32- and 56-mg groups were slightly worse (average change -0.08 items correct).
Safety and adverse effects	None reported.
Does the study answer the question?	No. Results showed no clinically important changes with the addition of tiagabine on the test battery. However, the sample included in this study was non random.
Effect due to factor in study?	No. All results could have occurred by chance. No statistical power calculation was performed. And no primary outcome measure specified.
Consistency of results with other studies?	
Directly applicable to guideline population?	The study included only patients with complex partial seizures.
Internal Validity	
Dodrill CB;Arnett JL;Sommerville KW;Sussman NM;	
Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy	
Ref ID	4765 1995
Study Type	Randomised Controlled Trial Funding Marion Merrell Power.
Number of participant	CGB 1g/day n=45; VGB 3g/day n=43; VGB 6g/day n=41; placebo n=45.
Inclusion/Exclusion Criteria	Inclusion criteria: Focal epilepsy whose complex partial seizures or partial seizures secondarily generalised were difficult to control; Each patient was receiving one or two marketed AEDs and no other experimental agents; Exclusion criteria: history of progressive neurologic disorder; frequent episodes of status epilepticus; WAIS-R verbal IQ or performance IQ<65; Ongoing or recent psychiatric disorder; Any other condition that may have affected study results.
Patient Characteristics	Placebo; VGB 1g; VGB 3g; VGB 6g: Age mean (sd, range): 33.88 (9.77, 20-60)vv 34.89 (8.38, 18-54) vs 34.26 (9.18, 18-53) vs 33.72 (9.66, 19-63). Females: 26 vs 19 vs 17 vs 15.
Recruitment	From 14 major medical centres.
Setting	USA.
Interventions/ Test/ Factor being investigated	Vigabatrin versus placebo.
Comparisons	Between treatment and placebo.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Cognitive and quality of life effects.

Results Significant reduction for vigabatrin group x time interaction in dominant hand tapping frequency (motor speed and flexibility) (p=0.01) and for design learning task (memory) p=0.04). No significant differences in any other test including measures of mood or behaviour.

The following cognitive tests were tested in the study; Lafayette Pegboard, Stroop Test, Benton Visual Retention, Controlled Oral Word, Symbol Digit Modalities, Auditory Verbal Learning, Wonderlic Personnel Test, Digit Cancellation. Participants in vigabatrin group demonstrated significantly higher mean scores of Stroop Test (interference sec) (worse performance) and significantly lower scores in Digit Cancellation scale (worse performance) compared to placebo.

The following health related quality of life tests were tested in the study; Profile of Mood States (POMS) (including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment, total mood disturbance subscales), Washington Psychosocial Seizure Inventory (WPSI) (including family background, emotional adjustment, interpersonal adjustment, vocational adjustment, financial status, adjustment to seizures, medicine and med. Management, overall functioning, lie scale and rare items subscales), Mood rating scale and none was significantly significant associated with the use of vigabatrin or placebo.

Safety and adverse effects Not reported.

Does the study answer the question? Yes for cognitive outcomes and quality of life outcomes.

Effect due to factor in study? No details of randomisation, allocation concealment or blinding so uncertainty if overall effect is due to the study intervention.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Dodrill CB;Arnett JL;Sommerville KW;Sussman NM;

Evaluation of the effects of vigabatrin on cognitive abilities and quality of life in epilepsy

Ref ID 4766

1993

Study Type Randomised Controlled Trial **Funding** See data entry for study by French et al, Reference Manager ID 4752.

Number of participant n=182 in original trial (see data entry for study by French et al, Reference Manager ID 4752) QoL data available for vigabatrin n=83/92 (90%) and n=85/90(94%) in placebo group.

Inclusion/Exclusion Criteria See data entry for study by French et al, Reference Manager ID 4752.

Patient Characteristics See data entry for study by French et al, Reference Manager ID 4752.

Recruitment See data entry for study by French et al, Reference Manager ID 4752.

Setting

Interventions/ Test/ Factor being investigated See data entry for study by French et al, Reference Manager ID 4752.

Comparisons	See data entry for study by French et al, Reference Manager ID 4752.
Length of Study/ Follow-up	See data entry for study by French et al, Reference Manager ID 4752.
Outcome measures studied	Cognitive abilities and quality of life in epilepsy. Tests of ability: Lafayette Grooved Pegboard, Stroop test, Benton Visual Retention Test, Controlled Oral Word Association Test, Symbol Digit Modalities Test, Rey Auditory Verbal Learning Test, Wonderlic
Results	<p>Tests of cognitive abilities</p> <p>There were no differential changes across the placebo and vigabatrin groups from the end of the baseline to the end of the drug treatment period. This was demonstrated by the absence of any statistically significant differences on the ANOVA group x time interaction effects.</p> <p>Quality of life The placebo and vigabatrin groups are compared on quality of life measures of adjustment and mood. Not a single statistically significant difference emerged at the 0.05 level.</p>
Safety and adverse effects	See data entry for study by French et al, Reference Manager ID 4752.
Does the study answer the question?	Vigabatrin appears to have little impact upon tests of either cognitive abilities or quality of life.
Effect due to factor in study?	See data entry for study by French et al, Reference Manager ID 4752.
Consistency of results with other studies?	
Directly applicable to guideline population?	See data entry for study by French et al, Reference Manager ID 4752.

Internal Validity

Elger C;Bialer M;Cramer JA;Maia J;Almeida L;Soares-da-Silva P;

Eslicarbazepine acetate: a double-blind, add-on, placebo-controlled exploratory trial in adult patients with partial-onset seizures

Ref ID 4862

2007

Study Type Randomised Controlled Trial **Funding** BIAL (Portela & C SA).

Number of participant ESL once a day 50/143, ESL twice a day 46/143 and Placebo 47/143,

**Inclusion/Exclusion
Criteria** Inclusion criteria; adults 18-65 yrs with at least four partial onset seizures per month being treated with one or two of the following AEDs (phenytoin, valproic acid, primidone, phenobarbital, lamotrigine, gabapentin, topiramate, clonazepam in stable doses during at least 2 months prior to randomization. Exclusion criteria: vagus nerve stimulation, primarily generalized seizures, known progressive neurological disturbance, history of status epilepticus within the past 3 months, seizure of nonepileptic origin, restricted legal competency and incapability to follow trial instructions, major psychiatric disorders, concurrent drug therapy with monoamine oxidase inhibitors or calcium channel blockers, use of OXC or CBZ during the last 6 months before the randomization visit, known hypersensitivity to OXC or CBZ, abuse of alcohol, drugs or medications, history of relevant medical disorder, second or third degree atrioventricular blockade not corrected with a pacemaker, abnormalities of sodium, hepatic function and white blood cell mounts, pregnancy, nursing or adequate contraception, participation in other clinical trials within the last 2 months.

Patient Characteristics Adults aged 18-65 yrs, all White with at least four partial onset seizures per month being treated with one or two of the following AEDs (phenytoin, valproic acid, primidone, phenobarbital, lamotrigine, gabapentin, topiramate, clonazepam in stable

	doses during at least 2 months prior to randomization
Recruitment	Not reported.
Setting	19 Centers in five European countries.
Interventions/ Test/ Factor being investigated	Treatment with Eslicarbazepine acetate (ESL) once daily and twice daily.
Comparisons	Comparison were made in the seizure frequency between the two treatment groups (ESL once and twice daily) and the placebo group. The two treatment groups were also compared to each other with regards to reduction in seizure frequency.
Length of Study/ Follow-up	The 12 week treatment phase followed by a 1 week tapering off phase.
Outcome measures studied	Primary outcome: % of patients with 50% or greater reduction in seizure frequency. Secondary outcomes were reduction in total seizure frequency at each 4 week period and the proportion of seizure free patients. Incidence of adverse effects.
Results	<p>During the 12 week treatment phase, the number of seizure free patients significantly increased in both ESL treatment groups compared to placebo. The proportion of seizure free participants were 10% for the group taking ESL once a day (400mg) and 4% for those taking twice a day(200mg) during the first 4 weeks. The following 4 weeks (weeks 5-8), there were 18% seizure free patients in the ESCL once a day group (800mg) and 13% in the ESCL twice a day group (400mg). The last four weeks, the proportion of seizure free patients was 24% for both ESL groups (once and twice daily, 1200mg and 600 mg). The proportion of seizure free patients in placebo was 11% for the first 8 weeks and 9% for the four following.</p> <p>A significantly higher proportion of patients were found with 50% or more reduction in seizure frequency between the ESL group once a day and the placebo (54% versus 28%, p=0.008). No significant difference was found on the 50% or more reduction in seizure frequency between the ESL group twice a day and the placebo (41% versus 28%, p=0.12).</p>
Safety and adverse effects	None adverse event was prevalent over 10% in the sample. The number of patients reporting adverse events were similar in the three treatment groups.
Does the study answer the question?	<p>A higher proportion of seizure free patients found in the ELS treatment group taking once daily compared to placebo.</p> <p>A significantly higher proportion of patients received ESL once daily had 50% or more reduction in seizure frequency compared to placebo.</p> <p>No significant differences in reduction of seizure frequency were found between the ESL group twice daily and the placebo.</p>
Effect due to factor in study?	Randomization procedure, allocation concealment and blindness were poorly reported. Preconsideration of statistical power of the study.Potential limitations on the study design are likely to lower confidence in the estimate of effect.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Elger C;Halasz P;Maia J;Almeida L;Soares-da-Silva P;Investigators Study Group.;

Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study

Ref ID 4863

2009

Study Type Randomised Controlled Trial **Funding** BIAL

Number of participant	sample size was 402/468 (82%); placebo n=102; ESL 400mg n=100; ESL 800mg n=98; ESL 1200mg n=102
Inclusion/Exclusion Criteria	inclusion criteria: adults ≥ 18 yrs with simple or complex partial seizures with or without secondary generalization for at least 12 months before screening, receiving one or two AEDs (in a stable dose) for at least 2 months before screening, had at least four partial onset seizures in the two 4 week periods of the baseline phase with no seizure free interval ≥ 21 consecutive days, had a negative pregnancy test, not breastfeeding, agreed to use acceptable contraception. Exclusion criteria: patients with only simple partial seizures without motor symptoms, with primarily generalized epilepsy, with a known rapid progressive neurologic disorder, with status epilepticus or cluster seizures within 3 months before screening, with seizures of psychogenic origin within the last 2 yrs, with a history of schizophrenia or suicide attempts, with an uncontrolled, relevant medical disorder, with a second or third degree atrioventricular blockade not corrected with a pacemaker, with relevant clinical laboratory abnormalities (liver enzymes at least two times the upper limit of normal or sodium < 130 mmol/L or white blood cell count $< 3,000$ cells/mm ³ , or creatinine clearance < 50 ml/min), with poor compliance, with a history of drug or alcohol abuse within the previous 2 yrs, patients with a known hypersensitivity to carbamazepine and oxcarbazepine, patients taking or had taken felbamate within 1 month before screening.
Patient Characteristics	Patient population was consisted of adults ≥ 18 yrs (mean age 39 yrs, range 18-76 yrs) with simple or complex seizures with or without secondary generalization for at least 12 months before screening receiving adjunctive therapy (AEDs). They were 100% Caucasian, 51% female.
Recruitment	Not clearly reported.
Setting	40 centers in 11 countries.
Interventions/ Test/ Factor being investigated	Eslicarbazepine acetate in three doses; 400mg, 800mg and 1200mg.
Comparisons	comparison were made between the treatments (ESL 400mg, 800mg and 1200mg) and the placebo group.
Length of Study/ Follow-up	4 weeks tapering off period.
Outcome measures studied	Primary outcome; seizure frequency/ 4 weeks. Secondary outcomes: % patients with $> 50\%$ reduction in seizure frequency, relative reduction in seizure frequency, number of days with seizure, seizure free patients, % patients with $\geq 25\%$ seizure exacerbation
Results	<p>The proportion of patients with at least a 50% reduction in seizure frequency was significantly higher in the ESL 1200mg group (43%, $p=0.0009$) and the ESL 800mg (34%, $p=0.0359$) than in the placebo (20%).</p> <p>The median relative reduction in seizure frequency during the 12 maintenance period was higher in the ESL 800mg (36%) and 1200mg (45%) than in the ESL 400mg (26%) and placebo (16%).</p> <p>A significantly higher proportion of patients in the ESL 1200 mg group (8%, $P<0.05$) achieved seizure freedom compared to patients in the 800mg group (4%, n.s), in the 400mg group (2%, n.s.) and placebo (2%).</p> <p>22% of patients in the placebo group showed exacerbation in seizure frequency than in any of the other ESL groups ($\leq 12\%$ in all groups).</p>
Safety and adverse effects	The overall incidence of adverse effects increased with increasing dose of ESL. Prevalence $> 10\%$ of AEs; 14.3% and 13.7% showed dizziness in ESL 800mg and ESL 1200mg respectively, 10.8% of patients in the ESL 1200mg group had headache and diplopia.
Does the study answer the question?	Yes. Treatment with ESL 800mg and ESL 1200mg as adjunctive therapies demonstrated higher relative and $> 50\%$ reduction in seizure frequency compared to ESL 400mg and placebo (for adults with refractory partial onset seizures). Safety analysis was performed.
Effect due to factor in study?	Overall the study was well conducted. The power of the study was adequate to demonstrate an effect of the study intervention. The main pitfalls of the study were the absence of report on allocation concealment. The study design and the methodology adopted in relation to data collection and outcome measures used was

appropriate to test the efficacy of ELS as an intervention.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Fakhoury TA;Hammer AE;Vuong A;Messenheimer JA;

Efficacy and tolerability of conversion to monotherapy with lamotrigine compared with valproate and carbamazepine in patients with epilepsy

Ref ID 671

2004 Aug

Study Type Randomised Controlled Trial **Funding** GlaxosmithKline.

Number of participant LTG n=98 vs CBZ n=46;
LTG n=105 vs VPA 53.

Inclusion/Exclusion Criteria
Inclusion criteria:
Aged 16 or over;
Diagnosed with epilepsy and experiencing any seizure type classified by International Classification of Seizures;
Treated with one AED for a minimum of 4 weeks prior to screening and had experienced at least 2 seizures during the 8 weeks before screening;
A clinical dtermined appropriate candidates for add-on therapy wiht lamotrigine, carbamazepine or valproate; and possible candidates for conversion to monothearyp with lamotrigine, carbamazepine, or valproate;
Females only eligible if had negative uringe or serium pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were incapable of bearing children.
Exclusion criteria:
Treated with more than one AED at screenig or if they were being treated with phenobarbital or primidone that could not be withdrawn over an 8-week period.

Patient Characteristics LTG vs CBZ; LTG vs VPA:
mean age (s.d): 41 (14.8) vs 40.3 (12.9); 38.3 (13.3) vs 39 (12.7);
number of females: 58 (59%) vs 25 (54%); 59 (56%) vs 33 (62%);
mean no. Of seizure during 2 months prior to screening: 14.2 (37.6) vs 17.7 (50.1);
6.2 (11) vs 8.3 (14.3);
Seizure type during 2 months prior to screening n(%):
- simple partial: 25 (26%) vs 15 (33%) ; 35 (33%) vs 15 (28%);
- complex partial: 56 (57%) vs 32 (70%); 65 (62%) vs 38 (72%);
- partial with secondary generalisation : 39 (40%)vs 14 (30%); 30 (29%) vs 19 (36%)
- other:24 (24%) vs 10 (22%); 20 (19%) vs 11 (221%).

Recruitment Not reported.

Setting US. Part of a larger study in 17 countries.

Interventions/ Test/ Factor being investigated Lamotrigine versus carbamazepine. Lamotrigine versus sodium valproate.

Comparisons Between treatments. 2 study arms.

Length of Study/ Follow-up Not reported.

Outcome measures studied % of patients receiving sustainable monotherapy with study medication; % seizure free or had >50% reduction in seizure frequency during monotherapy phase (weeks 21, 28); time to treatment failure; incidence of adverse events.

Results

LTG vs VPA:

Withdrawal due to adverse effects: 14/105 (13.3%) vs 11/53 (20.8%)
 Incidence of dizziness: 16/105 (15.2%) vs 6/53 (11.3%)
 Incidence of somnolence: 11/105 (10.5%) vs 7/53 (13.2%)
 Incidence of tremor: 5/105 (4.8%) vs 11/53 (20.8%)
 Incidence of nausea: 6/105 (5.7%) vs 7/53 (13.2%)
 Incidence of alopecia: 1/105 (1%) vs 6/53 (11.3%)
 Incidence of blurred vision: 11/105 (10.5%) vs 1/53 (1.9%)
 Incidence of headache: 3/43 (7%) vs 6/44 (13.6%)

We have a blinded study for LTG vs CBZ so data not used from this study for that comparison as this is an unblinded study.

Safety and adverse effects

See above results.

Does the study answer the question?

Yes.

Effect due to factor in study?

No power calculation and poor methodology so uncertainty in the overall effect due to study intervention.

Consistency of results with other studies?**Directly applicable to guideline population?**

Some indirect there was 20% who were 'other' seizure types in the LTG vs VPA group and over 20% in the LTG vs CBZ group.

Internal Validity

Grunewald RA;Thompson PJ;Corcoran R;Corden Z;Jackson GD;Duncan JS;

Effects of vigabatrin on partial seizures and cognitive function

Ref ID 4686

1994

Study Type

Randomised Controlled Trial

Funding

Marion Merrell Dow.

Number of participant

n=45 (n=22 in Vigabatrin n=23 in placebo group)

Inclusion/Exclusion Criteria

Inclusion criteria: patients with partial seizures refractory to optimal antiepileptic drug treatment, ability to keep an accurate seizure diary.

Patient Characteristics

Baseline characteristics

	Vigabatrin n=22	Placebo n=23
Age, median (range)	29(17-59)	27(16-55)
Age at onset median (range)	11(2-34)	10(1-22)

Twenty one women and 24 men, age range 15 to 61 years. N=35 had simple partial seizures, n=44 complex partial seizures, and 14 secondary generalised seizures. On study entry 26 patients were receiving monotherapy;. Eighteen were taking two and one three antiepileptic drugs.

Recruitment

Not reported.

Setting

Outpatient setting. UK.

Interventions/ Test/ Factor being investigated

Vigabatrin up to 1.5g twice daily as adjunctive therapy.

Comparisons

Vigabatrin is compared to placebo as adjunctive therapy to currently used AEDs.

**Length of Study/
Follow-up**

28 weeks: 8 weeks baseline and 20 weeks treatment.

**Outcome measures
studied**

Primary and secondary outcomes not specified. Seizure frequency and psychological tests.

Results

Seizure control

Seizure frequency at baseline and during double blind treatment

	Baseline			Weeks 12 to 20		
	SPS	CPS	SGS	SPS	CPS	SGS
Placebo group:						
Median	2	8	0	0	10	0
Back transformed mean	4.37	8.55	0.58	2.55	9.72	0.48
Range	0-55	0-124	0-13	0-249	0-111	0-3
Vigabatrin group						
Median	4	15	0	4	5	0
Back transformed mean	5.46	9.72	0.51	4.62	3.57**	0.35
Range	0-91	0-38	0-17	0-196	0-47	0-10

* p=0.009, ** p=0.001. Data include median numbers of each type of seizure recorded during eight week periods (median), antilogarithm of mean of logarithmically transformed seizure data (back transformed mean) and range. SPS=simple partial seizures, CPS= complex partial seizures; SGS=secondary generalised.

Adverse events

Two patients allocated Vigabatrin developed severe depressive symptoms and withdrew within four weeks of starting treatment. In both, symptoms improved within four weeks of Vigabatrin.

	Placebo n=23	Vigabatrin n=22
Weight gain	2	4
Headache	4	1
Constipation	1	5
Fatigue	3	4
Mild depression	2	4
Dizziness	1	3
double vision	2	3
Tremor	3	2
Impaired memory	0	2

The only difference that approached statistical significance was constipation (p=0.07)

Neuropsychological assessment.

Vigabatrin treatment was associated with a significant reduction in dominant hand tapping frequency (mean baseline tapping rate 85.6 in placebo group, 77.0 in treatment group, rising to 92 at the end of the double blind period in the placebo group but falling to 72.1 in the Vigabatrin treated group; group x time interaction p=0.01. The overall score of the design learning task also showed a Vigabatrin associated deterioration (mean baseline score 29.3 in placebo group, 31.4 in treatment group, rising to 33.8 in placebo group but falling to 30.3 in the Vigabatrin treated group; group x time interaction p=0.04. Other tests did not show a significant group x time interaction; in particular, Vigabatrin treatment was not associated with any significant change in measures of mood or behaviour in those who tolerated the drug.

**Safety and adverse
effects**

Two patient discontinued Vigabatrin because of depression.

Does the study answer the question? The study concludes that there was a >50% improvement in the control of complex partial seizures in 45% of patients during the double blind period of 20 weeks of treatment, and a statistically significant improvement in overall complex partial seizure frequency compared with the placebo control group. However, the study is small, no primary efficacy outcome has been specified, and is not powered to detect differences between the two groups. The results should only be considered exploratory.

Effect due to factor in study? No. The study is small, no primary efficacy outcome has been specified, and the study did not perform a power calculation. The results should only be considered exploratory.

Consistency of results with other studies?

Directly applicable to guideline population? All patients had partial seizures (simple partial, complex partial seizures, and secondary generalised seizures.)

Internal Validity

Jawad S;Richens A;Goodwin G;Yuen WC;

Controlled trial of lamotrigine (Lamictal) for refractory partial seizures

Ref ID 4757

1989

Study Type Randomised Controlled Trial **Funding** not mentioned.

Number of participant 24 participants (cross over).

Inclusion/Exclusion Criteria Inclusion: patients with drug-resistant seizures, aged 16–60 years, epilepsy uncomplicated by psychogenic attacks, partial seizures with or without secondary generalisation and seizures recognisable by a patient or relative, at least 4 partial seizures per month in the previous 3 months, no abnormal laboratory values of clinical significance, no more than 2 standard AEDs, stable AEDs for the previous 3 months and unlikely to change during study, compliant with treatment and able to record seizures and AEs, women not at risk of pregnancy
Exclusion:
- suffering from severe organic or psychiatric illness; progressive neurological disease;
and with tests revealing possible abnormality of bone marrow, liver or renal function other than those attributable to concomitant AEDs
- taking any chronic drugs other than AEDs or oral contraceptive; alcohol abuse;
- pregnancy, lactation or current exposure to risk of pregnancy
- mental retardation
- evidence of previous serious non-compliance

Patient Characteristics Type of epilepsy: Refractory
Type of seizures: Partial onset
Mean age/age range:
Total (n = 21): 37.3 years (SD 13.2);
LTG/placebo (n = 10): 38.9 years (SD 12.81);
Placebo/LTG (n = 11):35.9 years (SD 13.94);
Total (n = 21): 19–65 years;

LTG/placebo (n = 10): 23–64 years;
Placebo/LTG (n = 11): 19–65 years

Gender
Total (n = 21): men = 12, women =9;
LTG/placebo (n = 10): men = 5, women = 5;
Placebo/LTG (n = 11): men = 7, women = 8

Age at onset of seizures
Mean age at onset: total (n = 21): 9.7 years (SD 7.6);
LTG/placebo (n = 10): 12.6 years (SD 9.6);
Placebo/LTG (n = 11): 7.2 years (SD 4.3)

Mean duration of seizures:

Total (n = 21): 27.6 years (SD 15.2);
LTG/placebo (n = 10): 26.3 years (SD 16.0);
Placebo/LTG (n = 11):28.7 years (SD 15.2)

Recruitment Patients attending the epilepsy Unit of the University of Wales College of Medicine.

Setting University of Wales College of Medicine.

**Interventions/ Test/
Factor being
investigated** Lamotrigine

Comparisons Treatment and placebo.

**Length of Study/
Follow-up** 44 weeks in total.
8 weeks baseline phase.
12 weeks treatment period 1.
6 weeks washout period.
12 weeks treatment period 2.
6 weeks washout 2.

**Outcome measures
studied** >50% reduction in seizure frequency, withdrawal due to adverse events,
improvement in seizure days.

Results 1 out of the 3 patients who withdraw was due to experience of adverse events.
He had ataxia, tiredness, dyspnea, and diplopia. The patient died 18 days later of
carcinoma involving the liver - not believed to be attributable to LTG.
12/21 patients with partial seizures only had > 50% reduction in seizure frequency
with LTG.

Withdrawal due to adverse events: LTG 1/21 vs PCB 0/21.

**Safety and adverse
effects** Experience of adverse events is reported as rates of occurrence and not as
proportion of patients with that experience. The five most frequently reported adverse
events were tiredness, diplopia, drowsiness, ataxia and headache.

**Does the study
answer the question?** Uncertain. The methodology adopted was not a randomized clinical trial in order to
test the efficacy of lamotrigine over the placebo.

**Effect due to factor in
study?** The study design was poor, as no randomization procedure and allocation
concealment are reported. Uncertain about the overall effect was due to the
medication (lamotrigine) used.

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?** Indirect.

Internal Validity

Kalviainen R;Aikia M;Saukkonen AM;Mervaala E;Riekkinen PJ;

Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized, controlled
study

Ref ID 4702

1995

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=100. 50 in each group.

Inclusion/Exclusion Criteria	Inclusion criteria: at least 2 unprovoked epileptic seizures during the previous 2 years or one seizure and distinct EEG changes indicative of epilepsy of normal intelligence. Normal intelligence (IQ>85 in the WAIS) Exclusion criteria: Alcohol-related seizures, current alcohol or other drug abuse; Progressive neurological disorders; Mental retardation; Severe psychiatric problems; Other severe medical disorders.
Patient Characteristics	Mean age: 35 years (33 years in vigabatrin group and 37 years in carbamazepine group).
Recruitment	Not reported.
Setting	University hospital with an epilepsy centre.
Interventions/ Test/ Factor being investigated	Vigabatrin monotherapy versus carbamazepine monotherapy.
Comparisons	Treatment versus treatment.
Length of Study/ Follow-up	12 months.
Outcome measures studied	Efficacy: proportion of seizure freedom; proportion of responders; Safety: adverse events; visual evoked potential recordings and neuropsychological evaluation.
Results	Vigabatrin versus carbamazepine Proportion of seizure-free: 16/50 (32%) vs 26/50 (52%); Proportion with at least 50% reduction in seizure frequency: 14/50 (28%) vs 4/50 (8%); Proportion of participants having treatment withdrawn due to unacceptable seizure control: 13/50 (26%) vs 3/50 (6%); The proportion of participants having treatment withdrawn due to intolerable side effects: 0/50 (0%) vs 12/50 (24%); Cognitive Disturbance: 2/43 vs 3/45; Incidence of drowsiness: 19/43 vs 28/45; Incidence of dizziness: 3/43 vs 9/45; Incidence of visual disturbances: 7/43 vs 0/45.
Safety and adverse effects	See results.
Does the study answer the question?	Yes.
Effect due to factor in study?	
Consistency of results with other studies?	
Directly applicable to guideline population?	
Internal Validity	

Loiseau P; Hardenberg JP; Pestre M; Guyot M; Schechter PJ; Tell GP;

Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy

Ref ID 4710

1986

Study Type Randomised Controlled Trial

Funding not mentioned.

Number of participant	N=19 (crossover study)
Inclusion/Exclusion Criteria	Inclusion criteria: complex partial seizures or primary generalized epilepsy, a total frequency of at least one/week, despite treatment with no more than 3 standard AEDs, age 10-60 yrs, constant doses of AED during 5 weeks prior to study entry and informed consent. Excluded criteria: history or evidence of a progressive neurological disorder, serious medical disorders other than epilepsy (liver disease, renal dysfunction, cardiac disease, abnormal haematology results or allergic disease), pregnancy or risk of pregnancy.
Patient Characteristics	12/19 patients were female, 7/19 males aged from 10-58 years. The duration of epileptic disorders ranged from 2- 40 years (mean +/- sd, 13.4 +/-8.34 years). 17/19 had complex partial seizures, 8/19 had secondary generalization, 2/19 had generalized tonic or tonic clonic seizures.
Recruitment	Not addressed.
Setting	Not addressed.
Interventions/ Test/ Factor being investigated	Vigabatrin as an add on to a standard therapy in therapy resistant epileptic patients.
Comparisons	Comparison is made on the seizure frequencies between Vigabatrin and placebo groups.
Length of Study/ Follow-up	An initial 5 week observation phase with constant doses of AEDs, following 2 periods of 10 weeks each in which Vigabatrin/ placebo were administered and a final 5 week single blind period in which placebo was administered as add on therapy.
Outcome measures studied	>50% reduction in seizure frequency, adverse events, patient preference for drug/placebo.
Results	11/19 patients experienced a >50% reduction in seizure frequency (results are presented for the whole group of 19 patients). Withdrawal due to adverse evens among partial epilepsy patients: VIG: 1/19 Placebo:1/19
Safety and adverse effects	9/19 patients reported adverse events during treatment with Vigabatrin, 10/19 in placebo period. Three patients withdraw due to adverse events.
Does the study answer the question?	Yes, within the limitations of the study to clearly describe its randomization procedure and its blindness. The main conclusion was that using 3gr/day Vigabatrin as add on therapy was shown to reduce the weekly seizure frequency in 11 out of 19 patients by >50%.
Effect due to factor in study?	It is not certain that the effect observed in the study was due to the intervention as the report of the methodology adopted was not clear and there was no prior consideration of sample size based on the statistical power of the study.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

McKee PJ;Blacklaw J;Friel E;Thompson GG;Gillham RA;Brodie MJ;

Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients?

Ref ID 4693

1993

Study Type Randomised Controlled Trial

Funding Marrion merrell Dow.

Number of participant	n=24 crossover study.
Inclusion/Exclusion Criteria	Not specified.
Patient Characteristics	<p>Aged 17-53 years; 16 women; 8 men; Refractory epilepsy; 14 had complex partial seizures secondary generalised; 8 had complex partial seizures alone; 2 had generalised tonic-clonic seizures. Average of at least 2 generalised or one partial seizure a week during 3 months prior to recruitment. 11 were on monotherapy (9 carbamazepine, 1 phenytoin, 1 valproate) and 13 were on two AEDs (10 carbamazepine, 6 primidone, 4 valproate, 4 phenytoin, 2 Phenobarbital.</p>
Recruitment	Patients at the Western Infirmary Glasgow.
Setting	Hospital, Glasgow.
Interventions/ Test/ Factor being investigated	4 weeks run-in; 6 weeks 1g Vigabatrin twice daily or matched placebo; 6 weeks 1.5g Vigabatrin twice daily or matched placebo; 4 weeks washout then crossed over to same intervention.
Comparisons	Adjunctive Vigabatrin versus placebo.
Length of Study/ Follow-up	30 weeks.
Outcome measures studied	>50% reduction in seizure frequency VGB compared to placebo; withdrawal due to adverse events; incidence of adverse events.
Results	<p>>50% reduction in seizure frequency:</p> <p>All seizures (n=19) Phase 1: 9 Phase 2:6 overall: 8</p> <p>Partial seizures (n=17) phase 1: 7 phase 2: 6 overall: 8</p> <p>GTCs (n=12) phase 1: 3 phase 2: 3 overall: 3</p> <p>Does not give results for Vigabatrin and placebo separately. Phase 1 was VGB/placebo 1g twice daily for 6 weeks; phase 2 was VGB/placebo 1.5g twice daily for 6 weeks.</p> <p>Withdrawal due to adverse events: VGB 1/24 vs placebo 0/24.</p>
Safety and adverse effects	<p>Incidence of adverse events: VGB (2g, 3g) vs placebo (2g, 3g): tiredness: 7, 3 vs 0, 1; Dizziness: 3, 0 vs 1, 1.</p>
Does the study answer the question?	Author's conclusions: VGB is useful adjuvant therapy for treatment of partial seizures. There may be a ceiling to effective dosage. This demands individual dose titration for each patient.
Effect due to factor in study?	No . Very small crossover study with few details of randomisation, blinding or allocation concealment.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Meador KJ;Loring DW;Hulihan JF;Kamin M;Karim R;CAPSS-027 S;

Differential cognitive and behavioral effects of topiramate and valproate

Ref ID 602

2003

Study Type Randomised Controlled Trial **Funding** Ortho McNeil Pharmaceutical KJM

Number of participant n=76 randomised (n=34 in the topiramate group, n=29 in the valproate group and n=13 in the placebo group).

Inclusion/Exclusion Criteria
 Inclusion criteria: 16 to 55 years, IQ >70, three partial-onset seizures during a 28-day baseline phase, not pregnant, CT or MRI to confirm absence of a progressive cerebral lesion. AED other than CBZ had to be discontinued 28 days before the baseline visit.
 Exclusion criteria: nonepileptic seizures; treatable cause of seizures; progressive neurologic disorders; status epilepticus within past 3 months; history of major medical disease within past 2 years or malignancy within past 5 years. Patients previously treated with TPM were also excluded.

Patient Characteristics	TPM		VPA		Placebo	
	ITT	Completers,*	ITT	Completers,*	ITT	
Completers,*	n=34	n=27	n=27	n=29	n=25	n=13
Baseline characteristics						
Male, %	35	37	52	60	43	50
Age, y, mean (range)	41 (22–66)	41 (22–61)	37 (17–52)	37 (17–51)	40 (25–57)	41 (25–57)
Baseline monthly seizure rate, median (range)	6.6 (2–154)	7.7 (2–154)	8.9 (0–63)	8.9 (2–61)	7.9 (2–225)	8.1 (3–225)

Recruitment Not reported.

Setting 24 centres.

Interventions/ Test/ Factor being investigated Topiramate 400mg/d

Comparisons Topiramate 400mg/d compared to valproate 2,250mg/day and placebo as adjunctive therapy.

Length of Study/ Follow-up 24 weeks: 4 week baseline, 8 week titration phase and 12 week maintenance phase.

Outcome measures studied Recruitment difficulty led to termination of the study before enrolling the number of patients required to evaluate the primary seizure reduction efficacy variable. Neuropsychological and quality of life outcomes are presented.

Results Neuropsychological test results
 Changes from baseline to the end of the maintenance period were significant (ANCOVA) in 4 of 24 (17%) measures (SDMT, COWA, Stroop–word, and Stroop–color). Negative effects for topiramate vs placebo were observed for four variables; negative effects for valproate vs placebo were observed for one variable. Patients receiving topiramate performed worse than valproate treated patients on two

variables (SDMT and COWA) after 20 weeks of treatment.
SDMT=Symbol Digit Modalities Test, COWA=Controlled Oral Word Association Test.

Adverse events

Cognitive complaints

	TPM n=34	VPA n=29	Placebo n=13
Memory difficulty	6 (18)	5 (17)	0
Speech difficulty	4 (12)	2 (7)	1 (8)
Concentration/attention difficulty	3 (9)	3 (10)	1 (8)
Psychomotor slowing	3 (9)	1 (3)	0
Depression	6 (18)	4 (14)	1 (8)
Confusion	2 (6)	1 (3)	0
Language problems	2 (6)	2 (7)	2 (15)
Other cognitive problems	1 (3)	1 (3)	0

Values are n (%).

Safety and adverse effects

Unknown.

Does the study answer the question?

No. The study was terminated due to recruitment difficulties before enrolling the number of patients required to evaluate the primary seizure reduction efficacy variable. Only a subset of patients enrolled performed the neuropsychological tests.

Effect due to factor in study?

No. The study was terminated due to recruitment difficulties before enrolling the number of patients required to evaluate the primary seizure reduction efficacy variable. Only a subset of patients enrolled performed the neuropsychological tests.

Consistency of results with other studies?

Directly applicable to guideline population?

Patients had partial-onset seizures during the baseline phase.

Internal Validity

Schachter SC;

Tiagabine monotherapy in the treatment of partial epilepsy

Ref ID 4768

1995

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant n=11.
7 TGB and 4 Placebo.

Inclusion/Exclusion Criteria Diagnosis of epilepsy with at least six complex partial seizures in the 8 weeks before screening and were undergoing evaluation for epilepsy surgery.

Patient Characteristics Seizure types:
complex partial TGB 7; PCB 4;
simple partial TGB 5; PCB 2;
combined partial TGB 7; PCB 4;
secondarily generalised tonic-clonic TGB 4; PCB 4.

Recruitment At a single centre in the UK. Undergoing evaluation for epilepsy surgery.

Setting UK

Interventions/ Test/ Factor being investigated	Tiagabine versus placebo.
Comparisons	Treatment versus placebo.
Length of Study/ Follow-up	After 7 days there was 1 day washout a final evaluation was performed and previous AED therapy reinstated.
Outcome measures studied	Median 24 hour seizure rate change from baseline; withdrawal because seizure frequency exceeded escape criteria; adverse events.
Results	Withdrawal due to lack of efficacy: TGB: 2/7 PCB: 4/4 Incidence of adverse events: dizziness: 1/7 (14%) vs 1/4 (25%); abnormal thinking (difficulty in concentrating): 1/7 (14%) vs 0/4; insomnia 0/7 vs 1/4 (25%); paresthesia 2/7 (29%) vs 1/4 (25%); headache 1/7 (14%) vs 2/4 (50%); Amnesia 0/7 (14%) vs 0/4;
Safety and adverse effects	See results for adverse events.
Does the study answer the question?	This study gives withdrawal numbers and adverse events only and is a very small sample size.
Effect due to factor in study?	Not sure of effect as underpowered.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Schachter SC;Vazquez B;Fisher RS;Laxer KD;Montouris GD;Combs-Cantrell DT;Faight E;Willmore LJ;Morris GL;Ojemann L;Bennett D;Mesenbrink P;D'Souza J;Kramer L;

Oxcarbazepine: double-blind, randomized, placebo-control, monotherapy trial for partial seizures

Ref ID 4707

1999

Study Type	Randomised Controlled Trial	Funding	Sponsored by Ciba-Geigy Corporation (Novartis Pharmaceutical s corporation)
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Number of participant OXC n=51; Placebo n=51.

**Inclusion/Exclusion
Criteria**
Inclusion criteria:
Completed an evaluation for epilepsy surgery;
2-10 partial seizures within 48 hours of randomisation, including at least on e complex partial seizure and no more than two partial seizures evolving to secondarily generalised seizures (minimum between-seizure duration of 30 minutes);
Aged 11 to 65 years;
Weight over 45kg;
No AEDs within 48 hours of randomisation (except for lorazepam up to 8mg/day);
Normal routine clinical laboratory values;
Sub therapeutic plasma concentrations of AEDs prior to randomisation;
CT scan or MRI within the past 5 years that excluded a progressive cerebral lesion;
Normal electrocardiogram (EC);
Capability of satisfying protocol requirements;

Ability to provide informed consent;
 Women of childbearing potential enrolled only if they were not pregnant and were not lactating and if using a barrier method of contraception.
 Exclusion criteria: history of status epilepticus in 3 months preceding randomisation;
 Ingestion of benzodiazepines or barbiturates within 15 days of hospitalisation (other than lorazepam);
 Cardiac, hepatic, endocrine, gastrointestinal, renal, hematologic, oncologic, or progressive neurologic disorders;
 Seizures of metabolic, neoplastic or active infectious origin;
 Second or third degree atrioventricular block if not adequately treated with a cardiac pacemakers;
 Nonepileptic seizures within n2 years of randomisation;
 Major psychiatric disorder or medications that could affect trial participation;
 Suspected substance or alcohol abuse within 6 months of randomisation;
 Participation in another investigational drug trial within 30 days of randomisation;
 Use of calcium channel blockers or monoamine oxidase inhibitors;
 hypersensitivity to oxcarbazepine or its metabolites, lorazepam or carbamazepine;
 Treatment with Felbamate within 30 days of randomisation;
 History of oxcarbazepine therapy;
 History of non-compliance.

Patient Characteristics	Type of epilepsy Refractory Type of seizures Partial onset Aged 11 to 62 years (mean age: 33 years) Gender: men = 56, women = 46; OXC :men = 31, women = 20; placebo: men = 25, women = 26.
Recruitment	Patients who were to undergo pre surgical evaluations.
Setting	Not reported.
Interventions/ Test/ Factor being investigated	Oxcarbazepine versus placebo.
Comparisons	Between treatment and placebo comparison.
Length of Study/ Follow-up	Not reported. Patients could enter an open-label extension trial.
Outcome measures studied	Primary: time to meeting one of the exit criteria. Secondary % of patients who met one of the exit criteria.
Results	OXC vs placebo: Proportion of seizure free: 13/51 vs 1/51 were seizure free for entire 10 day phase; Withdrawal due to adverse events: 2/51 vs 0/51. Incidence of headache: 10/51 vs 10/51 Incidence of dizziness: 9/51 vs 6/51 Incidence of somnolence: 8/51 vs 0/51 Incidence of nausea: 10/51 vs 3/51 Incidence of vomiting: 5/51 vs 2/51 Incidence of pruritis: 9/51 vs 4/51 Incidence of diplopia: 6/51 vs 0/51 Incidence of fatigue: 5/51 vs 1/51
Safety and adverse effects	See results above.
Does the study answer the question?	Yes.
Effect due to factor in study?	Power: 47 in each group should complete the study for power of 85% and 48 and 49 completed the study. There was no details of allocation concealment and the study was only 10 days long so uncertainty in overall effect due to study intervention.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Schmidt D;Jacob R;Loiseau P;Deisenhammer E;Klinger D;Despland A;Egli M;Bauer G;Stenzel E;Blankenhorn V;

Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial

Ref ID 1113

1993 May

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Zonisamide group n=71;
Placebo group n=68;

Inclusion/Exclusion Criteria Exclusion criteria:
Patients with seizure types other than complex partial seizures, simple partial seizures or tonic-clonic seizures;
Patients presenting with a progressive cerebral lesion, significant mental retardation or any condition or medication supposed to interfere with the pharmacokinetics of the administered drugs as well as nursing women and those with childbearing potential;

Patients were withdrawn if there was an increase of seizure activity >50% compared to baseline; had serious or intolerable side effects as judged by the investigator; significant bone marrow depression; pregnancy or significant noncompliance;

Patient Characteristics Male and female caucasian outpatients;
18-59 years old;
An average of at least four complex partial seizures per month;
Uncontrolled by standard AEDs;
Were on up to three of the following drugs: carbamazepine n=52; phenytoin and phenobarbital n=40; carbamazepine and phenytoin n=36; carbamazepine and primidone n=20; carbamazepine and phenobarbital n=23; and phenytoin n=20;
Median rate of complex partial seizures in 4 months before enrolment: 10 per month.
No difference in sex between groups: males: zonisamide 57.7% vs placebo 58.8%;
No difference in mean age: 36.2 vs 33.4 years;
No difference in weight: 66.2 vs 65.5kg;
No difference in duration of epilepsy: 23.5 vs 20.9 years;
No difference in mean seizure rate of complex partial seizures: 10 vs 9.65 per month; or simple partial seizures 0 vs 0 or tonic-clonic seizures 0 vs 0.28.

Recruitment Not reported.

Setting 9 centres in Europe:

Interventions/ Test/ Factor being investigated Detailed history and complete physical and neurological exam obtained;
Patients were monitored at weekly and monthly clinical visits by patients' seizure diaries; physical and neurological examination and laboratory investigations;
EEGs recorded at screening and at the last visit of the double-blind phase;

Zonisamide capsules 100mg each and identical-appearing placebo capsules;
Initial dose of 1.5mg zonisamide/kg/day increased on day 8 to 3mg/kg/day and on day 15 to 6mg/kg/day; doses were increased after the 4 week titration period on the advice of an unblinded investigator in order to achieve plasma concentrations of 20-30Ug/ml;

Comparisons Zonisamide versus placebo.

Length of Study/ Follow-up 8-12 week baseline phase;
12 week double blind treatment phase;

Outcome measures studied	Reduction of frequency of complex partial seizures (median percentage change and proportion of patients with a 50% reduction in frequency for any type of seizures, the percent of seizure free days and global assessment).
Results	<p>>/=50% decrease in number of seizures:</p> <p>Zonisamide versus placebo:</p> <p>Complex partial: 20/66* vs 8/63; Simple partial: 4/6 vs 1/3; All partial: 20/66* vs 8/63; Generalised (tonic-clonic): 2/8 vs 4/7; Generalised and partial: 20/67* vs 6/64; * = significantly greater than placebo (p<0.05).</p> <p>10 patients (1.5%) treated with zonisamide had a 75% reduction in seizure frequency.</p>
Safety and adverse effects	<p>During the 12-week double-blind phase 42 patients (59.2%) who received zonisamide reported adverse events versus 19 patients (27.9%) in the placebo group.</p> <p>Adverse events >/=10%: Zonisamide versus placebo: fatigue 16/71 (22.5%) vs 8/68 (11.8%) p=0.093; dizziness 12/71 (16.9%) vs 3/68 (4.4%) p=0.018* somnolence 10/71 (14.1%) vs 3/68 (4.4%) p=0.050* anorexia 9/71 (12.7%) vs 1/68 (1.5%) p=0.011* abnormal thinking 8/71 (11.3%) vs 1/68 (1.5%) p=0.019* ataxia 8/71 (11.3%) vs 0 (0%) p=0.004* *=statistically significant. Chi square test.</p> <p>Withdrawn from study due to adverse events: 2/71 patients on zonisamide due to increase in seizure frequency noted in one patient and severe confusion, disorientation, fatigue and an unsteady gait in another patient. 0/68 from placebo group.</p>
Does the study answer the question?	The study focuses on the treatment of refractory partial epilepsy rather than generalised tonic-clonic. None of the authors conclusions related to generalised tonic-clonic seizures.
Effect due to factor in study?	Yes. Although no power calculation given there were 139 participants.
Consistency of results with other studies?	
Directly applicable to guideline population?	We are assuming that the generalised tonic-clonic seizures are primary generalised rather than secondary although it is a bit unclear in the reporting of the study.
Internal Validity	no mention of allocation concealment;

Sun MZ;Deckers CL;Liu YX;Wang W;

Comparison of add-on valproate and primidone in carbamazepine-unresponsive patients with partial epilepsy
Ref ID 5091 2009 Mar

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=136.
VPA: n=68 vs PRM n=68.

Inclusion/Exclusion Criteria Inclusion criteria:
8 years and older;
diagnosis of partial epilepsy;
well-defined types of seizures;
patients not becoming seizure free on CBZ as their first antiepileptic drugs with a seizure frequency of at least 2 seizures per month during the retrospective baseline period of 3 months;

Exclusion criteria:
 not satisfying the inclusion criteria;
 inability to give informed consent;
 absence and/or myoclonic seizures;
 acute or progressive neurological disorders;
 alcohol or other substance abuse;
 psychiatric disease;
 mental retardation;

Patient Characteristics	VPA vs Primidone: Males/females: 44;24 vs 45;23; Average age (years): 22.3 (8-58) vs 22.9 (8-50); Monthly seizure frequency: 6.2 (2-60) vs 6.8 (2-45); Seizure types: CPSY, SGTCS, SPS.
Recruitment	Neurologists from two hospitals identified eligible patients.
Setting	Shanxi medical university, China.
Interventions/ Test/ Factor being investigated	Sodium valproate versus primidone.
Comparisons	Comparisons between treatments.
Length of Study/ Follow-up	No follow-up.
Outcome measures studied	Seizure frequency. Adverse events.
Results	VPA vs PRM: At least 50% reduction in seizure frequency: 35/68 (51%) vs 23/68 (34%), risk difference 17% relative risk 1.52 (1.01 -2.28). Seizure reduction (100%): 18/68 (26%) vs 11/68 (16%) risk difference 10% RR 1.64 (95% CI 0.84-3.20). Withdrawn due to adverse effects: 3 vs 7.
Safety and adverse effects	None reported.
Does the study answer the question?	Yes.
Effect due to factor in study?	No - poor methodology.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Zamponi N;Cardinali C;

Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children

Ref ID 4607

1999

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant VGB n=38, CBZ n=32.

Inclusion/Exclusion Criteria	Inclusion criteria: newly diagnosed partial epilepsy
Patient Characteristics	VGB group: 21 boys, 17 girls mean age 7 years 4 months (range 6months to 10 years 3 months). In 35 cases epilepsy had occurred less than 1 month earlier. CBZ group: 17 boys and 15 girls, mean age 9 years 5 months (range 3 years to 13 years 2 months).
Recruitment	Not reported.
Setting	Neuropsychiatric dept, paediatric hospital, Italy.
Interventions/ Test/ Factor being investigated	Vigabatrin 50-60mg/kg/day or carbamazepine controlled release 15 to 20mg/kg per day.
Comparisons	Vigabatrin versus carbamazepine controlled release.
Length of Study/ Follow-up	2 years (at 1,3,6,12,18,24 months).
Outcome measures studied	Withdrawal due to adverse events; adverse events.
Results	States how many relapsed but not clear how many were seizure free to begin with. VGB vs CBZ: Withdrawal due to adverse events 1/38 vs 1/32. Irritability/excitability:0 vs 6 (15.7%) vs Weight gain 3 (9.3%) vs 10 (26.3%) Excessive sedation 6 (18.7%) vs 0 Urticarial rash 6 (18.7%) vs 0.
Safety and adverse effects	See above results for adverse events and withdrawal due to adverse events.
Does the study answer the question?	No, it is unclear and only reports adverse events clearly.
Effect due to factor in study?	No. Only 70 patients, no power calculation and few details on methodology. Open study.
Consistency of results with other studies?	
Directly applicable to guideline population?	Mixed population as some had the drug as first line and others had it as refractory treatment, although said all were newly diagnosed.

Internal Validity

Zhou B;Zhang Q;Tian L;Xiao J;Stefan H;Zhou D;

Effects of levetiracetam as an add-on therapy on cognitive function and quality of life in patients with refractory partial seizures

Ref ID 169

2008 Feb

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant n=28 (n=14 in the LEV group and n=14 in the placebo group)

Inclusion/Exclusion Criteria Inclusion criteria: adult patients (aged 16–70 years), partial-onset seizures (simple or complex partial with or without secondary generation, poorly controlled by at least one first-line AED at the time of the study, a minimum of eight seizures during the 8-week baseline period with a minimum of two seizures during each 4-week period. Participants were not seriously intellectually disabled (IQ>=80), and could read and comprehend the questions. Exclusion criteria: patients with progressive neurological disorders, severe internal organ diseases, pregnancy, alcohol addiction, or drug abuse.

Patient Characteristics Demographics of the LEV and placebo groups

Demographic	LEV group (N = 13)	Placebo group (N = 11)
Age (years)	28.2 ± 11.1	31.3 ± 9.8
Gender (% male)	53.8%	54.5%
Age at epilepsy onset (years)	18.5 ± 10.1	14.6 ± 7.5
Duration of epilepsy (years)	8.7 ± 6.4	16.5 ± 7.2
Seizure frequency at baseline (No. of seizures/week)	6.55 ± 10.79	6.15 ± 11.20
Education (years)	8.4 ± 3.9	8.2 ± 3.4
Number of antiepileptic drugs		
1	4 (30.7%)	3 (27.3%)
2	9 (69.3%)	8 (72.7%)

Note. Values are expressed as means ± SD, percentages (%), or number (No).

Recruitment Not reported.

Setting Outpatients - Epilepsy Clinic West China Hospital

Interventions/ Test/ Factor being investigated Levetiracetam up to 1500mg twice daily adjunctive to currently used AEDs.

Comparisons The comparison is between levetiracetam as adjunctive therapy and placebo.

Length of Study/ Follow-up 24 weeks: 8-week baseline period, 4 week titration phase and 12 week max dose phase.

Outcome measures studied Primary/secondary outcomes not specified. Study measured seizure frequency for the double blind period. It measured neuropsychological and quality of life outcomes after an extended 24 week open label phase. Seizure rates will be reported here.

Results Seizure frequency at end of double blind period

One patient (7.7%) in the LEV group was seizure-free. Six patients (46.2%) in the LEV group achieved >75% reduction in seizure frequency, compared with one patient (9.1%) in the placebo group. Five patients (38.5%) in the LEV group had no response, compared with nine patients (81.8%) in the placebo group. Thus, a total of eight patients in the LEV group (61.5%) had >50% reduction in seizure frequency (described as responders in some studies), compared with two patients (18.2%) in the control group (P < 0.05).

Adverse events not reported.

Safety and adverse effects Not reported.

Does the study answer the question? No. The study concludes that it has provided further evidence that levetiracetam as adjunctive therapy reduces seizure frequency. However, this is a small study and might not be able to confidently provide evidence of effectiveness.

Effect due to factor in study? No. This is a small exploratory study and does not have the power to provide evidence about effectiveness of the study drug.

Consistency of results with other studies?

Directly applicable to guideline population?

All patients who were enrolled were diagnosed with partial-onset seizures.

Internal Validity

Question: Which AEDs are clinically effective and cost-effective for people with idiopathic generalised epilepsy?

Grading: 1++

High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Noachtar S;Andermann E;Meyvisch P;Andermann F;Gough WB;Schiemann-Delgado J;Levetiracetam Study Group.;

Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures

Ref ID 157

2008 Feb 19

Study Type Randomised Controlled Trial **Funding** UCB Pharma SA.

Number of participant N= 62 to LEV and n= 60 to placebo. ITT population was n=61 for LEV and n=60 for placebo.

Inclusion/Exclusion Criteria Inclusions: if patients had myoclonic seizures on ≥ 8 days during the study baseline period and were receiving a stable dose of one AED for ≥ 4 weeks before the study entry. Exclusion: nonepileptic seizures within the previous year, signs suggestive of a progressive brain lesion; history of parital-onset seizures; status epilepticus within the previous 3 months; previous or current treatment with LEV; current use of vigabatrin or tiagabine; or current use of felbamate with less than 18 months exposure.

Patient Characteristics Male and female patients aged 12 to 65 years inclusive with a diagnosis of IGE with myoclonic seizures according to the ILAE classification of epileptic seizures were eligible. Diagnosis was based on clinical and EEG features consistent with IGE, absence of evidence of brain lesions, and diagnosis of JME, juvenile absence epilepsy (JAE), or epilepsy with generalised tonic-clonic seizures on awakening, in accordance with ILAE classification of epileptic syndromes. Most patients (75%) had a history of taking AEDs other than the one currently prescribed. The most common concomitant AEDs were valproic acid (57.9%) and lamotrigine (26.4%). During the baseline period, the averages (median/mean) for myoclonic seizures days/week and for all seizure days/week for the whole trial population were 1.7/2.5 and 2.2/2.8. All subjects had refractory IGE and experienced myoclonic seizures. Majority had Juvenile Myoclonic Epilepsy JME (88.5% in the LEV group and 98.3% in the placebo group).

Recruitment Not clear.

Setting Secondary care.

Interventions/ Test/ Factor being investigated Levetiracetam versus placebo.

Comparisons Levetiracetam versus placebo.

Length of Study/ Follow-up Efficacy outcomes were measured up to 16 week treatment. Adverse events were also reported in the conversion period (22 weeks).

Outcome measures studied Primary efficacy variable was $\geq 50\%$ reduction in myoclonic seizure days/week during the treatment period. Secondary were: responder rates for seizure days/week for all seizure types; median % reduction from baseline; and rates of seizure freedom.

Results Per protocol analysis: During the 16 week treatment, 35/60 (58.3%) for the LEV group and 14/60 (23.3%) for the placebo group reported at least a 50% reduction from baseline in the number of myoclonic seizure days/week (OR=4.77, 95% CI: 2.12 to 10.77; $p < 0.001$). During the 16 week treatment 10/60 patients (16.7%) receiving LEV were myoclonic seizure free compared to 2/60 on placebo (3.3%; $p = 0.03$); 8/60 patients (13.3%) on LEV and 0/60 on placebo (0.0%) were free from any seizure subtype ($p = 0.006$). During the 12 week evaluation period 15/60 (25.0%) receiving LEV and 3/60 receiving placebo (5.0%) were myoclonic seizure free ($p = 0.004$); 13/60 patients receiving LEV (21.7%) and 1/60 receiving placebo (1.7%) were free from any seizure subtype ($p < 0.001$). Health-related quality of life

The largest improvements (LEV group) were reported in health status (8.1) and seizure worry subscales (8.0). More patients receiving LEV than placebo reported improvement in their overall HRQoI (88.3% versus 60.4%).

ITT analysis: 10/62 (16.1%) in levetiracetam and 2/60 (3.3%) were myoclonic seizure free during up-titration and evaluation period. 8/62 (12.9%) in levetiracetam and 0/60 were seizure free (any seizure subtype) during up-titration and evaluation period. 35/62 (56.5%) in levetiracetam group and 14/60 (23.3%) in placebo experienced at least 50% reduction in myoclonic seizure frequency (up-titration and evaluation period).

During the evaluation period 15/62 (24.2%) in levetiracetam group and 3/60 (5%) in placebo were free from myoclonic seizures and 13/62 (21%) in levetiracetam and 1/60 (1.7%) in placebo were seizure free from any seizure subtype. The incidence of headache was 13/62 (21%) in levetiracetam group and 14/60 (23.3%) in placebo. The incidence of somnolence was higher in levetiracetam group (6/62) compared to placebo (1/60). A higher proportion of participants in levetiracetam group had experienced improvement in their health related quality of life (53/62) compared to placebo (36/60).

Safety and adverse effects

Somnolence was reported in the LEV group during the up-titration (6/60; 10.0%), but not in the evaluation period. It also occurred in 5 patients (10.6%) from the placebo group during conversion to LEV.

Four patients (3 on LEV) discontinued study medication due to adverse events.

Does the study answer the question?

LEV appears to be an effective and well-tolerated adjunctive treatment for patients with previously uncontrolled IGE with myoclonic seizures.

Effect due to factor in study?

Overall very well conducted study. However, is pharma funded.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct population and intervention.

Internal Validity

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Berkovic SF;Knowlton RC;Leroy RF;Schiemann J;Falter U;Levetiracetam N;

Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy.[see comment]

Ref ID 200

2007 Oct 30

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Levetiracetam group: 80 patients.
Placebo group: 84 patients.

Inclusion/Exclusion Criteria
Inclusion criteria:
Aged 4 to 65 years (weight \geq 20kg);
Confirmed electroclinical diagnosis consistent with idiopathic generalised epilepsy;
Experiencing GTC seizures despite treatment with one or two AEDs.
Had to have experienced \geq 3GTC seizures during the 8-week combined baseline period, with \geq 1 seizure during both the historical (4-week) and prospective (4-week) baseline periods;
Had to have been receiving a stable dose of one or two AEDs during the 8-week combined baseline period;
Vagal nerve stimulation within 4 weeks of study visit 1 was counted as one of the patient's concomitant AEDs;
Written informed consent from parents if under 18 years before study entry;

Exclusion criteria:
If CT or MRI done in last 5 years showed a progressive brain lesion;
Partial-onset seizures, including secondarily generalised TC seizures, pseudo seizures within the last year, seizures occurring only in clustered patterns and a history of status epilepticus while taking AEDs within the 3 months before study visit 1;
Patients with partial seizures, in addition to documented generalised seizures as part of an IGE syndrome were not excluded;

Patient Characteristics Levetiracetam vs placebo:

Mean age (years): 26.9 (sd=11.2) vs 30.6 (sd=12.1);
Sex (male/female): 34 (42.5%)/46 (57.5%) vs 39 (46.4%)/45 (53.5%);
Ethnicity (white/non-white): 57 (71.3%)/23 (28.7%) vs 64 (76.2%)/20 (23.8%);
Mean GTC seizure frequency per week (combined baseline): 1.27 (sd=2.46) vs 1.20 (sd=1.90);

Epilepsy syndrome:
- localisation-related - idiopathic 0 vs 1 (1.2%).
- generalised - idiopathic:
childhood absence epilepsy: 3 (3.8%) vs 4 (4.8%);
Juvenile absence epilepsy: 8 (10%) vs 11 (13.1%);
Juvenile myoclonic epilepsy: 24 (3%) vs 30 (35.7%);
Epilepsy with GTC seizures on awakening: 22 (27.5%) vs 27 (32.1%);
Other idiopathic generalised epilepsies: 18 (22.5%) vs 10 (11.9%);
Epilepsy syndrome unknown: 5 (6.3%) vs 2 (2.4%);

Seizure type:
partial seizures: 3 (3.8) vs 2 (2.4%);
generalised seizures: 80 (100%) vs 84 (100%);
- absence seizures 31 (38.8%) vs 47 (56%);
- atypical absence seizures: 1 (1.3%) vs 1 (1.2%);
- myoclonic seizures: 27 (33.8%) vs 35 (41.7%);
- clonic seizures; 0 (0) vs 1 (1.2%);
- tonic seizures 1 (1.3%) vs 5 (6%);
- tonic-clonic seizures: 80 (100%) vs 84 (100%);

Concomitant AEDs used by \geq 10% of patients during treatment period:
valproate 45 (53.2%) vs 44 (52.4%);
Lamotrigine: 22 (27.8%) vs 23 (27.4%);
Carbamazepine: 17 (21.5%) vs 14 (16.7%);
Topiramate: 11 (13.9%) vs 8 (9.5%);

	Phenytoin: 6 (7.6%) vs 11 (13.1%);
Recruitment	Not reported.
Setting	50 Centres (Europe, N. America, Mexico, Aus, NZ).
Interventions/ Test/ Factor being investigated	<p>Patients had a 4 week historical baseline period and a 4 week prospective single-blind placebo baseline period before randomisation to double blind period.</p> <p>Levetiracetam dose 3000mg/day for adults and 60mg/kg/day for paediatric patients and adolescents aged <16 years and weighing <50kg.</p> <p>4 week double-blind titration period followed by a 20 week evaluation period.</p> <p>Offer made after the study to continue with open-label Levetiracetam therapy as part of long-term follow-up study. Or they could discontinue over 4 weeks followed by a 2 week period without study medication. Maximum duration of study was 34 weeks.</p>
Comparisons	Levetiracetam versus placebo.
Length of Study/ Follow-up	Could go onto open label follow-up trial; max 34 weeks not reported here.
Outcome measures studied	% reduction in GTC seizure frequency from baseline; % reduction in seizure days per week (all seizures) from baseline; responder rates - GTC seizure frequency per week and seizure days per week (all seizures);
Results	<p>Responder rates: ITT analysis; Levetiracetam n=80 and placebo n=84. % of patients demonstrating $\geq 50\%$ reduction in GTC seizure frequency per week between the combined baseline and treatment: 57/80 in Levetiracetam vs 38/84 in placebo.</p> <p>Seizure-free: During the evaluation period the % remaining free of GTC seizures: 27/80 (34.2%) in Levetiracetam vs 9/84 (10.7%) in placebo, $p < 0.001$.</p> <p>During the titration and evaluation period, % of patients remaining free of all seizures: 19/80 in Levetiracetam vs 6/84 in placebo, $p < 0.009$.</p> <p>Incidence of adverse events: -incidence of nasopharyngitis; 11/80 (13.8%) in Levetiracetam and 4/84 (4.8%) in placebo -incidence of headache; Levetiracetam 8/80 (10%) and 10/84 (11.9%) in placebo -incidence of fatigue; Levetiracetam 8/80 (10%) and 7/84 (8.3%) in placebo QOLIE-31-P questionnaire: completed by 50 patients in Levetiracetam group and 60 in the placebo group at end of baseline and by 47 and 56 at end of evaluation period or at early discontinuation.</p> <p>38.3% reported important improvement in overall QoL since start of study treatment compared to 28.6% of those in the placebo group. Global evaluation scores improved (investigators and patients): Levetiracetam group 29.5% (58/73) and 77.6% (52/67) vs placebo group 57.1% (45/79) and 64 % (48/75).</p>
Safety and adverse effects	<p>No evidence of seizure exacerbation found with Levetiracetam.</p> <p>In treatment period (up-titration and evaluation) less patients in the Levetiracetam group than placebo experienced a $\geq 25\%$ increase in GTC seizure frequency/week 8/79 (10.1% vs 13/84 (15.5%) and all seizures days/weeks: 6/79 (7.6%) vs 20/84 (23.8%).</p> <p>One (1.3%) in Levetiracetam vs 5 (4.8%) in the placebo group discontinued due to adverse events.</p> <p>Most common adverse events - incidence: Levetiracetam n=79 vs placebo n=84:</p> <p>Nasopharyngitis; 11/79 (13.9%) vs 4/84 (4.8%); Headache: 8/79 (10.1%) vs 10/84 (11.9%);</p>

Fatigue: 8/79 (10.1%) vs 7/84 (8.3%);

Serious AEs resulting in hospitalisation or disability were reported in 3 Levetiracetam patients (3.8%) compared with 8 (9.5%) in the placebo group. 5 severe AEs were related to Levetiracetam.

Does the study answer the question?

Yes.

The authors concluded that adjunctive Levetiracetam is an effective and well-tolerated antiepileptic drug for treating generalised tonic-clonic seizures in patients with idiopathic generalised epilepsies.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Glaser TA;Cnaan A;Shinnar S;Hirtz DG;Dlugos D;Masur D;Clark PO;Capparelli EV;Adamson PC;

Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy

Ref ID 4968

2010 Mar 4

Study Type

Randomised Controlled Trial

Funding

National Institutes of Health (NS045911, 5 U10 HD037249, 1 UL1 RR026314 and P30 HD26979).

Number of participant

N= 453 children, n ethosuximide=156, n lamotrigine=149, n valproic acid=148 (451 were included in the safety analysis and 446 in the efficacy analysis).

Inclusion/Exclusion Criteria

Inclusion criteria: children between 2.3-13 years who had childhood absence epilepsy of new onset that was clinically diagnosed according to the International League Against Epilepsy classification of epilepsy syndromes (including frequent clinical absence seizures and reported normal development, had bilateral synchronous, symmetric spike waves (2.7 to 5 Hz) on a normal background with at least one electrographically reported seizure lasting 3 seconds or more on a 1-hour, awake video EEG, weighted 10 kg or more, had a body mass index below the 99th percentile, had a normal complete blood count and normal levels of serum alanine aminotransferase, serum aspartate aminotransferase, and bilirubin. The girls had to be premenarchal.

Exclusion criteria: had received antiseizure medication for more than 7 days before randomization, had a history of nonfebrile seizures other than absence seizures (e.g. afebrile generalized tonic-clonic or myoclonic seizures), had a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy (e.g. generalized tonic-clonic or myoclonic seizures), had a history of a severe dermatologic reaction to medication, or had a history of major psychiatric disease, autistic-spectrum disorder, or any clinically significant medical condition.

Patient Characteristics

the median age of cohort was 7 years 5 months; 17 (4%) children were under 4 years of age, 184 (41%) were 8 to less than 12 years of age, and 10 (2%) were 12 to 13 years of age. No significant differences were found in the three groups on the following baseline characteristics: gender, ethnicity, race, BMI>90th percentile.

Recruitment

Not reported.

Setting

32 sites across United States.

Interventions/ Test/ Factor being investigated	ethosuximide, valproic acid and lamotrigine as AEDs in childhood absence epilepsy.
Comparisons	1)Ethosuximide versus Lamotrigine 2)Valproic acid versus Ethosuximide 3)Valproic acid versus Lamotrigine
Length of Study/ Follow-up	Treatment for 16-20 weeks (end of trial); subjects without seizures at their last follow up visit continued to receive medication in double blind fashion for up to 2 more years.
Outcome measures studied	1) experience of adverse events (>10%) 2)attentional dysfunction (for children 4 years or older).
Results	<p>1)experience of adverse events: fatigue (ethosuximide 15/156 (10%), lamotrigine 13/149 (9%), valproic acid 18/148 (12%)), headache (ethosuximide 19/156 (12%), lamotrigine 12/149 (8%), valproic acid 12/148 (8%)), sleep problem (ethosuximide 10/156 (6%), lamotrigine 5/149 (3%), valproic acid 14/148 (10%)), nausea, vomiting or both (ethosuximide 23/156 (15%), lamotrigine 2/149 (1%), valproic acid 10/148 (7%)), stomach upset (ethosuximide 16/156 (10%), lamotrigine 4/149 (3%), valproic acid 8/148 (5%)), hyperactivity (ethosuximide 14/156 (9%), lamotrigine 10/149 (7%), valproic acid 15/148 (10%)), hostility (ethosuximide 4/156 (3%), lamotrigine 10/149 (7%), valproic acid 18/148 (12%)), personality change (ethosuximide 4/156 (3%), lamotrigine 9/149 (6%), valproic acid 16/148 (11%)).</p> <p>2)Attentional dysfunction: Secondary analysis in a subgroup of 104 participants in lamotrigine group and 106 in valproic acid group. CPT confidence index\geq0.60 (ethosuximide 35/106 (33%), lamotrigine 25/104 (24%), valproic acid 52/106 (49%)). Ethosuximide versus Lamotrigine; odds ratio (95%ci) 1.56 (0.85-2.85), P<0.001 Valproic acid versus Ethosuximide; odds ratio (95%ci) 1.95 (1.12-3.41), P=0.03 Valproic acid versus Lamotrigine; odds ratio (95%ci) 3.04 (1.69-5.49), P<0.001</p>
Safety and adverse effects	See results in Q2.
Does the study answer the question?	Yes. Ethosuximide is associated with fewer adverse events compared to valproic acid and lamotrigine. Significantly more participants in valproic acid had attentional dysfunction compared to participants in ethosuximide and lamotrigine.
Effect due to factor in study?	Yes. It is a well conducted double blind RCT with a reasonable sample size for the study to have enough statistical power to estimate the effect.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Marson AG;Appleton R;Baker GA;Chadwick DW;Doughty J;Eaton B;Gamble C;Jacoby A;Shackley P;Smith DF;Tudur-Smith C;Vanoli A;Williamson PR;

A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial

Ref ID 1496

2007

Study Type	Randomised Controlled Trial	Funding	Commissioned and sponsored by NHS R&D Health Technology Assessment Programme. Also supported by pharmaceutical companies with drugs in the study (approx 20% of the total costs of study).
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Number of participant	<p>Arm A: Total n=1721. CBZ n=378; GBP n=377; LTG n=378; OXC n=210; TPM n=378.</p> <p>Arm B: total n=716. VPA n=239; TPM n=239; VPS n=238.</p>
Inclusion/Exclusion Criteria	<p>Inclusion criteria: History of 2 or more clinically definite unprovoked epileptic seizures in the previous year and if treatment with a single AED represented the best therapeutic option. Patients with newly diagnosed epilepsy, those who had failed previous monotherapy (providing that did not include one of the drugs present in the randomisation) and patients in remission of epilepsy, who had relapsed after a withdrawal of treatment.</p> <p>Exclusion criteria: If patient or clinician felt treatment was contraindicated, if all seizures had been acute symptomatic seizures (including febrile seizures), they were aged 4 years or younger or if there was a history of progressive neurological disease.</p>
Patient Characteristics	<p>Arm B: Mean age +/- SD (years): Total: 22.5 +/- 14; LTG 22.8 +/- 14.3; TPM 22.3 +/- 13.3; VPA: 22.5 +/- 14.5. Gender: male vs female LTG:142 (59%)vs 97 (41%); TPM :142 (59%) vs 97 (41%); VPA: 143 (60%) vs 95 (40%). Treatment history: untreated: Total 628 (87.7%). LTG 210 (87.9%); TPM 209 (87.5%); VPA: 209 (87.8%); monotherapy (not optimally treated): Total 60 (8.4%) LTG 19 (8%); TPM 20 (8.4%); VPA: 21 (8.8%); recent seizures after remission: Total: 28 (3.9%); LTG 10 (4.2%); TPM 10 (4.2%); VPA 8 (3.4%). Epilepsy syndrome: - idiopathic partial: Total 3 (0.4%); LTG: 1 (90.4%); TPM 2 (0.8%); VPA: 0 (0%). - symptomatic or cryptogenic partial: Total 49 (6.9%); LTG 18 (7.5%); TPM 11 (4.6%); VPA 20 (8.4%); - idiopathic generalised: Total: 450 (62.9%); LTG: 145 (60.7%); TPM 151 (63.5%); VPA 154 (64.7%); - other syndrome: Total: 22 (3.1%); LTG 9 (3.8%); TPM 8 (3.4%); VPA (2.1%). - unclassified: Total: 191 (26.7%); LTG 66 (27.6%); TPM 66 (27.7%); VPA 59 (24.8%).</p>
Recruitment	<p>Patients presenting to participating clinicians were cued for entry if met inclusion criteria.</p>
Setting	<p>Multicentre study hospital outpatient clinics UK.</p>
Interventions/ Test/ Factor being investigated	<p>At start of study information was recorded including patient demographics, presence of a history of learning disability or developmental delay, prior neurological history including head injury, stroke, intracerebral infection and acute symptomatic seizures, and a history of epilepsy in a first-degree family member. Clinicians were asked to classify seizures and epilepsy syndromes according to ILAE classifications or at least differentiate between focal or generalised onset seizures. Where there was uncertainty patients were recorded as having unclassified convulsive or other unclassified seizures. Any EEG or brain imaging results at time of randomisation were recorded.</p> <p>Clinicians involved in the study were asked to choose either CBZ or VPA as the most appropriate treatment for an individual patient. When CBZ was chosen the patient entered arm A and were then allocated to either CBZ, GBP, LTG, OXC, or TPM in ratio of 1:1:1:1:1 (OXC was included in randomisation only after 1st June 2001). If VPA was chosen patients entered arm B and were randomised to either VPA, LTG or TPM in ratio of 1:1:1.</p> <p>Drug was randomised but drug, dosage and preparation were those used typically by the clinician.</p>
Comparisons	<p>Two arms. Arm A: carbamazepine versus gabapentin versus lamotrigine versus oxcarbazepine versus topiramate. Arm B: sodium valproate versus lamotrigine versus topiramate.</p>
Length of Study/ Follow-up	<p>Follow-up at 3, 6, 12 months and at successively yearly intervals from randomisation. First randomisation was Jan 1999 and continued to randomise until 31st August 2004. Patients were followed up at least until the end of the study (31st August 2005).</p>

Outcome measures studied

Primary clinical outcomes:
Time from randomisation to treatment failure. Time from randomisation to the achievement of a 1-year period of remission of seizures. Quality of life.

Results

Arm B:
The following outcomes were calculated on an ITT analysis; withdrawal due to lack of efficacy, withdrawal due to adverse events, incidence of tiredness/drowsiness/fatigue/lethargy (all participants in arm B) and incidence of other adverse events (sorted by descending total frequency: diarrhoea, headache, other neurological, sleep disturbance, tremor, vomiting, word finding difficulty, alopecia, accidental injury, dizziness/vertigo, worsening of seizures, anorexia, hallucinations, other haematological, other renal tract/genital, other skin and appendages, short of breath, vaginal bleeding) (all participants in arm B).
Time to first seizure and time to exit/withdrawal of allocated treatment ((IGE only) was calculated on data from a sample of 441 patients with IGE and no specified type of analysis.
Time to first seizure and time to exit/withdrawal of allocated treatment (entire recruitment period, generalised syndrome only) was calculated on data from a sample of 324 patients with IGE and no specified type of analysis.

ITT analysis:
Withdrawal due to adverse events;
25/239 (10.5%) in LTG, 57/239 (23.8%) in TPM and 35/238 (14.7%) in VPA;
Withdrawal due to lack of efficacy;
53/239 (22.2%) in LTG, 28/239 (11.7%) in TPM and 21/238 (8.8%)

HR estimates and 95% Ci (IGE only):
- time to first seizure: LTG vs VPS:1.73 (1.32 to 2.26); TPM vs VPA: 1.26 (0.96 to 1.65);
- time to treatment failure: LTG vs VPA: 1.56 (1.08 to 2.25); TPM vs VPA: 1.90 (1.33 to 2.71); p=0.12.

Time to first seizure - generalised syndromes only for entire recruitment period
HR (95% CI) Baseline drug
VPA: LTG 0.59 (0.45 to 0.77) TPM 0.80 (0.61 to 1.05)
LTG: VPA 1.69 (1.29 to 2.22) TPM 1.35 (1.04 to 1.76)
TPM: VPA 1.25 (0.95 to 1.64) LTG 0.74 (0.57 to 0.96)

Time to treatment failure for entire recruitment period (generalised syndrome only):
HR (95% CI): Baseline drug
VPA: LTG 0.65 (0.45 to 0.93) TPM 0.53 (0.37 to 0.76)
LTG: VPA 1.55 (1.07 to 2.24) TPM 0.82 (0.59 to 1.14)
TPM: VPA 1.89 (1.32 to 2.70) LTG 1.22 (0.88 to 1.70)

Incidences of adverse events:
-tiredness/drowsiness/fatigue/lethargy:25/239 (10.5%) in LTG, 25/239 (10.5%) in TPM, 18/238 (7.6%) in VPA,
- other (sorted by descending total frequency: diarrhoea, headache, other neurological, sleep disturbance, tremor, vomiting, word finding difficulty, alopecia, accidental injury, dizziness/vertigo, worsening of seizures, anorexia, hallucinations, other haematological, other renal tract/genital, other skin and appendages, short of breath, vaginal bleeding): 40/239 (16.7%) in LTG, 40/239 (16.7%) in TPM, 36/238 (15.1%) in VPA

QoL outcomes; QoL questionnaire sent to a sample of 397 patients with IGE. No specified type of analysis.

Two year anxiety scores:
LTG: TPM 0.97 (-0.28 to 2.22) VPA 0.89 (-0.34 to 2.12)
TPM: LTG -0.97 (-2.22 to 0.28) VPA -0.08 (-1.31 to 1.15)
VPA: LTG -0.89 (-2.12 to 0.34) TPM 0.08 (-1.15 to 1.30)

Two year depression scores:
LTG: TPM -0.08 (-1.03 to 0.87) VPA -0.48 (-1.41 to 0.45)
TPM: LTG 0.08 (-0.87 to 1.03) BPA -0.40 (-1.34 to 0.54)
VPA: LTG 0.48 (-0.45 to 1.41) TPM 0.40 (-0.54 to 1.34)

Two year AEP scores:
LTG: TPM 0.75 (-2.56 to 4.06) VPA 0.73 (-2.52 to 3.98)

TPM: LTG -0.93 (-3.29 to 5.14) VPA -0.37 to 2.00
 VPA: LTG -0.73 (-3.98 to 2.52) TPM 0.02 (-3.26 to 3.29)

Two year neurotoxicity scale score:

LTG: TPM -0.93 (-5.14 to 3.29) VPA -1.29 (-5.34 to 2.75)
 TPM: LTG 0.93 (-3.29 to 5.14) VPA -0.37 (-4.48 to 3.75)
 VPA: LTG 1.29 (-2.75 to 5.34) TPM 0.37 (-3.75 to 4.48)

Two year EQ-5D scores:

LTG: TPM -0.02 (-0.08 to 0.04) VPA 0.02 (-0.04 to 0.08)
 TPM: LTG 0.02 (-0.04 to 0.08) VPA 0.04 (-0.02 to 0.10)
 VPA: LTG 1.29 (-2.75 to 5.34) TPM 0.37 (-3.75 to 4.48)

Two year anxiety scores - ordinal

LTG: TPM 1.62 (0.71 to 3.72) VPA 1.40 (0.64 to 3.10)
 TPM: LTG 0.62 (0.27 to 1.42) VPA 0.87 (0.37 to 2.00)
 VPA: LTG 0.71 (0.32 to 1.58) TPM 1.16 (0.50 to 2.68)

Two year depression scores - ordinal

LTG: TPM 1.02 (0.38 to 2.78) VPA 0.82 (0.33 to 2.07)
 TPM: LTG 0.98 (0.36 to 2.67) VPA 0.81 (0.31 to 2.09)
 VPA: LTG 1.22 (0.48 to 3.08) TPM 1.24 (0.48 to 3.23)

Two year GQoL scores:

LTG: TPM 1.24 (0.66 to 2.34) VPA 1.17 (0.64 to 2.16)
 TPM: LTG 0.81 (0.43 to 1.53) VPA 0.95 (0.51 to 1.77)
 VPA: LTG 0.85 (0.46 to 1.57) TPM 1/06 (0.57 to 1.97)

Analysis of generalised epilepsy (data not published yet):

HRs (95% CI) for relative treatment effects:

	Time to 12-month remission	Time to treatment failure	Time to 1st seizure
LTG: VPA Absence:	0.74 (0.43, 1.26)	1.66 (0.75, 3.66)	1.63 (0.98, 2.72)
LTG: VPA TC on waking:	0.88 (0.44, 1.74)	1.14 (0.39, 3.35)	2.27 (0.95, 5.46)
LTG: VPA Other:	0.62 (0.39, 0.99)	1.71 (0.92, 3.18)	1.39 (0.88, 2.23)
TPM: VPA Absence:	1.02 (0.61, 1.72)	4.10 (1.89, 8.91)	1.098 (0.66, 1.81)
TPM: VPA TC on waking:	0.81 (0.41, 1.57)	2.44 (0.84, 7.07)	1.71 (0.71, 4.10)
TPM: VPA Other:	0.67 (0.43, 1.05)	1.23 (0.68, 2.24)	1.15 (0.72, 1.83)

n.b Time to 12-month remission HR<1 implies valproate favoured, time to treatment failure and time to 1st seizure HR>1 implies valproate favoured.

Safety and adverse effects

37% (LTG), 45% (TPM), 36% (VPA) patients reported at least one adverse event at some point in the study (ITT).

Incidence of adverse events (10% or over):

Tiredness/drowsiness/fatigue/lethargy: LTG: 15/239 (6%); TPM: 25/239 (10.5%); VPA: 18/238 (7.6%).

Other: LTG: 30/239; TPM: 40/239; VPS: 36/238; Other included: abdominal pain, dyspepsia, alopecia, other general, other visual disturbance, word finding difficulty, vomiting, aches and pains, other gastrointestinal, other musculoskeletal, other respiratory/pulmonary, diarrhoea, psychosis, anorexia, bruising, constipation, diplopia, renal/bladder stones, flu-like symptoms, hallucinations, infection, vaginal bleeding, arthritis, asthma, chest infection, childbirth, faints, hypertension, ischaemic heart disease/myocardial infarct, other cardiac/vascular, other haematological, psoriasis, short of breath, status epilepticus, UTI, urinary retention.

Does the study answer the question?

Yes. The authors concluded: There is a statistically significant difference between drugs for time to treatment failure for any reason and VPA is best option. Pair wise comparisons show it is statistically superior to topiramate which is the least favoured option and lamotrigine is intermediate.

Cumulative risk analysis of withdrawal for UAEs and ISC indicates that LTG is least likely to be associated with UAEs and TPM most likely. HRs for TPM indicate that it is statistically inferior to both VPA and LTG for failure due to UAEs. However LTG is

most likely to be associated with treatment failure due to ISC, with VPA least likely. LTG HRs indicate it is twice as likely to fail because of ISC than VPS which is significant.

Also that when analyses were restricted to those who were identified as having a generalised epilepsy syndrome, VPA is markedly more superior for time to treatment failure. It is significantly superior to TPM and LTG for the outcome.

For time to first seizure the drugs differ with VPA being the preferred option, LTG the worst and TPM intermediate between the two but significantly superior to LTG. The differences appear larger for patients with definite generalised epilepsy than for all patients randomised to arm B of the study.

In the generalised epilepsy analysis (unpublished) there was only one significant result which favoured valproate over topiramate in the treatment of absence seizures.

Effect due to factor in study?

Yes. Unblinded study but large pragmatic trial.

Consistency of results with other studies?

Directly applicable to guideline population?

The population had a lot of unclassified seizure type so not all of the population had idiopathic generalised epilepsy.

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Levisohn PM;Holland KD;

Topiramate or valproate in patients with juvenile myoclonic epilepsy: a randomized open-label comparison

Ref ID 252

2007 Jun

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Topiramate n=19;
Valproate n=9.

Inclusion/Exclusion Criteria Inclusion criteria:
adolescents/adults;
12-65 years old;
>/=25kg;
confirmed diagnosis of juvenile myoclonic epilepsy;
Diagnostic criteria included myoclonic jerks, seizure onset at 8-26 years of age and coexistent generalised tonic-clonic seizures with generalised epileptiform abnormalities on EEG consistent with JME;
Have active epilepsy in the form of myoclonus or >/=1 primary generalised tonic-clonic seizure in the 3 months before study entry;
topiramate or valproate could be initiated as monotherapy r as an adjunct to another AED (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy;
females of children-bearing potential had to be premenarchal, physically incapable of bearing children or practicing an acceptable method of contraception;

Exclusion criteria:
previous discontinuation of topiramate or valproate due to an adverse event;
abnormal cranial CT or MRI scan;
dementia or mental retardation;
progressive myoclonic epilepsy;
clinically unstable medical conditions;
history of nephrolithiasis;
SCOT and/or SGPT levels greater than 2 time the upper limit of the normal range;
co-therapy with a carbonic anhydrase inhibitor or barbiturate AED;
and use of an experimental medication or device within 30 days of study entry.

Patient Characteristics Topiramate versus valproate:

Age: 15 (9-42) vs 16 (12-34);
Gender, female: 13 (68%) vs 4 (44%);
Weight (kg): 66 (32-116) vs 72 (55-109);
Baseline seizure type:
-myoclonic 14 (74%) vs 9 (100%);
-PGTCS 12 (63%) vs 4 (44%);
-absence 2 (11%) vs 2 (22%);

Baseline AED:
None 12 (63%) vs 4 (44%);
Carbamazepine 3 (16%) vs 0;
Oxcarbazepine 1 (5%) vs 0;
Phenytoin 1 (5%) vs 2 (22%);
Lamotrigine 1 (5%) vs 1 (11%);
Valproate 1 (5%) vs 1 (11%);
Ethosuximide 0 vs 1 (11%);

Recruitment Not reported.

Setting Not reported.

Interventions/ Test/ Factor being investigated	<p>Target topiramate dosage was 3-4mg/kg/day (max 9mg/kg/day) for patients 12-16 years old and 200mg/day (maximum 600mg/day) for patients over 16 years of age; Valproate target dosages were 10mg/kg/day in patients 12-16 years of age and 750mg/day in those over 16 years (overall maximum 60mg/kg/day). Topiramate was provided in 25 or 100mg TOPAMAX tablets; valproate was provided as 125, 250 or 500mg depakote tablets;</p> <p>Topiramate versus valproate.</p>
Comparisons	Topiramate versus sodium valproate.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Reduction in seizures; evaluations of improvement; toxicity and neurotoxicity scores.
Results	<p>Topiramate vs valproate seizure reduction from baseline:</p> <p>ITT:</p> <p>Myoclonic: 50% to 75% reduction in seizures: 0 vs 1/9 (11%); 75 % to <100% reduction in seizures: 3/14 (21%) vs 1/9 (11%); 100% reduction in seizures: 9/14 (64%) VS 7/9 (78%);</p> <p>PGTCS: 50% to <75% reduction in seizures: 1/12 (8%) vs 0; 100% reduction in seizures: 10/12 (83%) vs 3/4 (75%); No seizures in preceding 12 weeks: 8 (42%) vs 4 (44%);</p> <p>Study completers:</p> <p>Myoclonic: 50% to <75% reduction in seizures: 0 vs 1/7 (25%); 75 to 100%reduction in seizures: 3/11 (27%) vs 0; 100% reduction in seizures: 7/11 (64%) vs 6/7 (86%);</p> <p>PGTCS: 50 to <75%: 1/10 (10%) vs 0; 100%: 8/10 (80%) vs 3/4 (75%); No seizures in preceding 12 weeks: 8 (67%) vs 4 (57%).</p>
Safety and adverse effects	<p>Participants withdrawn due to adverse events in topiramate group: 2 (11%) because of inadequate seizure control and 1 (5%) due to patient choice. 2 (11%) of patients were lost to follow-up. One (11%) valproate patient discontinued due to adverse events and one (11%) discontinued for other reasons.</p> <p>Systemic toxicity were higher in the valproate-treated patients. Neurotoxicity scores did not substantially differ between treatment groups.</p> <p>Most common adverse events occurring in two or more patients during randomised treatment.</p> <p>Topiramate vs valproate:</p> <p>headache: 5/19 (26%) vs 1/9 (11%) concentration/attention difficulty: 3/19 (16%) vs 1/9 (11%); fatigue: 2/19 (11%) vs 3/9 (33%); alopecia: 2/9 (11%) vs 3/9 (33%); dizziness: 2/19 (11%) vs 1/9 (11%); weight loss: 2/19 (11%) vs 0; paresthesia: 2/19 (11%) vs 0; psychomotor slowing: 2/19 (11%) vs 0; somnolence: 2/19 (11%) vs 0; nausea: 1/19 (5%) vs 3/9 (33%); weight gain: 0 vs 2/9 (22%); appetite increase: 0 vs 2/9 (22%); insomnia: 0 vs 2 /9 (22%); abnormal vision: 0 vs 2/9 (22%).</p>

Does the study answer the question?	Author concludes that topiramate may be an effective, well-tolerated alternative to valproate which warrants validation by a double-blind trial.
Effect due to factor in study?	There is no power calculation and the numbers are small with variations in the groups.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	Variation in the groups by seizure type and number

Question: How effective and cost-effective are anti-epileptic drugs for absence seizures

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Callaghan N;O'Hare J;O'Driscoll D;O'Neill B;Daly M;

Comparative study of ethosuximide and sodium valproate in the treatment of typical absence seizures (petit mal)

Ref ID 4628

1982

Study Type	Randomised Controlled Trial	Funding	Labaz, Warner-Lambert Pharmaceuticals.
Number of participant	28 in total, 14 in group A, 14 in group B.		
Inclusion/Exclusion Criteria	Inclusion: typical absence seizures only, EEG pattern of 3-per-second spike and wave activity. None of the children had received any other anticonvulsant drug treatment before referral for neurological assessment. Exclusion: other anticonvulsant drug prior to referral		
Patient Characteristics	In group A (ethosuximide) the mean age was 8 years and the age range was 4 to 14 years. 8 were male, 6 were female. The age of seizure onset was 2 to 5 years. In group B (sodium valproate) the mean age was 9 years and the age range was 5 to 15 years. 5 were male and 9 were female. The age of seizure onset was 3 to 6 years.		
Recruitment	Not reported.		
Setting	Cork, Ireland.		
Interventions/ Test/ Factor being investigated	Ethosuximide.		
Comparisons	Ethosuximide versus sodium valproate.		
Length of Study/ Follow-up	18 months to 4 years.		
Outcome measures studied	Seizure free, 50% reduction in seizures, side effects.		
Results	Seizure free: In group A (ethosuximide) 8 out of 14 patients became seizure free compared to 6 out of 14 in group B (sodium valproate). 50% reduction in number of seizures: In group A (ethosuximide) 3 out of 14 patients had 50% reduction in the number of seizures to 6 out of 14 in group B (sodium valproate). Two patients who failed to respond to ethosuximide responded well to sodium valproate and one patient who failed to respond to sodium valproate had a good response to ethosuximide. One patient who failed to respond to sodium valproate was refused permission for other treatment by parents. One patient (patient 9) did not respond to either drugs or both drugs in combination. Side effects: One patient developed acute pancreatitis while on sodium valproate and another developed obesity (returning to normal weight and seizure control maintained when on ethosuximide. Drowsiness in one patient on high doses of ethosuximide which subsided when reduced.		
Safety and adverse effects	Acute pancreatitis occurred in one patient on sodium valproate.		
Does the study answer the question?	The authors concluded that the two drugs were equally effective in the control of absence attacks. When patients did not respond to the initial drug a response occurred with the alternative drug in all but one child.		

Effect due to factor in study? Not sure. No power calculation given. High risk of bias/Unclear in methodology.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Coppola G;Auricchio G;Federico R;Carotenuto M;Pascotto A;

Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study

Ref ID 660

2004 Sep

Study Type Randomised Controlled Trial **Funding** States that the study was not sponsored by any commercial organisation.

Number of participant n=38 children. VPA: 19; LTG: 19.

Inclusion/Exclusion Criteria

Inclusion criteria:

- aged 3 to 13 years;
- newly diagnosed typical absence seizures (according to the ILAE 1981) associated with generalised, synchronous 3Hz (2.5-4Hz) spike and wave activity, lasting for over 3 seconds, occurring spontaneously or during one of two trials of 3-minute hyperventilation with 1-2 minute rest between trials;
- clearly observable clinical signs of typical absence seizures (such as staring or impairment of consciousness) on the video recording;
- normal clinical, neurologic, and computed tomography (CT) or magnetic resonance imaging (MRI) examination;
- informed consent by parents or caregivers.

Exclusion criteria:

- absences with marked eyelid or perioral myoclonus (eyelid or perioral myoclonia with absences);
- absences with marked limb and trunk rhythmic myoclonic jerks (myoclonic absence epilepsy);
- absences with single ictal myoclonic jerks of the limbs, trunk or head;
- absences with mild or not clinically detectable impairment of consciousness (eg juvenile myoclonic epilepsy);
- other types of epileptic seizures;
- stimulus-sensitive absences: photosensitive, pattern-sensitive, self-induced pattern-sensitive;
- irregular, arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency;
- central-temporal or occipital focal EEG discharges or abnormal background EEG activity;
- known or suspected structural brain lesion;
- progressive neurologic illness;
- psychiatric disorder requiring medication;
- chronic cardiovascular, renal, or hepatic disease, and in general any disease that could interfere with drug absorption, distribution, metabolism or excretion;
- long-term comedication with other drugs;
- suspected poor compliance.

Patient Characteristics

Gender: 17 male; 21 female;
Age: range (mean): 3 to 13 years (7.5years);
Disease status: all had newly diagnosed childhood or juvenile typical absence seizures; mean duration of epilepsy 6 months (range 1-17months); family history of epilepsy in 44.7% of patients and history of febrile seizures in 6 (15.8%); neurological and neuroradiological findings and cognitive levels normal in all patients;

Recruitment	Referred if showed signs of typical absences.
Setting	Epilepsy unit, Clinic of Child Neuropsych. Naples
Interventions/ Test/ Factor being investigated	When referred patients undertook a video-EEG recording of trials of 3 minutes of hyperventilation and intermittent photic stimulation to confirm the presence of absence seizures. The patients were then randomised to either LTG or VPA.
Comparisons	LTG monotherapy versus VPA monotherapy.
Length of Study/ Follow-up	The patients were seen at monthly intervals for 12 or less months and exited if not satisfactorily controlled at highest dosage.
Outcome measures studied	Primary efficacy measure: proportion of patients who remained seizure free during the treatment phase;
Results	Proportion of participants having treatment withdrawn (all due to lack of efficacy): total 9, VPA: 3; LTG: 6). Occurred after 3 months. Some patients continued their assigned treatment although they did not meet all the criteria for the definition of seizure freedom (definition: no clinical absences reported by external observers for at least the previous month and no electroclinical seizures detected by awake video-EEG with HV-EEG and in 24-hour ambulatory EEG monitoring). Seizure freedom at 1 month: VPA: 10 (52.6%); LTG: 1 (5.3%), p=0.004). Seizure freedom at 3 months: VPA: 12 (63.1%); LTG: 7 (36.8%), p=0.19).* Seizure freedom after 12 month follow-up: VPA: 13 (68.4%); LTG: 10 (52.6%), p=0.51).** *Dosage: VPA (mean 22.6mg/kg, range 20-25mg/kg; LTG (mean 6.5, range 2-11.5mg/kg). **Dosage: VPA (mean 25.4mg/kg, range 20-30mg/kg); LTG (mean 8.3mg/kg, range 2-12mg/kg).
Safety and adverse effects	Adverse events recorded in 2 (10.6%) of patients in VPA group (diarrhoea: 1; weight gain, one) and 6 (31.8%) in LTG (headache: 2; transient mild skin rash after 1 week of treatment: 1; diplopia: 1; nervousness; 1; increased appetite: 1). Side effects generally mild and transient and none lead to withdrawal of drug.
Does the study answer the question?	The authors concluded that both VPA and LTG can be efficacious against absence seizures, although VPA showed a much faster onset of action, partly because of its shorter titration.
Effect due to factor in study?	No. The authors state that at the time of the protocol design there was not enough sufficient information to make a hypothesis on efficacy of the two drugs so was an exploratory trial, and the sample size was set at 38 with no formal power calculation.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	
	Martinovic Z;
	Comparison of ethosuximide with sodium valproate as monotherapies of absence seizures
Ref ID	4896 1983
Study Type	Randomised Controlled Trial Funding Not reported.
Number of participant	Total n=20. Ethosuximide n=10, sodium valproate n=10.

Inclusion/Exclusion Criteria	Inclusion criteria: recent-onset seizures (not exceeding 6 months).
Patient Characteristics	Main characteristics ESM vs VPA: Mean age: 6.8 vs 6.3; Sex: female 8 vs 7, male 2 vs 3; Duration of disease (mean in days): 66 vs 58; Greatest no of seizures per day (mean) 27 vs 34.
Recruitment	Not reported.
Setting	Outpatient.
Interventions/ Test/ Factor being investigated	Blood counts obtained before given drug treatment. Parents were given record cards to note the no. of seizures and to inform doctor if observed any change in seizure pattern. EEG 15 days after treatment. Then at monthly intervals until complete seizure control achieved and then at 2 monthly intervals. Plasma concentrations 10-30 days after starting treatment and thereafter at time of seizure control or at time of appearance of other seizure types. EMIT assay method assessed drug plasma concentrations, dosage adjusted in accordance with these, increased later if not seizure-free.
Comparisons	Ethosuximide versus sodium valproate.
Length of Study/ Follow-up	For periods of 1 to 2 years.
Outcome measures studied	Seizure control; improvement 50-75%; time to seizure control; adverse events.
Results	<p>If parents did not cooperate fully from the trial the children were not retained in the study, six patients were not included.</p> <p>Proportion of seizure-free participants: ESM: 8/10 vs VPA 7/10. Patients improved 50-75% ESM: 2 VPA: 3. Time to achieve complete seizure control (days): mean (range) : ESM:23 (4-65) vs VPA: 45 (12-99). Mean time for EEG without paroxsms (months): ESM 4 (1-12) vs VPA 6 (2-11). Number of patients without EEG paroxysms at the end 8 vs 7. Number of patients with unspecific EEG changes 5 vs 4. At the end of follow-up (1-2 years): Number patients with EEG within normal limits after 1-2 years 3 vs 3.</p> <p>The addition of clonazepam resulted in more than 50% reduction in seizures in 3 patients who had myoclonic components (2 patients) and akinetic (1 patient). Tonic-clonic occurred in one patient on ethosuximide and was completely controlled by adding sodium valproate.</p>
Safety and adverse effects	Adverse effects were infrequent and mild. ESM: initial tiredness in 2 patients and nausea in 2 others. VPA: transient nausea in 3 patients, transient vomiting in 2 patients on onset of treatment and a decreased number of platelets (without thrombocytopaenia) in 4 patients.
Does the study answer the question?	Complete seizure control is possible in relatively short time in majority (15 out of 20 patients) with simple absence seizures with ESM or VPA. There was no significant differences in the efficacy of the two AEDs, except shorter time to achieve complete seizure control with ESM.
Effect due to factor in study?	No power calculation but sample size very small.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Sato S;White BG;Penry JK;Dreifuss FE;Sackellaes JC;Kupferberg HJ;

Study Type	Randomised Controlled Trial	Funding	NINCDS- National institute of neurological and communicative disorders and stroke.
Number of participant	45 in total. 16 drug naïve patients. 29 refractory patients. Group I: VPA: 10 (2 drug naïve, 8 refractory); ESM: 13 (4 drug naïve, 8 refractory). Group II: VPA: 12 (5 drug naïve, 7 refractory); ESM: 10 (5 drug naïve, 5 refractory). Crossover of non-responders: Group I: VPA: 7 (1 drug naïve, 6 refractory); ESM: 8 (2 drug naïve, 6 refractory). Group II: VPA: 7 (1 drug naïve, 6 refractory); ESM: 7 (3 drug naïve, 4 refractory)		
Inclusion/Exclusion Criteria	Inclusion: aged 3 to 18 years, females not of child bearing age, absence seizures observed by investigator occurred at least once in pre treatment 12 hour telemetered EEG, no evidence of neurologic illness, refractory patients must have been kept on the tolerated daily dosage of ESM for 1 month before study		
Patient Characteristics	Age range was 4 to 18 years, the mean age was 11.7 years. 18 patients were male, 27 were female.		
Recruitment	Patients attending epilepsy clinic at clinical Research Centre, University of Virginia Hospital.		
Setting	Clinical research centre, Uni of Virginia hosp. USA.		
Interventions/ Test/ Factor being investigated	Divided previously untreated (drug naïve) from refractory into two groups. Collected baseline data then randomised to either: VPA and placebo ESM, then (crossover of non-responder) ESM and placebo VPA) or vice versa.		
Comparisons	Group 1: Valproic acid (VPA) and placebo ethosuximide (ESM) then ethosuximide and valproic acid placebo. Group 2: vice versa.		
Length of Study/ Follow-up	Not reported.		
Outcome measures studied	In previously untreated patients: seizure free, side effects. In refractory patients: patients who had an 80% reduction in number of seizures.		
Results	<p>Group 1: VPA started on a daily dose of 15 to 20 mg/kg, 5 days later this was increased to a maximum of 30 mg/kg if 12 hour telemetered EEG showed generalised spike wave discharges. ESM started on a daily dose of 250-1500 mg.</p> <p>Group 2: VPA started on a daily dose of 12.5 to 20 mg/kg, increasing every 2 days for 2 weeks to a maximum of 60 mg/kg. ESM started on a daily dose of 250-1500 mg.</p> <p>Patients were initially in hospital for the first 10 days and were then followed every 2 weeks for each drug.</p> <p>The patients were split into two groups within the treatment groups, those who were previously untreated with anti-absence drugs and those who were not responsive to the currently available anti-absence drugs.</p> <p>Patients who did not respond to the first drug or who has serious adverse effects crossed over to the second drug.</p> <p>Previously untreated patients: Seizure free: 6 out of 7 patients who received VPA first became seizure free. 4 out of 9 patients who received ESM first became seizure free . 3 out of 5 patients who received VPA second became seizure free. 2 out of 2 patients who received ESM second became seizure free.</p> <p>Side effects Nausea was reported in 5 out of 12 patients in VPA group and in 3 out of 11 patients in the ESM group. Vomiting was reported in 1 out of 12 patients in VPA group and in 3 out of 11 patients in the ESM group. Drowsiness was reported in 4 out of 12 patients in VPA group and in 5 out of 11</p>		

patients in the ESM group.
Headache was reported in 1 out of 12 patients in VPA group and in 2 out of 11 patients in the ESM group.
Leukopenia was reported in 2 out of 12 patients in VPA group and in 3 out of 11 patients in the ESM group.
Thrombocytopenia was reported in 2 out of 12 patients in VPA group and in 0 out of 11 patients in the ESM group.

Refractory patients:

80% response:

3 out of 15 patients who received VPA first had an 80% response rate. 4 out of 14 patients who received ESM first had an 80% response rate.

2 out of 10 patients who received VPA second had an 80% response rate. 5 out of 12 patients who received ESM second had an 80% response rate.

Safety and adverse effects

Nausea, vomiting, drowsiness, headache, Leukopenia, and thrombocytopenia in previously untreated patients (see results).

Does the study answer the question?

The authors discuss that it is difficult to isolate the efficacy of VPA in refractory patients who were taking ESM and other medications. This was supported by the fact that naïve patients showed a statistically significant response to VPA treatment (9 became completely seizure free and 3 did not), whereas refractory patients showed a rather complex response pattern without a statistically significant correlation between EEG findings and VPA treatment.

Effect due to factor in study?

No. No power calculation given. Methodology very confusing. They have two groups receiving the same drugs but one at slightly different starting dosage for no apparent reason. Also split up patients by drug naïve/refractory, by comparison, and then by the crossover. Methodology poor.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Question: How effective and cost-effective are anti-epileptic drugs for myoclonic seizures

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Steinhoff BJ;Ueberall MA;Siemes H;Kurlemann G;Schmitz B;Bergmann L;

The LAM-SAFE Study: lamotrigine versus carbamazepine or valproic acid in newly diagnosed focal and generalised epilepsies in adolescents and adults

Ref ID 4668

2005

Study Type	Randomised Controlled Trial	Funding	Sponsored by GSK.
Number of participant	Focal Epilepsy group (FE) CBZ n=88 LTG n=88 Generalised Epilepsy Group (GE) VPA n= 30 LTG n=33		
Inclusion/Exclusion Criteria	Adolescents and adults aged ≥ 12 years. Seizure classification, EEG data, age at onset of the disease and syndrome classification were anonymously sent to one of the investigators, who if agreed with the syndrome classification would allow patients to continue. Three different epilepsy syndromes (juvenile absence epilepsy, juvenile myoclonic epilepsy, epilepsy with generalised tonic-clonic seizures on awakening) were included.		
Patient Characteristics	Mean ages (SD): FE group CBZ 43.1 ± 17.3 ; LTG 46.6 ± 18.8 GE group LTG 22.3 ± 13.0 ; VPA 23.3 ± 10.7		
Recruitment	Not reported.		
Setting	Germany. Secondary Care		
Interventions/ Test/ Factor being investigated	LTG versus CBZ or VPA in newly diagnosed focal and generalised epilepsies.		
Comparisons	LTG versus CBZ or VPA.		
Length of Study/ Follow-up	24-26 weeks.		
Outcome measures studied	percentage of seizure-free patients between weeks 17 and 24 was the primary efficacy outcome. Overall retention rates based on lack of efficacy or adverse events, adverse events and tolerability.		
Results	FE group Between treatment weeks 17 and 24, 94.3% of the CBZ patients (83/88) and 88.6% of the LTG patients (78/88) were seizure-free during that last period of study. Excluding the titration phase patients, the number of patients who stayed seizure-free during the whole study period without seizures during the titration phase was 73 (81.8%) with CBZ and 62 (70.5%) with LTG. The difference between CBZ and LTG was not significant. GE group (not extracted as we cannot tell which subtype or syndrome). Subgroup of patients with myoclonic seizures: 10 patients in the LTG group (30.3%) and 4 patients in the VPA group (13.3%). Among these patients 3/10 (30%) became seizure free while on LTG and 3/4 (75%) became seizure-free on VPA. No statistical data was given, but difference between VPA and LTG was not significant. Withdrawal due to lack of efficacy CBZ (FE group) n=0 LTG (FE group) n=1 LTG (GE group) n=2		

Safety and adverse effects	<p>VPA (GE group) n=0</p> <p>Withdrawal due to AE: CBZ (FE group) n=17 LTG (FE group) n=7 LTG (GE group) n=2 VPA (GE group) n=1</p> <p>Adverse Events: CBZ (FE group) (n=88) Fatigue 38 (43.2%) Amnesia 9 (10.2%) Pruritis 9 (10.2%)</p> <p>LTG (FE group) (n=88) Fatigue 13 (14.8%)</p> <p>LTG (GE group) n=33 Erythematous rash 4 (12.1%)</p> <p>LTG (both groups) (n=121) Fatigue 16 (13.2%)</p> <p>Valproate (GE group) (n=30) Increased appetite 7 (23.3%) Fatigue 5 (16.7%) Weight Increase 5 (16.7%)</p>
Does the study answer the question?	Reports on the effectiveness of LTG in a FE and GE group.
Effect due to factor in study?	No blinding. No clear inclusion/exclusion criteria, unclear risk of bias in this study.
Consistency of results with other studies?	
Directly applicable to guideline population?	Population was partially direct, as the GE group results were mainly amalgamated. Intervention direct to the question.

Internal Validity

Question: How effective and cost-effective are anti-epileptic drugs for primary generalised tonic-clonic seizures

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Bill PA;Vigonius U;Pohlmann H;Guerreiro CA;Kochen S;Saffer D;Moore A;

A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy

Ref ID 4726

1997

Study Type	Randomised Controlled Trial	Funding	International Adult Oxcarbazepine/Phenytoin Trial Group and Novartis Pharma
Number of participant	287 total: 143 to OXC and 144 to PHT		
Inclusion/Exclusion Criteria	Inclusion: Ages 16-65 years with newly diagnosed epilepsy with two seizures separated by at least 48 hours within 6 months before trial Exclusion: No AED drug except for emergency treatment; Pregnancy risk, status, psychiatric illness or mental retardation, progressive neurological disorder, alcoholism, drug abuse or significant organic disease.		
Patient Characteristics	OXC (n=143)	PHT (n=144)	
Age (mean; range)	27.1(16-63)yrs	26.6(15-91)yrs	
Gender (M/F)	82/61	92/52	
Race (Cauc/B/Other)	72/22/49	68/23/53	
Body wt.	63.6 (41-104)kg	64.9 (43-101)kg	
Recruitment	Unknown		
Setting	Argentina, Brazil, Mexico and South Africa		
Interventions/ Test/ Factor being investigated	Use of oxcarbazepine vs. phenytoin as monotherapy in newly diagnosed epilepsy patients		
Comparisons	oxcarbazepine vs. phenytoin		
Length of Study/ Follow-up	A flexible titration period of 8 weeks followed by 48 weeks of maintenance treatment		
Outcome measures studied	The primary efficacy variable was the proportion of seizure free patients who had at least one seizure assessment during the maintenance period. Secondary outcomes: Treatment group differences in time and rate of premature discontinuation		
Results	OXC (n=118)	PHT (n=119)	P-value
Seizure frequency per week: Mean/median	0.08/0	0.06/0	p=0.72
Total number of seizures mean/median	3.57/0	2.13/0	
Number of patients with:			
No seizures	70	69	
1 seizure	17	20	
2-15 seizures	26	26	
16-50 seizures	3	4	
More than 50 seizures	2	0	
Five patients receiving OXC and 16 patients receiving PHT treatment were withdrawn due to adverse experiences. There was a statistically significant difference between groups in favour of the OXC treatment (p=0.02). There was no significant treatment difference due to premature discontinuations (p=0.63). Physicians and patients' overall assessment of tolerability on a 4 point scale, favoured the OXC treatment (p=0.032 for physicians and p=0.026 for patients).			

Safety and adverse effects	5 patients in the OXC group and 16 in the PHT group discontinued for tolerability reasons. The most common side effects were somnolence, headache, dizziness, nausea, rash.
Does the study answer the question?	This trial provides support for the efficacy and safety of OXC as first line treatment in adults with PS
Effect due to factor in study?	Yes
Consistency of results with other studies?	See GRADE
Directly applicable to guideline population?	See GRADE
Internal Validity	Small sample size and high dropout rate

Biton V;Sackellares JC;Vuong A;Hammer AE;Barrett PS;Messenheimer JA;

Double-blind, placebo-controlled study of lamotrigine in primary generalized tonic-clonic seizures

Ref ID 457

2005 Dec 13

Study Type	Randomised Controlled Trial	Funding	Funded by GlaxoSmithKline, manufacturer of Lamotrigine
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Number of participant 184 entered into baseline phase
Lamotrigine: 58 entered the escalation phase
Placebo: 59 entered escalation phase

Inclusion/Exclusion Criteria

Inclusion criteria: At least 2yrs of age, weighing at least 13Kg, diagnosis of epilepsy with PGTC seizures (classified by the International Classification of Seizures), history of PGTC seizures with no focal onset, at least 3 PGTC seizures during the 8 week baseline study phase and at least 1 PCGT seizure in each 4 week period of the baseline phase, and receiving 1 or 2 antiepileptic drugs at a stable dose for at least 4 weeks before screening.

Exclusion criteria: History of partial seizures or interictal expression of partial seizures as revealed by EEG. Diagnosis of Lennox-Gastaut syndrome; use of any investigational drug within 30 days of study entry or previous exposure to lamotrigine; pregnancy, breastfeeding, attempting to become pregnant or being capable of bearing children but not using acceptable contraception; following the ketogenic diet; presence of a disease or condition that could interfere with the study conduct; abuse of alcohol or other substances; chronic treatment with medication that could influence seizure control; or planned vagal nerve stimulation or surgery to control seizures during the study.
(No further details or definitions provided).

Patient Characteristics

Lamotrigine vs Placebo:
Mean age: 26.9 vs. 24.9 years
Age range: 2 to 53 vs. 2 - 55 years
Female: n=29 (50%) vs. n=26 (44%)
Race: White 57% vs. 47%, Black 16% vs. 17%, Hispanic 28% vs. 36%
Age stratum: 2 to 12 yrs 21% vs. 19%, >12 yrs 79% vs. 81%
Mean age at first seizure: 11.9 vs. 12.1
Median number of all seizures per month: 2.3 vs. 3.0
Seizure classification*: tonic-clonic 100% vs 100%, absence 31% vs. 34%, myoclonic 29% vs. 27%, Other (clonic, tonic, atonic, unclassified) 15% vs. 17%
*a patient could have more than one generalised seizure type. Myoclonic seizures were counted as days of myoclonus.
Antiepileptic regimen at study entry: included valproate 43% vs. 47%, included an enzyme-inducing antiepileptic drug 47% vs. 41%, included another anticonvulsant 10% vs. 12%
No. of antiepileptic drugs at study entry: one drug 50% vs. 59%, two drugs 50% vs. 41%

Recruitment Not reported.

Setting	USA. No further details provided
Interventions/ Test/ Factor being investigated	Study comprised a baseline phase, an escalation phase during which study lamotrigine/placebo were titrated to a target dose and a maintenance phase where doses of lamotrigine/placebo and concomitant antiepileptic drugs were maintained.
Comparisons	Comparison between treatment (lamotrigine) and placebo
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Seizure frequency: \geq 25% reduction, \geq 50% reduction, \geq 75% reduction Patient and investigator ratings Tolerability
Results	<p>Primary outcomes: Seizure frequency: Median seizure counts during the baseline phase did not differ between the lamotrigine and placebo group for PGTC seizure ($p=0.325$) or for all generalised seizures ($p=0.297$).</p> <p>Significantly larger median reductions in seizure frequency occurred during the escalation phase, the maintenance phase and the escalation and maintenance phases combined for PGTC seizures and all seizures in patients treated with lamotrigine compared to placebo ($p<0.05$).</p> <p>During the combined escalation and maintenance phases, median reduction in seizure frequency was 66.5% with lamotrigine compared to 34.2% with placebo ($p=0.006$) for PGTC seizures, and 46.8% with lamotrigine compared to 15.9% with placebo for all generalised seizures ($p=0.04$).</p> <p>During the maintenance phase and the escalation and maintenance phase combined, significantly more patients in the lamotrigine group compared to the placebo group experienced greater than or equal to a 75% and 50% reduction from the baseline phase in frequency of PGTC seizures ($p<0.05$).</p> <p>Significantly more patients in the lamotrigine compared to the placebo group experienced greater than or equal to a 50% reduction in all generalised seizures in the maintenance phase and greater than 75% reduction in all generalised seizures in the maintenance phase and maintenance and escalation phases combined, from the baseline phase ($p<0.05$).</p> <p>Lamotrigine versus placebo:</p> <p>\geq50% reduction in the frequency of PGTC seizures: - maintenance phase: 42/58 (72.4%) vs 29/59 (49.2%), $p<0.05$; - escalation + maintenance phase: 37/58 (63.8%) vs 23/59 (39%), $p<0.05$;</p>
Safety and adverse effects	<p>Potential deterioration of control of other seizures, but authors report that there was no evidence of this.</p> <p>Tolerability: adverse events were reported in the double-blind period in 22% of patients in the lamotrigine group and 10% of patients in the placebo group - none of these were over 10% for any one adverse event.</p>
Does the study answer the question?	<p>Yes. Authors conclude that adjunctive lamotrigine is effective at controlling PGTC seizures and all generalised seizures and the efficacy profile of lamotrigine makes it an appropriate therapeutic option when it is not possible to determine whether a patient having generalised seizures has idiopathic or focal epilepsy.</p>
Effect due to factor in study?	<p>Authors report that a sample size of 104 patients was determined to provide 80% power to detect a difference between lamotrigine and placebo of 25% in the median percent reduction from baseline in the PGTC seizures at a significance level of 0.05 and an estimated SD of 45%.</p> <p>The results are more favourable for adults, but the sample sizes for 2 to 12 year olds were too small to permit definite conclusions.</p>

Consistency of results with other studies? Yes.

Directly applicable to guideline population? Direct.

Internal Validity Allocation concealment not reported

Callaghan N;Kenny RA;O'Neill B;Crowley M;Goggin T;

A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy

Ref ID 4629

1985

Study Type Randomised Controlled Trial **Funding** Supported by grants from Labaz, Geigy and Warner-Lambert.

Number of participant 181 recruited. 102 had generalised seizures, 79 had partial seizures. Generalised tonic clonic seizures: 28 in the carbamazepine group; 37 in the phenytoin group; 37 in the valproate group.

Inclusion/Exclusion Criteria Inclusion criteria:
Previously untreated;
Recently diagnosed;
General or partial seizures;
Minimum of 2 seizures over six months period before referral for assessment;

Patient Characteristics Patients with generalised tonic clonic seizures (without focal features):

Carbamazepine vs phenytoin vs valproate:
Sex: male: 13 vs 21 vs 20; female: 15 vs 16 vs 17;
Age (year) range (mean): 4-72 (26) vs 7-69 (26) vs 5-71 (23);
Duration of seizures prior to treatment months range (median): 0-132 (18) vs 3-156 (9) vs 0-120 (9);
Duration of treatment months range (median): 3-44 (15) vs 3-42 (18) vs 3-44 (24);
Total no of seizures since the onset of and range (median): 2-1277 (4) vs 2-900 vs 2-720 (3).

Patients with partial seizures with or without secondary generalised attacks:

Carbamazepine vs phenytoin vs valproate:
Sex: male: 15 vs 12 vs 14; female: 16 vs 9 vs 13;
Age (yr) range (mean): 8-75 (28) vs 7-64 vs 6-68 (25);
Duration prior to treatment months range (median): 0-180 (12) vs 6-168 (24) vs 3-36 (12);
Duration of treatment months range (median): 3-42 (14) vs 3-47 (24) vs 3-48 (24);
Total no. of seizures since the onset of attacks range (median): 2-1095 (6) vs 3-300 (6) vs 2-732 (26).

Recruitment Not reported.

Setting Cork, Ireland.

Interventions/ Test/ Factor being investigated Assessments at seizure clinic of response to treatment and side effects documented and sample of blood taken to estimate serum AED levels.

The participants were instructed to take the drug twice daily. If they did not respond to the first preference of drug the dose of that drug was decreased by 200mg decrements of sodium valproate and carbamazepine and by 100mg phenytoin at two weekly intervals and then second preference drug was allocated from randomisation list.

CBZ was prescribed in a dosage of 600mg daily for adults and 5-10mg/kg body weight for children; phenytoin in a dose of 300mg daily for adults and 5-10mg/kg

body weight for children; sodium valproate in a dose of 600mg daily for adults and 5-10mg/kg body weight for children.

Comparisons

Carbamazepine versus phenytoin vs sodium valproate.

**Length of Study/
Follow-up**

Patients are seen at one month after prescription then intervals of one to three months, depending on how they responded to treatment.

Follow up ranged from 3 to 9 weeks.

**Outcome measures
studied**

Response to treatment: excellent control - complete freedom from seizures; good control - greater than 50% reduction in seizure frequency; poor control no response or less than 50% reduction in seizure frequency.

Results

Response in patients with generalised seizures:

Phenytoin vs carbamazepine vs valproate: Control (number (%)):

Excellent control (complete freedom from seizures): 27 (73%) vs 11 (39%) vs 22 (59%). Total 60 (59%);

Good control (greater than 50% reduction in seizure frequency): 3 (8%) vs 10 (36%) vs 7 (19%). Total 20 (20%).

Poor control (no response or less than 50% reduction in seizure frequency): 7 (19%) vs 7 (25%) vs 8 (22%). Total 22 (21%).

Phenytoin vs carbamazepine - excellent control, $p < 0.01$.

Overall patients with primary generalised attacks: 71% achieved excellent or good control.

Overall response in patients with partial seizures with or without secondary generalised attacks:

Phenytoin vs carbamazepine vs valproate: Control (number (%)):

Excellent control: 12 (57.1%) vs 11 (33.5%) vs 12 (44.4%). Total 35 (44.3%).

Good control: 4 (19%) vs 12 (38.7%) vs 9 (33.3%). Total 25 (31.6%).

Poor control: 5 (23.8%) vs 8 (25.8%) vs 6 (22.2%). Total 19 (24%).

[partial also subdivided for partial complex and simple partial].

When compared response in patients with generalised seizures and those with partial seizures, with or without secondary generalised attacks, the overall response was better in patients with generalised seizures ($p < 0.05$).

Withdrawal of treatment: 26 patients, 8 taking carbamazepine, 7 valproate and 11 phenytoin. 4 relapsed, 1 taking carbamazepine, 2 taking phenytoin and one taking sodium valproate. Not mentioned whether these were generalised or partial seizure types.

**Safety and adverse
effects**

12 patients dropped out. 10 with generalised seizures and 2 with partial seizures.

Of these 5 with generalised took phenytoin, 3 carbamazepine and 2 sodium valproate.

One with partial seizures was taking phenytoin, one carbamazepine.

**Does the study
answer the question?**

Yes.

Authors conclusion was that sodium valproate, carbamazepine and phenytoin are effective in the control of generalised and partial seizures, and that all three drugs can be prescribed as anti-convulsant of first choice. Irrespective of the drug prescribed, partial seizures were less responsive to treatment.

**Effect due to factor in
study?**

Unsure as no blinding and no power calculation given.

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?**

Yes.

Internal Validity No blinding;

Christe W;Kramer G;Vigonius U;Pohlmann H;Steinhoff BJ;Brodie MJ;Moore A;

A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy

Ref ID 4770

1997

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant 249 in total, 128 in oxcarbazepine, 121 in sodium valproate

Inclusion/Exclusion Criteria Inclusion: aged 15 to 65 years, newly diagnosed epilepsy with PS or GTCS, at least 2 seizures at least 48 hours apart in previous 6 months, no previous AED except for emergency treatment in previous 3 weeks
Exclusion: pregnancy or risk of becoming pregnant, history of status epilepticus, severe psychiatric illness or severe mental retardation, progressive neurological disorder, alcoholism or drug abuse, significant other organic disease

Patient Characteristics In the oxcarbazepine group the mean age was 32.45 years (range 15 to 65 years), 60 out of 128 were male. The mean weight was 69.9 kg (range 42 to 119 kg). 76 patients had partial seizures with or without secondary generalised seizures and 52 had generalised seizures without partial onset.

In the sodium valproate group the mean age was 32.47 years (range 15 to 64 years), 67 out of 121 were male. The mean weight was 70.2 kg (range 44 to 115 kg). 78 patients had partial seizures with or without secondary generalised seizures and 43 had generalised seizures without partial onset.

Recruitment Between November 1990 and first quarter 1995

Setting Europe, brazil, south Africa

Interventions/ Test/ Factor being investigated 300mg oxcarbazepine

Comparisons 300 mg sodium valproate

Length of Study/ Follow-up No follow up reported

Outcome measures studied Number of patients who were seizure free, side effects, withdrawal

Results The trial was conducted in Belgium, Brazil, France, Germany, Netherlands, South Africa, Spain, UK

The trial was split into two periods, an 8 week titration and 48 week maintenance period. No concomitant AEDs were allowed. During the titration period patients received 300 mg oxcarbazepine or sodium valproate, this was gradually increased depending upon response, there was no fixed titration schedule. After 8 weeks patients were on daily doses of 900 to 2400 mg oxcarbazepine or sodium valproate, this dose was continued for the maintenance period. However this dose could be changed according to response.

214 patients reached the maintenance period, of these 212 had at least 1 seizure assessment during the maintenance period and were therefore included in the results

Number of patients who were seizure free:
In the oxcarbazepine group 60 out of 106 were seizure free compared to 57 out of 106 in the sodium valproate group

In the oxcarbazepine group 46% of patients with partial seizures (with or without secondary generalised seizures) were seizure free compared to 48% of patients with partial seizures (with or without secondary generalised seizures) in the sodium valproate group

In the oxcarbazepine group 72% of patients with generalised seizures (without partial onset) were seizure free compared to 62% of patients with generalised seizures (without partial onset) in the sodium valproate group

Withdrawal:

A total of 52 patients in the oxcarbazepine group withdrew compared to 41 in the sodium valproate group. In the oxcarbazepine group 15 patients withdrew due to adverse events compared to 10 in the sodium valproate group.

In the oxcarbazepine group 6 withdrew due to allergic reaction, 1 due to pregnancy, 1 due to nausea, 1 due to drowsiness, 5 due to other adverse experiences, 14 due to non-compliance, 6 due to unsatisfactory therapeutic effect, 4 due to lost to follow up, 7 due to protocol violation, 3 due to administrative reasons, 2 due to concomitant illness and 1 due to death.

In the sodium valproate group 4 withdrew due to hair loss, 2 due to pregnancy, 2 due to nausea, 5 due to other adverse experiences, 7 due to non-compliance, 6 due to unsatisfactory therapeutic effect, 7 due to lost to follow up, 3 due to protocol violation, 5 due to administrative reasons, 2 due to concomitant illness, and 1 due to abnormal laboratory results.

Side effects:

In the oxcarbazepine group 115 out of 128 had at least 1 adverse event compared to 106 out of 121 in the sodium valproate group

Safety and adverse effects

In the oxcarbazepine group 115 out of 128 had at least 1 adverse event compared to 106 out of 121 in the sodium valproate group. In the oxcarbazepine group 15 patients withdrew due to adverse events compared to 10 in the sodium valproate group.

Does the study answer the question?

There was no significant difference in the number of patients becoming seizure free, withdrew or had at least 1 adverse event between the oxcarbazepine group and the sodium valproate group.

Effect due to factor in study?

Certain, as the methodology of the study was robust and the final sample size had the statistical power to detect an effect of the study intervention.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Guerreiro MM;Vigonius U;Pohlmann H;de M;Fejerman N;Antoniuk SA;Moore A;

A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy

Ref ID 4615

1997

Study Type Randomised Controlled Trial **Funding** None reported

Number of participant 193 in total, 97 in oxcarbazepine, 96 in phenytoin

Inclusion/Exclusion Criteria Inclusion: aged 5 to 18 years, newly diagnosed epilepsy with PS or GTCS, at least 2 seizures at least 48 hours apart in previous 6 months, no previous AED except for emergency treatment in previous 3 weeks

Exclusion: pregnancy or risk of becoming pregnant, history of status epilepticus, severe psychiatric illness or severe mental retardation, progressive neurological disorder, alcoholism or drug abuse, significant other organic disease

Patient Characteristics In the oxcarbazepine group the mean age was 10.22 years (range 5 to 17 years), 41 out of 97 were male. 80 were Caucasian, 11 were black, 6 were of other race. The mean weight was 36.4 kg (range 16 to 72 kg). 73 patients had partial seizures with or without secondary generalised seizures, 22 had generalised seizures without partial onset and 2 had no main type of seizure. 18 patients had localization-related idiopathic syndrome, 7 had localization-related symptomatic syndrome, 46 had localization-related cryptogenic syndrome, 11 had generalised idiopathic syndrome, 6

had generalised cryptogenic or symptomatic syndrome, 2 had had generalised symptomatic syndrome, 6 had other syndromes and 1 was not classified.

In the phenytoin group the mean age was 10.85 years (range 6 to 17 years), 50 out of 96 were male. 80 were Caucasian, 6 were black, 10 were of other race. The mean weight was 40.7 kg (range 21 to 96 kg). 78 patients had partial seizures with or without secondary generalised seizures, 17 had generalised seizures without partial onset and 1 had no main type of seizure. 20 patients had localization-related idiopathic syndrome, 5 had localization-related symptomatic syndrome, 50 had localization-related cryptogenic syndrome, 11 had generalised idiopathic syndrome, 5 had generalised cryptogenic or symptomatic syndrome, 1 had had generalised symptomatic syndrome, and 4 had other syndromes.

Recruitment	Between 1991 and first quarter 1995
Setting	Brazil and Argentina
Interventions/ Test/ Factor being investigated	300mg oxcarbazepine
Comparisons	100 mg phenytoin
Length of Study/ Follow-up	No follow up reported
Outcome measures studied	Number of patients who were seizure free, side effects, withdrawal
Results	<p>The trial was split into two periods, an 8 week titration and 48 week maintenance period. No concomitant AEDs were allowed. During the titration period patients received 150 mg oxcarbazepine or 50 mg phenytoin, this was gradually increased depending upon response, there was no fixed titration schedule. After 8 weeks patients were on daily doses of 450 to 2400 mg oxcarbazepine or 150 to 800 mg phenytoin, this dose was continued for the maintenance period. However this dose could be changed according to response.</p> <p>161 patients reached the maintenance period, of these 158 had at least 1 seizure assessment during the maintenance period and were therefore included in the results</p> <p>Number of patients who were seizure free: In the oxcarbazepine group 49 out of 81 were seizure free compared to 46 out of 77 in the phenytoin group</p> <p>In the oxcarbazepine group 60% of patients with partial seizures (with or without secondary generalised seizures) were seizure free compared to 62% of patients with partial seizures (with or without secondary generalised seizures) in the phenytoin group</p> <p>In the oxcarbazepine group 59% of patients with generalised seizures (without partial onset) were seizure free compared to 54% of patients with generalised seizures (without partial onset) in the phenytoin group</p> <p>Withdrawal: In total 24 patients withdrew from the oxcarbazepine group compared to 34 in the phenytoin group. In the oxcarbazepine group 8 patients withdrew due lost to follow up, 2 due to adverse events, 6 due to non-compliance, 4 due to unsatisfactory therapeutic effect, 3 due to protocol violation and 1 due to concomitant illness In the phenytoin group 9 patients withdrew due lost to follow up, 14 due to adverse events, 5 due to non-compliance, 3 due to unsatisfactory therapeutic effect, 2 due to protocol violation and 1 due to discontinuations at baseline</p> <p>Side effects: In the oxcarbazepine group 79 out of 96 had at least 1 adverse event compared to 84 out of 94 in the phenytoin group</p>
Safety and adverse effects	In the oxcarbazepine group 79 out of 96 had at least 1 adverse event compared to 84 out of 94 in the phenytoin group. In the oxcarbazepine group 2 patients withdrew due to adverse events compared to 14 in the phenytoin group.

Does the study answer the question? There was no significant difference in the number of patients becoming seizure free between the oxcarbazepine group and the phenytoin group. More patients in the phenytoin group experienced side effects and more patients withdrew from the phenytoin group due to adverse events compared to the oxcarbazepine group.

Effect due to factor in study? Yes.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Ramsay RE;Widler BJ;Murphy JV;Holmes GL;Uthman B;Slater J;

Efficacy and safety of valproic acid versus phenytoin as sole therapy for newly diagnosed primary generalised tonic-clonic seizures.

Ref ID 4682

1992

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant N=86 Valproate and n=50 Phenytoin.

Inclusion/Exclusion Criteria Inclusion: only patients with newly diagnosed primary Generalised Tonic-Clonic Seizures (GTCS); at least 2 GTCS occurred within 14 days of starting the study; and that no antiepileptic agents had been administered previously.
Exclusion: presence of neurological disease other than epilepsy or; evidence for focality to the epilepsy, either by history, neurologic examination, or EEG criteria.

Patient Characteristics Although the study was restricted to patients with GTCS, some patients also experienced seizures of other types (i.e., atonic, myoclonic, or absence seizures). There was a greater representation of coexistent seizure types in the valproate groups. Seventeen patients in the valproate group and only one in the Phenytoin group had other generalised seizure types (myoclonic, absence, or atonic). The mean age was 21.1 years in the valproate group and 20.6 in the Phenytoin group.

Recruitment Not reported. 16 participating centres.

Setting Outpatient setting.

Interventions/ Test/ Factor being investigated Pharmacological interventions. Valproate versus Phenytoin. Valproate was started at 10-15mg/kg daily; the drug was given as 250mg capsules of Depakene. Phenytoin was started at 3-5mg/kg daily and was given as 100mg capsules of Dilantin. The dosage was gradually increased thereafter until trough serum concentrations of at least 50mg/ml of valproate or 9 mg/ml of Phenytoin were reached. Dosage was titrated depending on the occurrence of seizures or side-effects.

Comparisons Valproate versus Phenytoin.

Length of Study/ Follow-up None reported.

Outcome measures studied Seizure recurrence rates, serum drug levels and adverse events.

Results Of the 136 patients originally enrolled in the study, 10 were none valuable. Eight were found to have partial seizures. Three of these patients had evidence of both generalized and partial seizures. Additional analysis was done excluding patients found to have partial seizures.

The 6 month recurrence rates for tonic-clonic seizures were 49± 6% for patients with spike-wave abnormalities and 24± 7% for those without spike-wave abnormalities

(p=0.031). In this group, the 6 month recurrence rates for tonic-clonic seizures were 36± 6% for the valproate group and 47 ± 9% for the Phenytoin group (mean ± SEM, p=NS). In the 77 patients with generalised spike-wave abnormalities, the 6 month recurrence rates for tonic-clonic seizures were 42 ± 8% for the valproate group and 63 ± 11% for the Phenytoin group (p=NS).

Early termination n=26 for the valproate group and n=15 in the Phenytoin group (this includes withdrawal due to side-effects, which is listed below).

Safety and adverse effects

Fourteen percent of the Phenytoin group (n=50) withdrew due to adverse events compared to 4% of the valproate group (n=86). The only statistically significant difference was the higher percentage of patients in the Phenytoin group with low serum glucose (29% vs. 13% in the valproate group; p=0.037). Other adverse events included 12% of nausea in the valproate group compared to 4% in the Phenytoin (p=0.210), and 9% somnolence in the valproate group compared to 10% in the Phenytoin group (p>0.999).

Does the study answer the question?

No significant difference in the efficacy or safety of valproate and Phenytoin in the treatment of primary GTCS.

Effect due to factor in study?

No.

Consistency of results with other studies?

Directly applicable to guideline population?

Yes.

Internal Validity

Open design.

Rastogi P;Mehrotra TN;Agarwala RK;Singh VS;

Comparison of sodium valproate and phenytoin as single drug treatment in generalised and partial epilepsy

Ref ID 4662

1991

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant 94 - 49 received sodium valproate and 45 received Phenytoin

Inclusion/Exclusion Criteria Inclusion: Patients with at least 2 fits per month

Patient Characteristics 70 males and 24 females ranging in age from 8-52 years.

Recruitment Not described

Setting Epilepsy Clinic at SVBP Hospital, Meerut India

Interventions/ Test/ Factor being investigated Sodium valproate 15 mg/kg/day in 3 divided doses with increments as needed; Phenytoin in dose of 5 mg/kg/day as a single bedtime dose and increased as needed

Comparisons Sodium valproate vs. Phenytoin for control of seizures

Length of Study/ Follow-up None reported.

Outcome measures studied Seizure reduction: excellent (100% reduction), good (75-99% reduction), fair (50-74% reduction) and poor (less than 50% reduction).

Results

Sodium Valproate Response					
Seizure Type	Patients (49)	Excellent	Good	Fair	Poor
Tonic Clonic	28	16(57%)	8(29%)	3(10%)	1(4%)
Tonic	5	2 (40%)	2(40%)	1(20%)	--
Myoclonic	2	--	2(100%)	--	--
Simple partial	8	5(62.5%)	2(25%)	1(12.5%)	--
Complex partial	3	--	1(33.3%)	--	2(66.7%)
Sec. gen. of Partial seizures	3	1(33.3%)	2(66.7%)		

Phenytoin Response					
Seizure Type	Patients (49)	Excellent	Good	Fair	Poor
Tonic Clonic	27	18(67%)	7(26%)	2(7%)	--
Tonic	5	3 (60%)	1(20%)	1(20%)	--
Simple partial	8	2(25%)	4(50%)	1(12.5%)	1(12.5%)
Complex partial	1	--	--	1(100%)	--
Sec. gen. of Partial seizures	4	--	1(25%)	3(75%)	

Safety and adverse effects

The most common side effects seen with valproate included GI disturbances (12%), drowsiness (6.12%), and weight gain (2.04%). Side effects with phenytoin included gum hyperplasia (17.7%), nystagmus (13.33%), ataxia (2.2%), GI disturbances (4.44%) and drowsiness(4.44%).

Does the study answer the question?

It appears that while sodium valproate and Phenytoin were equally effective in controlling generalised epilepsy, valproate was a better drug for controlling partial seizures.

Effect due to factor in study?

Yes

Consistency of results with other studies?

See GRADE

Directly applicable to guideline population?

See GRADE

Internal Validity

Allocation concealment

Richens A;Davidson DL;Cartlidge NE;Easter DJ;

A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult EPITEG Collaborative Group

Ref ID 123

1994

Study Type Randomised Controlled Trial

Funding Unknown.

Number of participant 140 in sodium valproate (SV) arm and 141 in the carbamazepine (CBZ) arm.

Inclusion/Exclusion Criteria

Inclusion: Idiopathic generalised tonic clonic seizures or partial seizures with or without generalisation with two seizures in the previous six month. Patients had to be over age 16. Excluded: Patients with an accompanying renal, hepatic or CNS disorder, abnormal liver function tests, low platelet count or other blood dyscrasia; with absences or myoclonic jerks alone; females who were pregnant, lactating or planning a pregnancy. No other anticonvulsants were permitted.

Patient Characteristics

The distribution of age, sex, weight, EEG, medical history, intellectual status, seizure type, and seizure frequency was similar in each treatment group. The mean age of SV and CBZ groups was 33 years and 34 years respectively.

Recruitment

Not discussed.

Setting

22 outpatient clinics in the United Kingdom.

Interventions/ Test/ Factor being investigated The long term efficacy and tolerability of SV and CBZ in untreated newly diagnosed adults.

Comparisons SV vs. CBZ.

Length of Study/ Follow-up Three years.

Outcome measures studied Seizure remission (length of time patient was seizure free).

Results There was no difference between SV and CBZ in the 12 month remission rates in patients with primary generalised seizures. In partial seizures, similar overall 12 month remission rates were achieved for each treatment (SV 72% and CBZ 76%) by the end of the three year trial. Patients with primary generalised seizures had higher 12 month remission rates on SV (76%) than on CBZ (62%, RR=1.41, 95% CI 0.91-2.18). Patients with partial seizures had similar overall remission rates (62% vs. 66%) on either drug. Neither difference was statistically significant.

Study reported that those who received sodium valproate were significantly more likely to remain on the treatment than those who received carbamazepine (RR=0.34, CI 0.16 -0.72) but the figures were not given to report withdrawal.

Safety and adverse effects Skin rashes occurred significantly more often in CBZ patients than in SV patients ($p < 0.05$) and CBZ was associated with higher withdrawal rates because of adverse events (15% vs. 5%) in the first six months, including dizziness, headaches and ataxia - all non significant. Drug events with SV included weight gain ($p < 0.05$). Tremor, alopecia and appetite increase.

Does the study answer the question? SV and CBZ were both associated with a high degree of overall seizure control regardless of seizure type and both have good long term tolerability in adult patients with newly diagnosed epilepsy.

Effect due to factor in study? Yes.

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE.

Internal Validity

Steiner TJ;Dellaportas CI;Findley LJ;Gross M;Gibberd FB;Perkin GD;Park DM;Abbott R;

Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin

Ref ID 4705

1999

Study Type Randomised Controlled Trial **Funding** Wellcome Foundation Ltd.

Number of participant 181 patients with newly diagnosed untreated partial seizures or secondarily or primary generalised tonic-clonic seizures were randomised to two treatment groups. One group (n = 86) received LTG titrated over 6 weeks from a starting dose of 100 mg/day. The other (n = 95) received PHT titrated from 200 mg/day.

Inclusion/Exclusion Criteria Inclusion: ages 14-75 after two or more partial, secondarily generalised or primary generalised tonic-clonic seizures in the previous 6 months
Exclusion: absence seizures; previous AEDs; clinically significant abnormal lab values; other chronic medical disorders, severe mental subnormality; abuse of alcohol and pregnancy or risk of pregnancy.

Patient Characteristics	LTG, n=86	PHT, n=95	All, n=181
Male/female (%)	55/45	57/43	56/44
Age (yr)			
Median	28 (13-70)	27 (13-74)	28(13-74)
Weight (kg)			

	Median	68	68	68
	Age at first seizure (yr)			
	Median	25	25	25
Recruitment	Unknown			
Setting	UK (authors from 6 settings)			
Interventions/ Test/ Factor being investigated	Comparison of LTG with PHT monotherapy for efficacy and tolerability in previously untreated patients with newly diagnosed epilepsy			
Comparisons	Comparison between lamotrigine and Phenytoin.			
Length of Study/ Follow-up	6 week titration and a treatment phase for less than or equal to 48 weeks.			
Outcome measures studied	Primary: Percentages of patients remaining on treatment and seizure free and the numbers of seizures with each treatment during the last 24 and 40 weeks of the study. Secondary: time to first seizure and time to discontinuation.			
Results	<p>The percentages of patients remaining on each treatment and seizure free during the last 24 and 40 weeks of the study, and times to first seizure after the first 6 weeks of treatment (dose-titration period), did not differ significantly between the treatment groups. Time to discontinuation, a composite index of efficacy and safety, likewise did not distinguish between treatments.</p> <p>In last 24 weeks: for primary generalised tonic-clonic the proportion of seizure-free participants was 19 (44%) in the Lamotrigine group vs 17 (34%) in the Phenytoin group. 95% CI for difference was -10.30%.</p> <p>In last 40 weeks: for primary generalised tonic-clonic the proportion of seizure-free participants was 13 (30%) in the Lamotrigine group vs 16 (32%). 95% CI for difference was -21.17%.</p> <p>For primary generalised tonic-clonic the time to first seizure after the first 6 weeks of treatment was 1.5 (95% CI 0.7-3.2).</p> <p>Adverse events led to discontinuation of 13 (15%) patients from LTG and 18 (19%) from PHT.</p> <p>Adverse events affected more than 10% of patients:</p> <p>LTG :</p> <p>Asthenia 14/86*</p> <p>Rash 12/86</p> <p>Headache: 9/86</p> <p>Dizziness: 8/86</p> <p>Somnolence: 6/86*</p> <p>Ataxia: 0/86</p> <p>PHT</p> <p>Asthenia 28/95*</p> <p>Rash 12/95</p> <p>Headache: 9/95</p> <p>Dizziness: 8/95</p> <p>Somnolence: 6/95*</p> <p>Ataxia: 0/95</p> <p>* P<0.05</p> <p>A quality-of-life instrument, the SEALS inventory, favoured LTG. Patients taking PHT showed the biochemical changes expected of an enzyme-inducing drug, whereas those taking LTG did not.</p>			
Safety and adverse effects	Adverse events led to discontinuation of 13 (15%) patients from LTG and 18 (19%) from PHT. The adverse-event profile for LTG was dominated by skin rash [discontinuation of 10 (11.6%) patients compared with five (5.3%) from PHT] rather than central nervous system side effects: asthenia, somnolence, and ataxia were each significantly more frequent in the PHT group. The high rate of rash with LTG was probably due to the high starting dose and may be avoidable.			

Does the study answer the question? LTG and PHT monotherapy were similarly effective against these seizure types in patients with newly diagnosed epilepsy. LTG was better tolerated, more frequently causing rash, but with a lower incidence of central nervous system side effects

Effect due to factor in study? Yes

Consistency of results with other studies? See GRADE

Directly applicable to guideline population? See GRADE

Internal Validity High discontinuation rate

Turnbull DM;Howel D;Rawlins MD;Chadwick DW;

Which drug for the adult epileptic patient: phenytoin or valproate?

Ref ID 4672

1985

Study Type Randomised Controlled Trial **Funding** Sanofi

Number of participant 140 in total sample with 70 in each arm, valproate and Phenytoin respectively.

Inclusion/Exclusion Criteria Inclusion: a history of two or more seizures in the previous three years; over age 16 and had received no previous anticonvulsant.

Patient Characteristics	Valproate (70 patients)	Phenytoin (70 patients)
Age (years)	16-69 (30 median)	16-70 (30 median)
Gender		
Female	36	31
Male	34	39

Recruitment Unknown.

Setting Dept of Neurology, Royal Victoria Infirmary.

Interventions/ Test/ Factor being investigated Valproate vs. Phenytoin in newly diagnosed adult patients with epilepsy.
 PHT 100mg 3 times a day; VPA 200mg 3 times a day; if further seizures occurred medication was increased PHT depending on plasma concentration if less than 10mg/l the dose was increased by 50mg/day and if greater than 10mg/l it was increased by 25mg/day, doses were further increased until seizures stopped or adverse effects seen; valproate was increment of 1200mg/2100mg and 3000mg/day given in 3 divided doses regardless of serum concentration.

Comparisons Comparison is made between two treatments< valproate vs. Phenytoin

Length of Study/ Follow-up 48 months.

Outcome measures studied Achievement of a two year remission and 'time to first seizure'.

Results	Valproate	Phenytoin
No. of patients	70	70
No achieving 2 year remission	36	31
No controlled for <2 years	12	11
No continuing to have seizures	10	11
Idiosyncratic adverse effect requiring drug withdrawal	0	5
Death	3	3
Non-compliant or lost to follow-up	9	9

In patients with tonic clonic seizures 27 of 37 patients on valproate and 22 of 39 on Phenytoin achieved 2 year remission.

In patients with partial seizures 9 of 31 patients on valproate and 9 of 31 on Phenytoin achieved 2 year remission.

Sodium valproate and Phenytoin in the treatment of tonic clonic or partial seizures showed no significant difference in the efficacy as regards time to two year remission. However patients with a clinical history of partial seizures did significantly less well than those with a history of tonic clonic seizures only ($p < 0.025$) and to time to first seizure ($p < 0.001$). There were not figures to report time to first seizure in evidence review.

Safety and adverse effects

Valproate dose related adverse effects: tremor, irritability and restlessness and alopecia. Phenytoin dose related adverse effects: nystagmus, ataxia, tremor, diplopia and mental change. Idiosyncratic effects of Phenytoin: skin eruption, erythoderma and jaundice.

Does the study answer the question?

This study showed no major difference in efficacy between sodium valproate and Phenytoin in adults with recent onset of epilepsy.

Effect due to factor in study?

Yes

Consistency of results with other studies?

See GRADE

Directly applicable to guideline population?

See GRADE

Internal Validity

High drop out rate

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Aucamp AK;

Clobazam as adjunctive therapy in uncontrolled epileptic patients.

Ref ID 4683

1985

Study Type Randomised Controlled Trial

Funding Not reported

Number of participant 12 patients in total.

Inclusion/Exclusion Criteria Inclusion: uncontrolled longstanding epilepsy – 2 or more seizures in the 2 weeks before trial, patients were institutionalized.

Patient Characteristics All patients were institutionalized.
Age range 17 to 53 years. 50% were male, 9 patients had generalised tonic-clonic seizures, 3 had focal with secondary generalised seizures
Patients with generalised tonic-clonic seizures: 2 were taking carbamazepine, 3 were taking carbamazepine and diphenylhydantoin, 3 were taking carbamazepine and sodium valproate, 1 was taking diphenylhydantoin and Phenobarbital

Patients with focal with secondary generalised seizures: 1 was taking carbamazepine, 1 was taking carbamazepine and diphenylhydantoin, 1 was taking carbamazepine and sodium valproate

Recruitment Not reported.

Setting South Africa.

Interventions/ Test/ Factor being investigated Clobazam 0.5 mg/kg/day in three equal doses.

Comparisons Identical placebo.

Length of Study/ Follow-up No follow up reported.

Outcome measures studied Number of patients who were seizure free

Results Cross over trial, 9 weeks on each treatment with a 5 week wash out
Serum levels of at least one or more of the existing anticonvulsant medications were within the accepted therapeutic range, no change of dosage was allowed

Number of patients who were seizure free:
Overall:
While treated with Clobazam 8 out of 12 patients were seizure free, while on placebo 1 out of 12 patients was seizure free.

Patients with generalised tonic-clonic seizures:
While treated with Clobazam 7 out of 9 patients were seizure free, while on placebo 1 out of 9 patients was seizure free.

Patients with focal with secondary generalised seizures:
While treated with Clobazam 1 out of 3 patients was seizure free, while on placebo 0 out of 3 patients were seizure free.

Safety and adverse effects No patients reported any side effects

Does the study answer the question? More patients became seizure free while being treated with Clobazam compared to those treated with placebo. There were no side effects reported in either treatment group

Effect due to factor in study? No.

Consistency of results with other studies?

Directly applicable to guideline population? Yes.

Internal Validity

Biton V;Montouris GD;Ritter F;Riviello JJ;Reife R;Lim P;Pledger G;

A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group

Ref ID 4708

1999

Study Type Randomised Controlled Trial **Funding** Not reported

Number of participant 80 patients in total, 39 in Topiramate group, 41 in placebo group

Inclusion/Exclusion Criteria

Inclusion: aged over 4 years, weighed over 25 kg, women had to be premenarchal or post menopausal or practicing an acceptable method of birth control, a history of PGTC seizures with or without other generalised seizure types. Patients could be receiving 1 or 2 standard AEDs. Had 3 or more PGTC seizures during the baseline period, at least 1 each 4 weeks, EEG findings consistent with generalised epilepsy but no significant other findings

Exclusion: history of partial-onset seizures, a treatable cause of seizure (e.g. metabolic disturbance, toxic exposure, active infection or neoplasm), progressive neurological disease, clinically diagnosed Lennox-Gastaut syndrome, evidence of use of experimental device within 60 days before enrolment, treatment with acetazolamide, zonisamide, triamterene, vitamin C (>2mg per day), antacids, calcium supplements within 3 months before enrolment. A history of generalised tonic-clonic status epilepticus (within previous 3 months) while receiving appropriate AED therapy, seizures occurring only in cluster patterns, significant medical disease (within previous 2 years), psychiatric or mood disorder (within previous 6 months) attempted suicide, nephrolithiasis, malignancy, alcohol or drug abuse.

Patient Characteristics

In the Topiramate group 24 out of 39 were male. The mean age was 26.8 sd 12.8 years; the age range was 5 to 59 years; 31 were aged over 16 years old. 32 were white, 6 were black and 1 was Hispanic. The mean weight was 71.8 sd 28.5 kg, the range was 22 to 143 kg. The mean number of PGTC seizures per month was 5 (range 1 to 298). The mean number of all seizures was 15.3 (range 1-1134). 39 had tonic-clonic seizures, 13 tonic-clonic only seizures, 16 had absence seizures, 9 had tonic seizures, 8 had myoclonic seizures, 2 had drop attack seizures, 2 atypical absence seizures, 1 had colic seizures and 1 had other types of seizures. Background AEDs: 9 had one AED, 19 had two AEDs and 11 had more than two AEDs. 19 had valproic acid, 12 had Phenytoin, 11 had carbamazepine, 6 had Lamotrigine, 8 had Phenobarbital, 6 had clonazepam and 5 had gabapentin.

In the placebo group 21 out of 41 were male. The mean age was 25.6 sd 13.4 years; the age range was 3 to 50 years; 28 were aged over 16 years old. 36 were white and 5 were black. The mean weight was 61.3 sd 25.1 kg, the range was 17 to 129 kg. The mean number of PGTC seizures per month was 4.5 (range 1 to 300). The mean number of all seizures was 17.5 (range 2-79,109). 40 had tonic-clonic seizures, 13 tonic-clonic only seizures, 16 had absence seizures, 10 had tonic seizures, 8 had myoclonic seizures, 5 had drop attack seizures, 4 atypical absence seizures, 1 had colic seizures and 1 had other types of seizures. Background AEDs: 9 had one AED, 22 had two AEDs and 10 had more than two AEDs. 20 had valproic acid, 13 had Phenytoin, 9 had carbamazepine, 10 had Lamotrigine, 3 had Phenobarbital, 6 had clonazepam, 3 had gabapentin and 6 had primidone.

Recruitment Not reported.

Setting 17 sites in USA and 1 in Costa Rica.

Interventions/ Test/ Factor being investigated	Topiramate – dose based on patients weight.
Comparisons	Matching placebo.
Length of Study/ Follow-up	No follow up reported.
Outcome measures studied	Number who were seizure free, number who had 75% reduction in the number of seizures, number who had 50% reduction in the number of seizures, withdrawal, side effects.
Results	<p>20 week trial, with 8 weeks of titration and 12 week stabilization period.</p> <p>For patients weighing 25 to 33.9 kg during the titration period weeks 1 to 4 patients had 50 mg in the pm, during weeks 5 to 6 they received 50 mg twice a day; during the stabilization period weeks 7 to 8 patients received 75 mg twice a day and during weeks 9 to 20 they received 75 mg twice a day. They had a target dose of 5.2 to 7 mg/kg/day.</p> <p>For patients weighing 34 to 42.9 kg during the titration period weeks 1 to 4 patients had 50 mg in the pm, during weeks 5 to 6 they received 50 mg twice a day; during the stabilization period weeks 7 to 8 patients received 75 mg twice a day and during weeks 9 to 20 they received 100 mg twice a day. They had a target dose of 5.2 to 6.6 mg/kg/day.</p> <p>For patients weighing greater than or equal to 43 kg during the titration period weeks 1 to 4 patients had 50 mg in the pm, during weeks 5 to 6 they received 75 mg twice a day; during the stabilization period weeks 7 to 8 patients received 150 mg twice a day and during weeks 9 to 20 they received 200 mg twice a day. They had a target dose of 9.3 mg/kg/day.</p> <p>Number who were seizure free: PGTC seizures: In the Topiramate group 5 out of 39 became seizure free compared to 2 out of 40 in the placebo group.</p> <p>All generalised seizures: In the Topiramate group 2 out of 39 became seizure free compared to 0 out of 41 in the placebo group.</p> <p>Number who had 75% reduction in the number of seizures: PGTC seizures: In the Topiramate group 13 out of 39 had a 75% reduction in the number of seizures compared to 5 out of 40 in the placebo group.</p> <p>All generalised seizures: In the Topiramate group 10 out of 39 had a 75% reduction in the number of seizures compared to 3 out of 41 in the placebo group.</p> <p>Number who had 50% reduction in the number of seizures: PGTC seizures: In the Topiramate group 22 out of 39 had a 50% reduction in the number of seizures compared to 8 out of 40 in the placebo group.</p> <p>All generalised seizures: In the Topiramate group 18 out of 39 had a 50% reduction in the number of seizures compared to 7 out of 41 in the placebo group.</p> <p>Withdrawal: In the Topiramate group 5 patients withdrew, 2 due to patient choice, 1 due to limiting adverse events and 1 due to non compliance and 1 due to inadvertent premature discontinuation. In the placebo group 3 patients withdrew, 1 due to patient choice, 1 due to limiting adverse event and 1 due to lost to follow up.</p> <p>Side effects: In the Topiramate group: 26% had somnolence, 15% had anorexia, 13% had difficulty with memory, 10% had nervousness, 10% had psychomotor slowing, 41% had upper respiratory tract infection, 10% had pharyngitis, 18% had fatigue, 15% had weight loss, 13% had headache, 10% had dizziness, 10% had speech disorders and related speech problems and 10% had abdominal pain.</p> <p>In the placebo group: 15% had somnolence, 7% had anorexia, 0% had difficulty with memory, 0% had nervousness, 2% had psychomotor slowing, 32% had upper</p>

respiratory tract infection, 5% had pharyngitis, 7% had fatigue, 2% had weight loss, 20% had headache, 15% had dizziness, 2% had speech disorders and related speech problems and 5% had abdominal pain.

Safety and adverse effects

In the Topiramate group: 26% had somnolence, 15% had anorexia, 13% had difficulty with memory, 10% had nervousness, 10% had psychomotor slowing, 41% had upper respiratory tract infection, 10% had pharyngitis, 18% had fatigue, 15% had weight loss, 13% had headache, 10% had dizziness, 10% had speech disorders and related speech problems and 10% had abdominal pain.

In the placebo group: 15% had somnolence, 7% had anorexia, 0% had difficulty with memory, 0% had nervousness, 2% had psychomotor slowing, 32% had upper respiratory tract infection, 5% had pharyngitis, 7% had fatigue, 2% had weight loss, 20% had headache, 15% had dizziness, 2% had speech disorders and related speech problems and 5% had abdominal pain.

Does the study answer the question?

More patients became seizure free or had a reduction in the number of seizures when treated with Topiramate compared to those treated with placebo

Effect due to factor in study?

No.

Consistency of results with other studies?

Directly applicable to guideline population?

Yes.

Internal Validity

Allocation concealment.

Brodie MJ;Richens A;Yuen AW;

Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group

Ref ID 4808

1995 Feb 25

Study Type Randomised Controlled Trial **Funding** Supported by the Wellcome foundation.

Number of participant N= 260; n=131 lamotrigine and n=129 carbamazepine.

Inclusion/Exclusion Criteria No specific inclusion and/or exclusion criteria.

Patient Characteristics Patients 13 years and older with newly diagnosed epilepsy with partial seizures without secondary generalisation, and primary or secondary generalised tonic-clonic seizures. No patient had received previous treatment with an AED. Lamotrigine group had a median baseline seizure count of 4 (mean 36) versus 3 mean (mean 22) for the carbamazepine group.

Recruitment Not reported.

Setting 8 centres in the UK.

Interventions/ Test/ Factor being investigated Pharmacological interventions. Patients received increasing doses of identical 50mg lamotrigine or 200mg carbamazepine tablets. At the end of 4 weeks, all patients were taking 150mg lamotrigine or 600mg carbamazepine daily. During weeks 6-24 the daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant adverse events had been reported provided the drug concentration was in the lower half of the target range or lower.

Comparisons Lamotrigine versus carbamazepine.

Length of Study/ Follow-up For 48 weeks.

Outcome measures studied	time to first seizure and adverse events.
Results	<p>No significant difference between the drugs in time to first seizure after 6 weeks treatment for the whole study population (hazard ratio 0.8, 95% CI 0.6-1.2), or for the subgroup with partial seizures with or without secondary generalisation or the subgroup with primary tonic-clonic seizures.</p> <p>Percentage seizure-free (for primary generalised tonic-clonic seizures) at last 40 weeks: LTG: 37% - calculated as 22/60 CBZ: 35% - calculated as 22/62</p> <p>Percentage seizure-free (for primary generalised tonic-clonic seizures) at last 24 weeks: LTG: 47% - calculated as 28/60 CBZ: 47% - calculated as 29/62</p> <p>Percentage seizure-free (for partial seizures with or without generalisation) at last 40 weeks: LTG: 22% CBZ: 31%</p> <p>Percentage seizure-free (for partial seizures with or without generalisation) at last 24 weeks: LTG: 35% CBZ: 37%</p> <p>Percentage seizure-free (all seizures) at last 40 weeks: LTG: 26% CBZ: 29%</p> <p>Percentage seizure-free (all seizures) at last 24 weeks: LTG: 39% CBZ: 38%</p> <p>A greater proportion of the LTG group completed the study compared to the CBZ group (65 vs. 51%, p=0.018).</p>
Safety and adverse effects	<p>Adverse events: Headache 30% LTG group vs. 25% CBZ group (95% CI -6 to 16); Astenia 21% LTG group vs. 29% CBZ group (95% -18 to 3); rash 19% LTG vs. 19% CBZ group (95% CI -10 to 9); nausea 15% LTG group vs. 12% CBZ group (95% CI -3 to 14); dizziness 12% LTG vs. 17% CBZ (95% CI -13 to 4); sleepiness 12% LTG group vs. 22% CBZ group (95% CI -19 to -1); and flu-like symptoms 11% LTG group vs. 8% for the CBZ group (95% CI -3 to 11). The only significant adverse event is sleepiness.</p> <p>Nineteen patients withdrew from the LTG group (n=131) and 35 withdrew from the CBZ group (n=129).</p>
Does the study answer the question?	Similar efficacy for both LTG and CBZ. LTG seems to be better tolerated.
Effect due to factor in study?	No.
Consistency of results with other studies?	
Directly applicable to guideline population?	Yes.
Internal Validity	No ITT analysis.

Feksi AT;Kaamugisha J;Sander JW;Gatiti S;Shorvon SD;

Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. ICBERG (International Community-based Epilepsy Research Group)

Study Type	Randomised Controlled Trial	Funding	Ciba Geigy for financial and logistic support and the National Society for Epilepsy for logistic support.
Number of participant	N=302, 129 females.		
Inclusion/Exclusion Criteria	Inclusion criteria: age 6-65 years, residency in Nakuru District, a history of generalised tonic-clonic seizures (with or without other seizure types) and of more than 2 attacks in the previous year, no treatment with AEDs in the previous 3 months, no history of alcohol or drug abuse, and a strong likelihood that the patient would comply with treatment (judged by the investigator).		
Patient Characteristics	<p>All 302 patients had generalised tonic-clonic seizures (with or without other seizure types), and in 115 cases there was evidence on focal onset. Cause was established on clinical grounds alone in 23% of the patients. The mean age was 21 years. Mean duration of seizure disorder was 7 years (range 1-40). Only 26% of the patients had received AEDs.</p> <p>Generalised tonic-clonic seizures: n=179 Secondly generalised seizures: n=61 Partial with secondary generalisation: n=54 Generalised tonic-clonic and other generalised seizures: n=8</p>		
Recruitment	Via Health Worker and invitation to attend an epilepsy clinic at Nakuru Provincial General Hospital.		
Setting	Epilepsy Clinic in Kenya		
Interventions/ Test/ Factor being investigated	<p>Carbamazepine was started at a low dose and then increase fortnightly until the minimum maintenance dose was reached, whilst phenobarbitone was started at the minimum maintenance level. Dosage was increased when seizures occurred more than 3 weeks after the last increment; otherwise dosage was not changed. If seizures occurred and patients also had side-effects, the dose was either reduced to previous dosage levels, or if severe, the drug was withdrawn.</p> <p>6-10 year olds (1st Maintenance) CBZ- 400mg PB-30 mg</p> <p>11-15 year olds (1st maintenance period) CBZ- 500mg PB- 45mg</p> <p>>16 years old (1st Maintenance) CBZ- 600mg PB- 60mg</p>		
Comparisons	Carbamazepine versus phenobarbitone.		
Length of Study/ Follow-up	Up to 12 months		
Outcome measures studied	Seizure freedom, reduction/increase in seizure frequency, and adverse events.		
Results	<p>Seizure freedom at 6 to 12 months: CBZ (n=126): 65 (52%) PB (n=123): 67 (54%)</p> <p>>50% reduction in seizures CBZ (n=126): 37 (29%) PB (n=123): 28 (23%)</p> <p>N=249 (82%) completed the 12 month follow-up. The difference in drop-out rates between the two AEDs is non-significant.</p>		

Safety and adverse effects Of the 249 patients who completed the trial, 104 (CBZ: 46 and PB: 58) reported 154 adverse events.
More adverse events were reported with PB (86) than CBZ (68) ($p < 0.01$).
Deaths (with one due to paraquat intoxication, other non treatment related):
CBZ- 2
PB- 4

Does the study answer the question? The two drugs were equally effective.

Effect due to factor in study? No indication of ITT analysis in study, therefore may be biased.

Consistency of results with other studies?

Directly applicable to guideline population? Study conducted in a Kenyan population.

Internal Validity No ITT

Verity CM; Hosking G; Easter DJ;

A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. The Paediatric EPITEG Collaborative Group

Ref ID 4673

1995

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant VPA $n=130$; CBZ $n=130$. 118 VPA and 126 were evaluated on ITT basis.

Inclusion/Exclusion Criteria
Inclusion: primary generalised epilepsy or partial with or without generalisation.
5-16 years old;
Newly diagnosed epilepsy or seizures recurred after withdrawal of AEDs but not received any AEDs in 6 months prior.
Had at least 2 generalised tonic-clonic or partial seizures with/without generalisation in previous 6 months.
Exclusions:
Children with accompanying renal hepatic or other CNS disorders who had abnormal liver function tests, a low platelet count or other bloody dyscrasia;
Children with absences or myoclonic jerks alone;
Girls on contraceptive medication at entry;
No concomitant AEDs allowed during study, and if needed were withdrawn.

Patient Characteristics VPA vs CBZ:
boys 54 (mean age 9.7 years), girls 64 (mean age 9.9 years);
boys 59 (mean age 9.5 year), girls 67 (mean 9.3 years).
Mean no of seizures in 6 months prior to entry: 3 in each group.
No children over 15 years.

Recruitment Not reported.

Setting 63 outpatient clinics in UK/Ireland.

Interventions/ Test/ Factor being investigated Sodium valproate versus carbamazepine.

Comparisons Sodium valproate versus carbamazepine.

Length of Study/ Follow-up See above.

Outcome measures studied Withdrawal due to lack of efficacy and adverse events.

Results

VPA vs CBZ04/07/2010

Withdrawal due to lack of efficacy: 14/118 (12%) vs 16/126 (13%)

Withdrawal due to adverse events: /118 (7%) vs 7/126 (5%) in 1st 6 months:
14/118 vs 8/126 at 12 months.

11 further (4 VPA and 7 CBZ treatment failures due to poor seizure control and adverse events on sub-optimal drug doses.

Can't use efficacy data as not over 80% for PGTC or partial.

Over 10% incidence of adverse events:

somnolence 11/118 vs 25/126.

fatigue: 6/118 vs 13/126.

Safety and adverse effects

See results above.

Does the study answer the question?

Yes.

Effect due to factor in study?

No details of allocation concealment or blinding so uncertainty that overall effect is due to the study intervention.

Consistency of results with other studies?**Directly applicable to guideline population?**

Indirect as mixture of partial with or without secondary generalisation and primary generalised tonic clonic, majority had PGTC but not 80%.

Internal Validity

Question: How effective and cost-effective are anti-epileptic drugs for Infantile spasms

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Appleton RE;Peters AC;Mumford JP;Shaw DE;

Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms

Ref ID 4610

1999

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total: 40 patients.
Vigabatrin arm: 20 patients.
Placebo arm: 20 patients.

Inclusion/Exclusion Criteria Inclusion criteria:
Aged 1 to 20 months;
Newly diagnosed and previously untreated infantile spasms whose EEG demonstrated classic or modified hypsarrhythmia;
Infants whose parents/guardians could give informed consent and investigators thought them capable of completing a seizure diary and attending clinic as required;

Exclusion criteria:
Use of any medication, including prednisolone, hydrocortisone, or ACTH, that could be considered an AED within 2 months before entry into the study.

Patient Characteristics Placebo vs vigabatrin:

Male: 8 vs 11.
Age in months at onset of spasms: mean (range): 6 (1-15) vs 7 (2-18).
Age in months at entry into study : mean (range)*: 8 (4-17) vs 8 (5-20).
Duration of spasms in weeks before entry: mean (range): 7 (2-12) vs 6 (2-13).
EEG findings:
- typical hypsarrhythmia: 13 vs 15.
- modified hypsarrhythmia: 7 vs 5.
Denver developmental test:
- normal: 2 vs 1.
- suspect (borderline abnormal): 15 vs 14.
- untestable (severely abnormal): 0 vs 4.
- missing data: 3 vs 1.

* Only two patients were older than 12 months (17 and 12 months, respectively) on study entry.

Recruitment Not reported.

Setting Canada,Finland,France,Hungary,Holland,Serbia & UK.

Interventions/ Test/ Factor being investigated Patients were given starting dose of 50mg/kg/day of either vigabatrin or placebo and this was continued for 24 hours.
If spasms were not ceased completely the dosage was increased to 100mg/kg/day and maintained for a further 48 hours.
The investigator assessed spasm frequency and if needed increased to 150mg/kg/day.
Once a dose was established for >48 hours the dose could be changed only if there were safety concerns.
After the double-blind period (5 days) there was an open phase where dosage of vigabatrin could be altered or another AED prescribed in addition to vigabatrin.

The open phase included some of the patients who had been non-responders in the VGB treated group and the placebo group. They received vigabatrin as monotherapy or as polytherapy - with ACTH/sodium valproate or prednisolone. 15/16 of the monotherapy and 4/20 of the polytherapy group became spasm free. We will not include this data in the meta-analysis as comparing monotherapy to polytherapy is not relevant to the review.

Comparisons Comparisons between treatment and placebo.

**Length of Study/
Follow-up**

There was a five day double-blind period.
Those patients continuing with the study entered a 24-week open phase.

**Outcome measures
studied**

Outcomes: cessation of spasms; reduction in spasms; resolution of hypsarrhythmia; relapse rates.

Results

Vigabatrin vs placebo:

The last 24 hours of the double-blind period compared to baseline:

*Complete spasm control: 7 (35%) vs 2 (10%); $p=0.063$.
Average percentage reduction in spasms: 77.9% (CI 95%= 55 to 89%) vs 25.9% (CI 95%= -56 to 65%); $p=0.020$.
* >70% improvement in reduction in spasms: 8 (40%) vs 3 (15%).
No change or increase in frequency of spasms: 4 (20%) vs 9 (45%).

The last two hours of the double-blind period compared to baseline:

Average percentage reduction in spasms: 71.9% (CI 95%= 42 to 86%) vs 54.6% (CI 95% 4 to 78%).
* >70% improvement in reduction in spasms: 13 (76%) vs 11 (55%).
* The number of spasm-free patients was not recorded by the 2-hour monitoring method.

The open phase - 36 (90%) of the double-blinded patients entered the open phase, 16 (44%) from the vigabatrin group and 20 (56%) from the original placebo group. Four failed to reduce spasm frequency adequately. Five withdrew from the open phase because of lack of response to vigabatrin and two were lost to follow-up.

On completion of the open study:

Number of spasm free: 4/20 who originally randomised to receive vigabatrin monotherapy vs 11/20 originally randomised to receive placebo.

* = relevant outcomes to the guideline.

**Safety and adverse
effects**

Treatment-emergent adverse events during the double-blind phase (none withdrew): One or more adverse event occurred in: 12 (60%) vs 6 (30%). Fisher's exact test, $p=0.111$.

The most common side effect in the vigabatrin group:
- drowsiness: 8 patients.
- behaviour change (marked irritability): 1 patient.

Open phase:

24 (67%) of patients had one or more adverse event, including bronchitis (8); drowsiness (7), rhinitis (7), fever (5),k throat irritation (4), and otitis media (4). None were clinically serious and none withdrew.
One child died of acute respiratory infection and a cardiac arrest and was receiving many AEDs and the death was not considered to be related to the study drug.

**Does the study
answer the question?**

Yes.

Main conclusions of the authors: vigabatrin has shown efficacy for infantile spasms and could be considered as the drug of first choice.

They found with the 24 hour assessment of spasm frequency that vigabatrin was more effective than placebo in reducing spasms, however when they used 2 hour data this reduction was not statistically significant between the groups. This could be explained by variability of the time of day that the spasms appeared.

Spasm freedom was higher in the vigabatrin group compared with the placebo group but this did not reach statistical significance ($p=0.063$). Explanation could be that there was a short double-blind period.

**Effect due to factor in
study?**

Power: Type 1 error of 0.05 and power of 90%, 12 protocol correct patients needed in each group to show a 45% difference between the two groups, therefore allowing a drop-out rate of 20%, 15 patients were needed in each treatment group, giving a study sample of 30 patients.

Methodology was good.

Yes overall effect likely due to the study intervention.

Consistency of results with other studies?

Yes.

Directly applicable to guideline population?

Direct.

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Askalan R;Mackay M;Brian J;Otsubo H;McDermott C;Bryson S;Boyd J;Snead C;Roberts W;Weiss S;

Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms

Ref ID 604

2003

Study Type Randomised Controlled Trial **Funding** Supported in part by Bloorview Children's Hospital Foundation.

Number of participant Total: 9 patients.
Vigabatrin arm: 6
ACTH arm: 3

Inclusion/Exclusion Criteria Inclusion criteria:
Aged 3 to 16 months at onset of spasms.
Families who could comply with follow-up visits.

Exclusion criteria:
Previous exposure or known allergy to vigabatrin or corticosteroids.
A known visual disturbance.
Have a medical condition for which corticosteroids would be contraindicated.

Patient Characteristics Gender: 4 males, 5 females.
2 females and 1 male in the vigabatrin group and 3 males and 3 females in the ACTH group.
4 patients had symptomatic infantile spasms and 5 patients had idiopathic infantile spasms.

Recruitment Patients who presented to the Hospital for Sick Children in Toronto were recruited.

Setting Toronto, Canada.

Interventions/ Test/ Factor being investigated Patients were evaluated for cause of infantile spasms with CT and or MRI and metabolic, infectious and genetic work-up. Baseline psychologic evaluation and ophthalmologic assessments were performed. All participants had prolonged daytime video-EEG to capture awake and sleep states and document their infantile spasms.

The infants were categorised by aetiology (symptomatic or idiopathic) and by sex, which made up 4 possible cells, each cell was randomised to vigabatrin or ACTH using a computerised programme.

For cognitive and motor development the Bayley Scales of Infant development, Second Edition, was administered at baseline and 3, 12, and 24 months after start of treatment.

Phase 1:
ACTH group: received 150 IU/m²/day of ACTH divided into two doses given intramuscularly for a period of 1 week and then reduced to 75 IU/m²/day in a single dose for a second week.

Vigabatrin group: vigabatrin 100mg/kg/day which was increased to 150mg/kg/day divided into two doses orally by the third day and continued at that dose for the remaining 2 weeks.

Both groups had a sleep and waking EEG at end of first week and a 4 and 8 hour daytime video-EEG to capture sleep and walking state at the end of the second week to see the response to treatment.

Phase 2:
2 weeks of treatment. Responders remained in their initial group and completed tapering off for 12 weeks for ACTH or 18 months for vigabatrin.
Non-responders crossed over to the alternate drug and while tapering off the other drug (1 week).
A sleep and walking EEG was obtained for all patients at end of phase 2 (4 weeks).

Comparisons	Comparisons between treatments. Vigabatrin versus ACTH.
Length of Study/ Follow-up	4 weeks of treatment. Followed up at 2 weeks, 4 weeks, 3 months, 12 months and 24 months after beginning medication.
Outcome measures studied	Cognitive and motor development; language; autistic symptomology; cessation of spasms; resolution of hypsarrhythmia.
Results	<p>Most received treatment within 1 to 2 months of presentation. 3 patients had 3 to 6 month history of infantile spasms prior to initial evaluation. All patients had modified hypsarrhythmia prior to start of treatment.</p> <p>All patients had resolution of spasms and hypsarrhythmia on EEG after 2 weeks of treatment. But 2/3 of the ACTH group and 3/6 of the vigabatrin group continued to have moderate to severe abnormal EEGs after 2 weeks of treatment. These patients were crossed over to the alternate drug.</p> <p>Cognitive outcomes: Baseline cognitive assessment done at 5-13 months of age showed that 7/8 had mild to significant cognitive delay before starting treatment. Follow-up cognitive assessments at 19 to 34 months of age: 4 patients (including the only ACTH responder) showed improved cognitive function after treatment. All four had idiopathic infantile spasms. Of the three vigabatrin responders two had worsening cognitive delay and the third remained significantly delayed.</p>
Safety and adverse effects	None reported.
Does the study answer the question?	<p>Partially regarding outcomes of cessation of spasm and cognitive outcomes.</p> <p>The authors found that patients with idiopathic infantile spasms had a more favourable outcome. They say that because of the small sample it cannot determine which of the two drugs is more effective. Although looking at the trends vigabatrin may be more effective of patients with symptomatic infantile spasms; patients with idiopathic infantile spasms tended to have a better cognitive outcome and patients with symptomatic infantile spasms tend to develop both epilepsy and autism.</p>
Effect due to factor in study?	No, study too small and methodology was unclear.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	allocation concealment, blinding, small sample

Baram

High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study

Ref ID 1

1996

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total: 29 patients.
ACTH arm: 15.
Prednisone arm: 14.

Inclusion/Exclusion Criteria Inclusion:
Parental consent to randomised treatment;
No previous steroid or ACTH treatment;
Presence of hypsarrhythmia or its variants (assessed by a 24-hour video EEG)

Presence and frequency of epileptic myoclonic events.

Exclusion:

Severe hypertension;

Resolution of spasms after shunt placement;

Parental refusal;

Unavailability of legal guardian;

Patient Characteristics

Twelve infants had Hispanic surnames - six in each group; 11 infants were white non-Hispanic - five in ACTH group); three Asian; three African American.

22 infants had symptomatic IS with known or suspected cause; seven had cryptogenic IS but only two were entirely developmentally and neurologically normal at time of diagnosis.

Mean age prednisone group 7.5 vs. ACTH group 5.1. Difference was not statistically significant ($p=0.06$, Mann-Whitney test).

Cryptogenic aetiology, gender, other seizures, duration of IS did not differ statistically significantly between the treatment groups.

Recruitment

Consecutive infants (in Hospital) who fulfilled criteria.

Setting

Children's Hospital Los Angeles.

**Interventions/ Test/
Factor being
investigated**

Two weeks treatment of either ACTH (ACTHARGEL) 75 U/m²/day intramuscularly twice daily vs. prednisone 1mg/kg/day given orally twice daily.

Parents kept seizure diaries and monitored seizure frequency;

Monitoring of side effects such as hypertension and hyperglycemia: glycosuria was checked for duration of treatment and blood pressure measured bi-weekly;

After 2 weeks a repeat video-EEG (lasting 4 to 24 hours including a full sleep-wake cycle) was performed and clinical and EEG response was assessed;

Those who had not responded to treatment (had not complete cessation of IS events and hypsarrhythmia) were offered the alternative treatment;

Responders were tapered off ACTH or prednisone.

Comparisons

Comparisons made between treatments: ACTH vs. prednisone.

**Length of Study/
Follow-up**

Followed up for two weeks. Then non-responders crossed over to the other treatment for two weeks.

**Outcome measures
studied**

Cessation of seizures;

Results

Cessation of seizures:

ACTH: 13/15 86.6% responded by EEG and clinical criteria; seizures stopped in an additional infant (EEG remained hypsarrhythmic so considered a failure).

Prednisone: 4/14 (28.6) responded by EEG and clinical criteria).

The difference in response rate between groups was significant: $p=0.002$ X² test; even after accounting for confounding effect of age: Mantel-Haenszel test 3.94 (CI 1.44-10.77, $p=0.0026$).

The 2 infants who failed ACTH received prednisone for 2 weeks, one responded on clinical and EEG criteria.

Of 10 infants failing prednisone, nine received ACTH (for 2 weeks) and 8 responded (88%).

2/5 infants who were ineligible for the study received ACTH and responded.

Adverse events:

Irritability and voracious appetite were the most frequent side effects, but no infant required stopping or modifying treatment.

**Safety and adverse
effects**

Adverse events: Side effects such as hypertension and hyperglycaemia were monitored: glycosuria was checked for the duration of treatment and blood pressure checked bi-weekly.

Irritability and voracious appetite were the most frequent side effects, but no infant required stopping or modifying treatment.

**Does the study
answer the question?**

Partially regarding cessation of seizures with ACTH and prednisone.

The authors concluded that in their study a 2-week course of high-dose ACTH is superior to 2 weeks of prednisone for treatment of infantile spasms (from both clinical and EEG criteria).

Effect due to factor in study? Not sure. No concealment allocation and no power calculation given.

Consistency of results with other studies? Authors say Hrachovy (1991) found a comparable efficacy for ACTH.

Directly applicable to guideline population? Direct.

Internal Validity No allocation concealment;

Chiron C;Dumas C;Jambaque I;Mumford J;Dulac O;

Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis

Ref ID 4616

1997

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total: 22 patients were randomised.
Vigabatrin arm: 11.
Hydrocortisone arm: 11.
6 non-responders and one infant with severed hydrocortisone side effects were crossed over at the end of the first month from hydrocortisone to vigabatrin for another month.

Inclusion/Exclusion Criteria Inclusion:
Tuberous sclerosis according to Gomez criteria;
Epileptic spasms recorded on EEG or seen by experienced physician;
Diffuse interictal paroxysmal activity

Patient Characteristics Vigabatrin vs hydrocortisone:

Gender:
Male 5 vs 5.
Female 6 vs 6.

Age at onset of infantile spasms : (months, mean, sd):
3-9 (5.8+/-1.8) vs 1-14 (5.9+/-3.2).

Age at onset of vigabatrin (months, mean, sd):
4-9 (6.6+/-1.7) vs 2-17 (7.9+/-4.4).

Duration of IS before vigabatrin (days, mean, sd):
15-90 (24.4+/-25.6) vs 15-300 (36.4+/-31.9).

All showed statistically non-significant differences.

Recruitment Selected from several French centres.

Setting French health centres.

Interventions/ Test/ Factor being investigated 150mg/kg/day vigabatrin vs 15mg/kg/day hydrocortisone.
After the end of the first month, those who did not respond were crossed over to the alternative treatment. While vigabatrin was withdrawn over 24 hours and hydrocortisone was tapered off over 2 weeks.

A daily seizure calendar maintained by the parent or guardian plus an EEG was used to assess cessation of spasms. The EEG was done at 1 and 2 months.

Adverse events were reported to or noted by the investigator.

Comparisons Comparison between treatments: vigabatrin vs hydrocortisone.

Length of Study/ Follow-up Final assessment at 2 months after randomisation (initial non-responders) or cross-over (responders).

Outcome measures studied	Cessation of spasms; resolution of hypsarrhythmia; relapse rates; adverse events.
Results	<p>Cessation of spasms:</p> <p>After 1 month: 11/11 vigabatrin and 5/11 hydrocortisone patients were spasm-free ($p < 0.01$).</p> <p>The 6 non-responders to hydrocortisone and one infant who had severe side effects after hydrocortisone were crossed over to vigabatrin: All 7 responded to vigabatrin.</p> <p>Mean time to response: Vigabatrin: 4 days (range 0.5-14 days, SEM=1.53) vs hydrocortisone: 12.8 days (range 3-30 days, SEM=4.37), $p = 0.058$.</p> <p>If look at whole population of responders to vigabatrin ($n = 18$) mean time to response after initiation of vigabatrin (2.5 days, SEM=0.96), $p < 0.01$.</p> <p>Psychomotor evaluation: 17 patients were measured for developmental quotient at baseline and it was found to be lower in the vigabatrin group (mean=51, $n = 9$) than in the hydrocortisone group (mean=74, $n = 8$). No deteriorations were found but some children showed a slight increase in their developmental quotient.</p>
Safety and adverse effects	14 children had at least one adverse event. Vigabatrin: 5 patients (3 during initial treatment, two after cross-over). Hydrocortisone: 9 patients. $P = 0.006$.
Does the study answer the question?	Yes as it includes cessation of spasms, psychomotor evaluation and adverse events. The authors concluded that vigabatrin should be considered as the first choice treatment for infantile spasms due to tuberous sclerosis.
Effect due to factor in study?	No as only 22 participants and an open study with unclear methodology.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	allocation concealment; blinding;
Dreifuss F;Farwell J;Holmes G;Joseph C;Lockman L;Madsen JA;Minarcik CJ;Rothner AD;Shewmon DA;	
Infantile spasms. Comparative trial of nitrazepam and corticotropin	
Ref ID	4636 1986
Study Type	Randomised Controlled Trial Funding Not reported.
Number of participant	Total: 52 patients. Nitrazepam arm: 27. ACTH arm: 25. Number where drug efficacy was evaluated: Nitrazepam: 27. ACTH: 21.
Inclusion/Exclusion Criteria	Inclusion criteria: 1 to 24 months old; Infantile spasms documented by a hypsarrhythmic or modified hypsarrhythmic pattern on the EEG; Administration of Phenobarbital, Phenytoin, carbamazepine, or succinimides for the control of other seizures was allowed; No immunisations to be done during the study's four-week treatment period; Exclusion:

No prior treatment with ACTH, steroids or NTZ;
Concomitant administration of valproic acid derivatives or benzodiazepines other than nitrazepam was not permitted;

Patient Characteristics Nitrazepam group vs ACTH group figures in brackets is for those whose efficacy data was evaluated):

Sex:
Male: 14 (14) vs 15 (12).
Female: 13 (13) vs 10 (9).

Age in months:
Mean: 8.70 vs 8.04.
Range 2-23 vs 3-21.

Spasm frequency at baseline:
Mean 174.3 vs 176.1.
Range 6-542 vs 10-1616.

Recruitment Over a three year period of recruitment. No further details given.

Setting 8 centres in USA: medical centres and hospitals.

**Interventions/ Test/
Factor being
investigated** Before enrolment, patients were hospitalised for 24 hours and underwent complete neurologic evaluation. The videotapes and polygraphic recordings were scored by an assessor who was unaware of the treatment sequence of the recording of the drug treatment group to which the patient had been assigned.
Nitrazepam group received doses of 0.2mg/kg/day in two divided doses or 1mg twice daily (whichever greater). This was adjusted twice weekly by increments of 0.3 to 0.4mg/kg/d. This was reduced if it was too rapid for the patients. A maintenance dosage of 4.80 to 9.00mg/d was achieved in most by the end of the third week and kept constant for the remainder of the study if possible.
Corticotrophin gel was given as a single daily intramuscular dose of 40 units.
At the end of the four weeks each patient was hospitalised for 24 hours, where a second videotape-polygraphic recording was made.

Comparisons Between treatments: nitrazepam vs ACTH.

**Length of Study/
Follow-up** Four weeks.

**Outcome measures
studied** Reduction in seizure frequency;

Results Mean reduction in seizure frequency (from baseline):
Nitrazepam:
122.1 +/- 20.8 seizures per day
p<= 0.05, two-sided comparison

ACTH:
89.7 +/- 23.6 seizures per day
p<= 0.05, two-sided comparison

* The proportion of patients experiencing a reduction in seizure frequency by at least 50% was:

Nitrazepam: 18 (67%).
ACTH: 12 (57%).

[* Outcome of interest].

**Safety and adverse
effects** Side effects (percentage of patients who developed):

Nitrazepam:
Drowsiness: 50%.
Pooling of secretions in the upper respiratory passages: 45%.
Muscle hypotonia: 40%.
New seizure activity: 26%

ACTH group:
Leukocytosis: 52%.

Irritability: 40%.
 Hypertension: 30%.
 Emesis: 30%.
 Peripheral oedema: 20%.
 New seizure activity: 19%.
 Cushing old faces: 15%.
 Melena: 8%.
 Hypernatremia: 4%.

Three of the ACTH group were no included in the analysis as they had side effects:
 - two were removed after less than one week because of side effects (hypertension and melena).
 - one patient died while asleep before a final evaluation could be made. The cause of death was not determined.

Four further ACTH patients had treatment discontinued early due to side effects but were entered into the analysis as completed from 14 to 22 days.

The two treatments were compared for their effect on blood pressure by calculating slopes of systolic blood pressure over time:
 Nitrazepam n=26, mean 0.14, SEM 0.46.
 ACTH n=23, mean 1.53, SEM 0.47.
 p<0.005.
 BP measurements were unavailable for one patient in the nitrazepam group and for two patients in the ACTH treatment group.

Does the study answer the question?

Yes partially. There are two outcomes of interest to us included in this study.

The authors state that both treatments resulted in a statistically significant reduction in spasm frequency from that of baseline but the difference between treatments was not significant.

The number of patients who experienced side effects was similar in the two treatment groups but the ACTH group were qualitatively more severe and required the discontinuation of the treatment for 6 of the patients.

Effect due to factor in study?

No power calculation given. But methodology not clear.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Concealment allocation; uneven no.s;

Hrachovy RA;Frost JD;Kellaway P;Zion TE;

Double-blind study of ACTH vs prednisone therapy in infantile spasms

Ref ID 49

1983

Study Type

Randomised Controlled Trial

Funding

Grant NS11535 and Contract NS-9-2321 from the National Institute of Neurological and Communicative Disorders and Stroke.

Number of participant

Total: 24 infants.
 ACTH arm: 12 patients.

Inclusion/Exclusion Criteria

Inclusion:
 Patients with infantile spasms and hypsarrhythmic EEG patterns on serial 24-hour video and polygraphic monitoring.
 15 had previously been given various anticonvulsants, including phenobarbital,

phenytoin, clonazepam, sodium valproate, and diazepam;

None had received ACTH or corticosteroid therapy for their spasms;

Patient Characteristics Aged 3 and a half to 24 months; 22 patients were under 1 year of age;

Recruitment Not reported.

Setting Not reported.

**Interventions/ Test/
Factor being
investigated** Informed consent obtained from each infant's parent or guardian after a full explanation of the procedure;
Baseline 24-hour monitoring study;
Patient assigned at random to either ACTH gel 20 U/day or prednisone placebo or prednisone 2mg/kg/day and an ACTH gel placebo for two weeks;
If patient responded in first two weeks dosage was immediately tapered and drug discontinued over a one-week period. Then the patient was monitored at 2 and 6 weeks after discontinuation of therapy, to substantiate a continued response.
If patient did not respond after the first two weeks therapy was continued (ACTH gel 30U/day or prednisone 2mg/kg/day) for an additional four weeks and then the dosage was tapered and the drug discontinued over a 2-week period.
Final 24-hour monitoring study performed.
No responders were crossed over to the other drug after a one week 'washout' period and protocol was repeated.
Those who responded to neither were treated with clonazepam (0.03 to 0.18 mg/kg/day) for 8 weeks and 24 hour monitoring was continued during this time to evaluate response.

Comparisons Treatment versus treatment.
ACTH vs. prednisone.
ACTH also had a prednisone placebo and the prednisone group received an ACTH placebo.

**Length of Study/
Follow-up** Baseline 24 -hour monitoring period.
After randomisation patients were followed up at two weeks.
They were monitored at 2 weeks and 6 weeks after discontinuation of treatment.
If no response after first two weeks treatment was continued for 4 weeks.

**Outcome measures
studied** Response to therapy (defined as total cessation of spasms and disappearance of the hypsarrhythmic EEG pattern); relapse rates.

Results Overall response: 67% (16/24) of the patients responded to either ACTH (9 patients) or prednisone (7).

Results of initial and crossover phases:
ACTH initial drug: 42% (5/12) responded.
Prednisone initial drug: 33% (4/12) responded.
ACTH at crossover: 50% (4/8) responded.
Prednisone at crossover: 43% (3/7) responded when prednisone was the crossover drug.

Duration of treatment:
Of those who responded 75% (12/16) received only a two -week course of therapy (ACTH 7, prednisone 5) after which the medication was tapered and discontinued and 25% received a six-week course of therapy (ACTH 2, prednisone 2).

Side effects of hormonal therapy:
- hypertension of >140/90 in 25% (6/24) of the patients. In four of these hypertension developed with both drugs, in two only with prednisone.
- Cerebral shrinkage occurred 62% (10/16) of those on ACTH gel 20U/day or prednisone 2mg/kg/day showed evidence of increased ventricular size or increased subarachnoid space or both compared to baseline CT scans. Of the patients who had a 3rd CT scan 4-6 weeks after discontinuance of all hormonal therapy 42% (6/14) showed these changes.

Clonazepam response: of the 8 patients who did not respond to ACTH or prednisone, 7 were given clonazepam. None responded.

**Safety and adverse
effects** See side effects.

Does the study answer the question?	Partially, the only outcomes are cessation of seizures and adverse events. The authors conclude that there was no major difference in stopping the spasms an between ACTH and that of prednisone.
Effect due to factor in study?	Power calculation of 24 infants given and they had 24 infants included in the study. The methodology not described well and so can not be sure effect overall is due to intervention.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	Allocation concealment;

Lux AL;Edwards SW;Hancock E;Johnson AL;Kennedy CR;Newton RW;O'Callaghan FJ;Verity CM;Osborne JP;

The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial

Ref ID 4649

2004

Study Type	Randomised Controlled Trial	Funding	Grant from the Bath Unit for Research in Paediatrics. FJKO'C was supported by the wellcome trust and AL and EH by Cow and Gate.
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Number of participant Total: 107 patients.
Vigabatrin: 52.
Hormonal treatment - prednisolone: 30; tetracosactide: 25.

Inclusion/Exclusion Criteria

Inclusion criteria:
Clinical diagnosis of infantile spasms by the consultant in charge and a hypsarrhythmic or similar EEG with almost continuous, high-voltage multifocal spike and wave.

Exclusion criteria:
Aged under 2 months or over 12 months old;
Diagnosis or high risk of tuberous sclerosis;
Previous treatment (within past 28 days) with or a contraindication to Vigabatrin or hormonal treatments;
A lethal or potentially lethal disorder other than infantile spasms;
Inability of parents or guardians to give informed signed consent or to know when spasms stop;
Known that leaving the UK within 1 month or randomisation;
Enrolment in a concurrent trail that used treatment that may affect the outcome measures of the trial or one that was labour-intensive for the patients, guardians or medical practitioners.

Patient Characteristics Vigabatrin vs prednisolone vs tetracosactide

Gender:
Male: 32 vs 18 vs 14
Female: 20 vs 12 vs 11
Median age (IQR) in completed months at onset of spasms: 5 (4-7) vs 5 (4-6)* vs 5 (3.5-7)#.
Median age (IQR) at randomisation (months): 6 (4-9) vs 6 (4-8) vs 6 (5-8).

Mean duration of spasms (IQR) at randomisation (months): 1 (0-1) vs 0 (0-1.5)* vs 1 (0-1)#

Higher risk of neurodevelopmental delays**: 22 vs 15 vs 12.
Chromosomal abnormality: 2 vs 2 vs 0.
Syndrome: 2 vs 3 vs 2.

Neonatal encephalopathy with seizures: 8 vs 4 vs 5.
Cerebral palsy before spasms: 10 vs 8 vs 4.
Delayed development before spasms: 19 vs 13 vs 12.

Underlying aetiology:

Prenatal: 15 vs 8 vs 6

Perinatal: 9 vs 5 vs 3.

Postnatal: 0 vs 2 vs 1.

Other (uncertain classification) 6 vs 2 vs 2.

No aetiology found: 21 vs 13 vs 12.

Not known (cranial imaging not reported) 1 vs 0 vs 1.

*unknown in two infants. # Unknown in one infant. ***Some infants had more than one risk factor.

Recruitment

Local consultants enrolled infants from 150 hospitals in the UK.

Setting

Hospitals, UK. Central randomisation - Bath, UK.

Interventions/ Test/ Factor being investigated

Prednisolone (originally Prednesol, Glaxo Wellcome, then soluble prednisolone tablets after a change of license); Tetracosactide depot and Vigabatrin. The drugs were randomised to 1:1:2 respectively.

Prednisolone was given orally (10mg four times a day for 2 weeks increasing to 20mg three times a day after 1 week if spasms continued).

Tetracosactide depot was given intramuscularly (0.5mg on alternated days for 2 weeks and increased to 0.75mg on alternate days after 1 week if seizure control had not been achieved.

Those on prednisolone or tetracosactide after 2 weeks received a reducing dose of prednisolone with reductions of 10mg every 5 days or, if on the higher dose of treatment, 40mg daily, then 20mg, then 10mg for 5-day periods.

Vigabatrin was given orally in two divided doses per day (50mg/kg per day for the first two dose; increasing to 100mg/kg/per day after 24 hours and if the spasms continued to 150mg/kg per day after 96 hours.

A daily diary was used to record the treatment given, the number of spasm clusters, the largest no. of spasms in a cluster, any treatment missed and any adverse events. T

The local investigator reviewed diaries on day 14. Diaries and the investigator's report were used to confirm the days on which spasms occurred.

B.P and urine were checked. BP twice a day for 2 days then weekly and urine checked for glucose at 48 hours and weekly.

Comparisons

Comparisons between treatments.

Length of Study/ Follow-up

Follow-up 14 days then every 3 months until aged 14 months.

Outcome measures studied

Cessation of spasms; resolution of hypsarrhythmia; relapse rates; development at 14 months old; seizure rates at 14 months old.

Results

Cessation of spasms:

40/55 infants (73%) allocated hormonal treatment: prednisolone group: 21, tetracosactide 19.

Vigabatrin group: 28/52 (54%) - difference 19%, 95% CI 1%-36%; $X^2=4.1$, $p=0.043$.

Cessation of spasms occurred in 53 (64%) of 83 infants who the initial EEG was reported as hypsarrhythmia and in 15 (63%) of 24 in who the EEG was not (hormonal treatments 30/39 (77%) and 10/16 63%) respectively: Vigabatrin 23/44 (52%) and 5/8 (63%).

Safety and adverse effects

Vigabatrin vs prednisolone vs tetracosactide:

No. of infants with adverse events: 28 vs 19 vs 11.

Treatment unchanged: 19 vs 14 vs 8*.

Treatment not increased as protocol required: 7 vs 3 vs 2*.

Treatment reduced: 2 vs 1 vs 1*.

Specific adverse events:

Gastrointestinal: 11 vs 7 vs 5.
 Irritability: 2 vs 12 vs 7.
 Drowsiness 14 vs 5 vs 1.
 Infection: 5 vs 3 vs 0.
 Increased appetite: 1 vs 4 vs 3.
 Dermatological: 2 vs 1 vs 3.
 Fluid and electrolyte (including high blood pressure): 0 vs 3 vs 2.
 Neuropsychiatric (including sleep disturbance): 4 vs 1 vs 0.
 Hypertonia: 0 vs 1 vs 1.
 Treatment for varicella exposure: 0 vs 1 vs 1.
 Other: 5 vs 3 vs 4.

*Treatment actions not mutually exclusive.

The authors point out that adverse events were reported in similar numbers for hormonal and Vigabatrin treatments. These events didn't occur in the three infants not receiving their allocated treatments. One had a blood pressure of above 120/90mm Hg, but was asymptomatic and did not need treatment. Infants showed increased irritability and appetite on hormonal treatments and more drowsiness on Vigabatrin.

Treatment had to be stopped for one child in each hormonal group.

No deaths occurred in the first 14 days after randomisation. Blood pressure above 110/80mm Hg occurred in 11 (20%) of 55 infants allocated to hormonal treatments (7 (23%) on prednisolone, 4 (16%) on tetracosactide) and above 120/90mm Hg in 8 (15%) of 55 (four (13%) on prednisolone, four (16%) on tetracosactide), and two infants allocated prednisolone were given diuretics. Glycosuria was recorded in one patient allocated to tetracosactide, but no infants needed treatment for this or for treatment to be stopped for diabetes mellitus.

Does the study answer the question?

Partially as includes cessation of spasms and adverse events as outcomes.

Effect due to factor in study?

The authors concluded that cessation of spasms was more likely in infants given hormonal treatments than those who were given Vigabatrin. Adverse events were common in both treatments.

For 90% power they needed 250 patients. They had to finish study early due to absence of funds and the authors said that the number of infants enrolled by the end of December 2002 should give them nearly 80% power to detect the difference in effect seen by Vigevan (1997). There was adequate randomisation and allocation concealment but a lack of blinding of participants or outcome assessors which could have a bias.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct for the prednisolone and Vigabatrin interventions but not applicable for the tetracosactide intervention. The population is of direct interest.

Internal Validity

No blinding.

Omar FZ;Al-AbdulWahab NO;Ali BM;Karashi FA;Al-Musallam SA;

Vigabatrin versus ACTH in the treatment of infantile spasms

Ref ID 3134

2002

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant

36 were selected but 4 were excluded because of irregularities in follow-up as their families resided far away.
 Total: 32.
 ACTH group: 16.
 Vigabatrin group: 16.

Inclusion/Exclusion Criteria	Inclusion criteria: Diagnosed clinically as having spasms based on EEG changes and clinically.
Patient Characteristics	Age: 3 and 10 months of age (mean age 5.2 months). Gender: Males: 20; Females: 12. 25 patients (78.1%) showed hypsarhythmia and 7 patients (21.8%) had burst suppression pattern 28 patients (87.5%) showed typical flexor spasms and 4 (12.5%) showed extensor spasms. Newly diagnosed and had not been previously treated before. Aetiology: Cryptogenic: 16 (50%). Hypoxic ischemic encephalopathy at birth: 4 (12.5%). Tuberous Sclerosis: 2 (6.25%). Cortical dysplasia: 1 (3.125%). Prematurity: 2 (6.25%). Metabolic: 3 (9.375%). Others: 4 (12.5%).
Recruitment	Not reported.
Setting	Sulaimania Children Hospital, Saudi Arabia.
Interventions/ Test/ Factor being investigated	Complete history taken from mother or caregiver. Systemic examination performed on all patients including systems review, chorionic villus sampling, respiratory, abdomen as well as general growth and presence or absences of dysmorphism. Skin examination by wood's light and neurodevelopmental evaluation was conducted. One group received ACTH (20 IU intramuscular daily) and the other received vigabatrin (average 87mg/kg/day) monotherapy.
Comparisons	Comparison between treatments: ACTH vs vigabatrin.
Length of Study/ Follow-up	Median follow-up: 6.4 months (range 2 months- 1 year).
Outcome measures studied	Seizure cessation; Partial recovery (improvement but not complete disappearance); Time taken to recovery.
Results	ACTH vs vigabatrin: Seizure cessation: 12 patients (75%) seizures completely disappeared vs 11 patients (68.7%). Partial recovery: 4 patients (25%) vs 5 patients (31.2%). Time taken for recovery was shorter in vigabatrin group: median 5 days. Time to initial improvement: 10 infants (62.5%) had a median response time of 9 days, in the first 10 days vs 9 infants (56.25%) in 4 days.
Safety and adverse effects	Response was more appreciated in the vigabatrin group with a known etiology. Vision was checked by Ophthalmologist before and at 6 monthly intervals for at least one year after stopping vigabatrin - no significant changes found at 6 months. Other side effects: weight gain, somnolence, agitation were encountered in the vigabatrin group but were mild and did not require the cessation of medication. Side effects were noted in the younger age group (5 months or below): 14 patients (78.5%) out of 16 suffered side effects in the ACTH group vs 4/16 patients (25%) in the vigabatrin group had some drowsiness, none had visual disturbances.
Does the study answer the question?	Partially as includes cessation of seizures. The author concluded that vigabatrin is an effective therapy for infantile spasms and has been shown to be as effective as ACTH, with less hospital dependency and milder side effects.

Differences were probably due to the underlying aetiology.

Effect due to factor in study?

No the methodology is unclear so cannot have certainty.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

allocation concealing, randomisation,blinding.

Vigevano F;Cilio MR;

Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study

Ref ID 4613

1997

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant

Total: 42 infants.
Vigabatrin arm: 23.
ACTH arm: 19.

Inclusion/Exclusion Criteria

Inclusion:
Newly diagnosed and previously untreated infantile spasms.

Patient Characteristics

Vigabatrin vs ACTH

Gender:
Males: 14 vs 7.
Females: 9 vs 12.

Cryptogenic: 7 vs 8.
Symptomatic: 16 vs 11.

Age at onset: 2.5-9 months (mean 5.8) vs 2-9 months (mean 5.3).

Recruitment

Recruited between November 1, 1992 and October 31, 1995. Does not report how.

Setting

Italy. Not reported where.

Interventions/ Test/ Factor being investigated

All patients had an ictal video-EEG recording before treatment and CT scan or MRI. They were classified as cryptogenic and symptomatic. Therapy was started 1-3 weeks after the onset of spasms.

Phase 1:
Randomised to receive either 100-150mg vigabatrin in two daily doses or 10 IU Depot ACTH in one morning dose.
If spasms did not cease after 20 days of therapy or they had intolerance the patient received the alternative drug for at least 20 days (crossover phase 2).

ACTH dosage was constant; Vigabatrin was administered initially ~100mg/kg/day once a day. If efficacy was poor and no side effects after 3 days the vigabatrin dose was increased to 125mg/kg per day then to 150mg/kg day after another 3 days.

EEG was recorded every 10 days with prolonged (at least 2 hours) video-EEG recording of a sleep/wake cycle.

Comparisons

Comparison between treatments:
Vigabatrin versus ACTH.

Length of Study/ Follow-up

Follow-up of study was 40 days: 20 days for phase 1 and 20 days for phase 2.

Outcome measures studied	No outcome measures explicitly stated. Cessation of spasms; adverse events.
Results	<p>Vigabatrin vs ACTH:</p> <p>Cessation of spasms: 11 (48%) vs 14 (74%), p=0.12.</p> <p>Phase 1 and Phase 2 results:</p> <p>Cessation of spasms: 2/5 (40%) vs 11/12 (92%) p=0.052. Total efficacy results 12/28 (46%) vs 25/31 (81%) p=0.007.</p>
Safety and adverse effects	<p>Side effects:</p> <p>Vigabatrin vs ACTH: 3 (13%) vs 7 (37%) not statistically significant p=0.14.. Drowsiness: 2 (9%) vs 0. Hypotonia 2 (9%) vs 0. Irritability 1 (4%) vs 7 (37%). Hypertension 0 vs 7 (37%).</p> <p>Discontinuation due to side effects: 1 (4%) vs 1 (5%).</p>
Does the study answer the question?	<p>Partially. It has cessation of spasms and adverse events reported.</p> <p>The authors conclude that vigabatrin offers an effective and possibly safer therapy for managing infantile spasms than ACTH. It should be considered for use as first-line therapy for infantile spasms.</p>
Effect due to factor in study?	No. No power calculation and methodology is limited, it is open and has no statement of concealed allocation.
Consistency of results with other studies?	
Directly applicable to guideline population?	Yes.
Internal Validity	Allocation concealment; blinding.

Question: How effective and cost-effective are anti-epileptic drugs for Lennox-Gastaut syndrome

Grading: 1++

High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Motte J;Trevathan E;Arvidsson JF;Barrera MN;Mullens EL;Manasco P;

Lamotrigine for generalized seizures associated with the Lennox-Gastaut syndrome. Lamictal Lennox-Gastaut Study Group.[erratum appears in N Engl J Med 1998 Sep 17;339(12):851-2]

Ref ID 4614

1997

Study Type	Randomised Controlled Trial	Funding	Glaxo Wellcome
Number of participant	169 in total Lamotrigine:79; Placebo:90		
Inclusion/Exclusion Criteria	Inclusion: aged 3 to 25 years, more than one type of predominantly generalised seizure (including tonic-clonic seizures and drop attacks) for at least 1 year, aged under 11 years old when epilepsy first started, seizures at least every other day or with similar average frequency, intellectual impairment or clinical impairment of intellectual impairment, recent electroencephalogram demonstrating an abnormal background and pattern of slow spike-and-wave complexes. Exclusion: progressive neurodegenerative disorder, receiving more than 3 antiepileptic drugs, weighed less than 15 kg and taking valporate		
Patient Characteristics	In the lamotrigine group the mean age was 9.6 (sd 5.2) years, 54 were male, the mean weight was 32.5 (sd 18.1) kg, the mean height was 129.4 (sd 27) cm. 74 were white, 3 were black and 2 were of other race. Concomitant treatment with antiepileptic drugs: 53 valporate, 16 carbamazepine, 10 phenytoin, 11 other. 73 had moderate or severe intellectual impairment, 31 had a history of infantile spasms, 20 had a history of status epilepticus, 3 did not know if they had a history of status epilepticus. In the placebo group the mean age was 10.9 (sd 5.9) years, 45 were male, the mean weight was 34.3 (sd 19.7) kg, the mean height was 130.9 (sd 26.8) cm. 84 were white, 3 were black and 3 were of other race. Concomitant treatment with antiepileptic drugs: 50 valporate, 30 carbamazepine, 13 phenytoin, 9 other. 82 had moderate or severe intellectual impairment, 37 had a history of infantile spasms, 24 had a history of status epilepticus, 2 did not know if they had a history of status epilepticus.		
Recruitment	Not reported.		
Setting	Not reported		
Interventions/ Test/ Factor being investigated	Lamotrigine added to patients standard antiepileptic drugs		
Comparisons	Placebo added to patients standard antiepileptic drugs		
Length of Study/ Follow-up	16 weeks of treatment 4 weeks of follow up was reported		
Outcome measures studied	Number of patients who had greater than 50% reduction in the frequency of seizures, adverse events.		
Results	The study reported that valporate can inhibit the clearance of lamotrigine and increase plasma lamotrigine concentrations. Therefore patients were assigned to one of 4 dosage schedules (see below). These were according to weight and if the patient was taking valporate. At the end of treatment the drug was gradually discontinued, continuing the double blinded method) by reducing to dose to 50% for 2 weeks then 25% for another 2 weeks. Dosage schedule: For patients weighing less than or equal to 25 kg and who were taking valporate; for weeks 1 and 2 they were given 5 mg lamotrigine, for weeks 3 and 4 they were given 10 mg, weeks 5 and 6 they were given 25 mg, week 7 and 8 the were given 50 mg, for weeks 9 to 16 they were given 50 to 100 mg.		

For patients weighing more than 25 kg and who were taking valproate; for weeks 1 and 2 they were given 10 mg lamotrigine, for weeks 3 and 4 they were given 25 mg, weeks 5 and 6 they were given 50 mg, week 7 and 8 they were given 100 mg, for weeks 9 to 16 they were given 100 to 200 mg.

For patients weighing less than or equal to 25 kg and not taking valproate; for weeks 1 and 2 they were given 25 mg lamotrigine, for weeks 3 and 4 they were given 50 mg, weeks 5 and 6 they were given 100 mg, week 7 and 8 they were given 200 mg, for weeks 9 to 16 they were given 200 to 300 mg.

For patients weighing more than 25 kg and not taking valproate; for weeks 1 and 2 they were given 50 mg lamotrigine, for weeks 3 and 4 they were given 100 mg, weeks 5 and 6 they were given 200 mg, week 7 and 8 they were given 300 mg, for weeks 9 to 16 they were given 300 to 400 mg.

Number of patients who had greater than 50% reduction in the frequency of seizures: In the lamotrigine group 33% had a greater than 50% reduction in the frequency of all major seizures compared to 16% in the placebo group. 26/78 vs 14/89 (p=0.01)

In the lamotrigine group 37% had a greater than 50% reduction in the frequency of drop attacks seizures compared to 22% in the placebo group. 28/75 vs 20/89 (p=0.04).

In the lamotrigine group 43% had a greater than 50% reduction in the frequency of tonic-clonic seizures compared to 20% in the placebo group. 26/60 vs 13/64 (p=0.007).

Adverse events:

In the lamotrigine group 11/79 (14%) patients had pharyngitis, 10/79 (13%) had fever and 10/79 (13%) had infection.

In the placebo group 9/90 (10%) patients had pharyngitis, 12/90 (13%) had fever and 7/90 (8%) had infection.

Safety and adverse effects

Adverse events:

In the lamotrigine group 11/79 (14%) patients had pharyngitis, 10/79 (13%) had fever and 10/79 (13%) had infection.

In the placebo group 9/90 (10%) patients had pharyngitis, 12/90 (13%) had fever and 7/90 (8%) had infection.

Does the study answer the question?

Yes.

In the lamotrigine group 33% had a greater than 50% reduction in the frequency of all major seizures compared to 16% in the placebo group. 26/78 vs 14/89 (p=0.01).

In the lamotrigine group 11/79 (14%) patients had pharyngitis, 10/79 (13%) had fever and 10/79 (13%) had infection.

In the placebo group 9/90 (10%) patients had pharyngitis, 12/90 (13%) had fever and 7/90 (8%) had infection.

Effect due to factor in study?

This was a well conducted double blind randomized study. However, no prior consideration of statistical power has been made.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Sachdeo RC; Glauser TA; Ritter F; Reife R; Lim P; Pledger G;

A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate YL Study Group

Ref ID 4606

1999

Study Type

Randomised Controlled Trial

Funding

Number of participant	A total of 98 patients at 12 centres in the USA entered the double blinded phase. Forty-eight patients were randomly assigned to adjunctive therapy with Topiramate and 50 patients were assigned to receive adjunctive placebo therapy
Inclusion/Exclusion Criteria	Patients were excluded if they had a history of recent significant cardiovascular, respiratory, hepatic, renal, gastrointestinal or hematologic illness, or malignancy; seizures due to progressive disease; documented status epilepticus within 3 months of baseline; drugs or alcohol abuse; a psychiatric or mood disorder requiring medication or electroconvulsant therapy within 6 months of baseline; poor compliance with therapy; anoxic episodes requiring resuscitation within 1 years before the study; nephrolithiasis; treatment with an experimental drug or use of an experimental device within 60 days of baseline; treatment with a ketogenic diet or adrenocorticotrophic hormone within 6 months before the study; use of benzodiazepines on more than an occasional basis; presence of clinically significant EKG abnormalities; or history of an inability to take medication or maintain a seizure calendar.
Patient Characteristics	Participants aged 1 to 30 years were eligible if they had an EEG showing a slow spike and wave pattern and seizure types including drop attacks and atypical absence seizures, with a frequency of at least 60 seizures during the month prior to the baseline phase while being maintained on one or two standard AEDs. At study enter 39/98 of the patients were receiving maintenance doses of one concomitant AED, 56/98 were receiving two AEDs, and 3/78 were receiving 3 concomitant AEDs (one patient randomised to placebo and 2 patients randomised to topiramate)
Recruitment	Not reported.
Setting	
Interventions/ Test/ Factor being investigated	Topiramate versus placebo
Comparisons	Topiramate versus placebo
Length of Study/ Follow-up	
Outcome measures studied	Outcomes reported were cessation and reduction in drop attacks and overall reduction of all seizure types.
Results	<p>Placebo n=50 and Topiramate n=48.</p> <p>The trial consisted of a baseline phase of four weeks and an 11 week treatment phase. The participants were titrated up to a dose of 6 mg/kg/day or their maximal tolerated dosage of either topiramate or placebo over the first three weeks of the treatment period.</p> <p>Results were given for 97 participants.</p> <p>This study reported the effect of treatment on drop attacks and the reduction of overall seizures. Thirteen out of 46 (28%) of the topiramate participants achieved a $\geq 50\%$ reduction in drop attacks compared to 7/49 (14%) of the control group ($p=0.071$). A $\geq 75\%$ reduction in drop attacks was achieved in 8/46 (17%) of the topiramate group compared to 3/49 (6%) in the control group. One out of 46 participants treated with topiramate had complete cessation of their drop attacks compared with none of the 50 participants treated with placebo.</p> <p>The percentage of patients with $\geq 50\%$ reduction from baseline in major seizure during the double-blind was 15/46 (33%) for the topiramate group and 4/50 (8%) for the control group ($p=0.002$). Eight participants treated with topiramate and two participants treated with placebo had a 75% to 100% reduction.</p> <p>This study did not report the effect of treatment on stopping or reducing the number of absence, tonic, clonic, myoclonic, tonic-clonic or partial seizures or the effect on stopping all seizure types.</p> <p>Adverse events (at least 10% of study arm): Placebo (n=50): 22% somnolence; 20% anorexia; 10% nervousness; 10% behavioural problems; 4% fatigue; dizziness 0%; weight loss 0%. Topiramate (n=48): 42% somnolence; 40% anorexia; 21% nervousness; 21% behavioural problems; 19%</p>

fatigue; 10% dizziness; 10% weight loss.

Safety and adverse effects

No participant was reported as having had treatment stopped due to adverse effects and no deaths were reported.

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Glauser T;Kluger G;Sachdeo R;Krauss G;Perdomo C;Arroyo S;

Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome.[see comment]

Ref ID 901

2008 May 20

Study Type Randomised Controlled Trial

Funding None reported

Number of participant 138 in total
Rufinamide: 74; Placebo: 64

Inclusion/Exclusion Criteria
Inclusion: aged 4 to 30 years, history of multiple seizure types including atypical absence seizures and drop attacks, minimum of 90 seizures in previous month, EEG within previous 6 months showing slow spike-and-wave complexes (<2.5Hz), weighed at least 18kg, fixed regime of 1 to 3 concomitant antiepileptic drugs during baseline period, CT or MRI confirming absence of progressive lesion
Exclusion: on more than 3 antiepileptic drugs, pregnant or not using adequate contraception, correctable etiology of their seizures, history of generalised tonic-clonic status epilepticus within previous 30 days, history of clinically significant nonneurological medical condition

Patient Characteristics
In the rufinamide group 46 were male, 62 were white, 6 were black and 6 were of other race. The median age was 13 years and the range was 4 to 35 years. The median weight was 35.9kg, range 15.5 to 138.5kg, 35 were from USA, 29 from Europe, 10 from Brazil. The median duration of lennox-gastaut syndrome was 7.9 years, range 0.1 to 32.7 years. 44 had used valproate, 30 had used lamotrigine, 20 topiramate, 14 clonazepam and 12 carbamazepine.
In the placebo group 40 were male, 53 were white, 4 were black and 7 were of other race. The median age was 10.5 years and the range was 4 to 37 years. The median weight was 33.5kg, range 16.2 to 86kg, 28 were from USA, 27 from Europe, 9 from Brazil. The median duration of lennox-gastaut syndrome was 7.5 years, range 0.1 to 34.7 years. 35 had used valproate, 19 had used lamotrigine, 17 topiramate, 7 clonazepam and 12 carbamazepine.

Recruitment Not reported

Setting Not reported

Interventions/ Test/ Factor being investigated Rufinamide, the target dose of 45mg/kg was achieved by 65 patients (87.8%)

Comparisons Placebo, the target dose of 45mg/kg was achieved by 64 patients (all patients)

Length of Study/ Follow-up

Outcome measures studied Number of patients who were seizure free, number of patients who had at least 50% reduction in seizure frequency; adverse events; drop outs

Results
Number of patients who were seizure free:
No patients were seizure free in either group.

Number of patients who had at least 50% reduction in seizure frequency per 28 days:
In the rufinamide group the number of patients who had at least 50% reduction in tonic-atonc seizure frequency per 28 day was greater than in the placebo group 42.5% compared to 16.7% (OR 3.81, p=0.002).
In the rufinamide group the number of patients who had at least 50% reduction in total seizure frequency per 28 day was greater than in the placebo group 31.1% compared to 10.9% (p=0.0045).

Drop outs:
10 patients in the rufinamide group dropped out; 6 due to adverse events, 3 due to unsatisfactory, 1 due to withdrawal of consent.

5 patients dropped out of the placebo group; 2 due to protocol violations, 1 due to unsatisfactory treatment effect, 1 due to administrative problems and 1 withdrawal of consent.

Adverse events:

In the rufinamide group 60 patients had adverse events. 18 had somnolence, 16 had vomiting, 10 had pyrexia, 4 had diarrhea.

In the placebo group 52 patients had adverse events. 4 had somnolence, 4 had vomiting, 11 had pyrexia, 7 had diarrhea.

Safety and adverse effects

In the rufinamide group 60 patients had adverse events. 18 had somnolence, 16 had vomiting, 10 had pyrexia, 4 had diarrhea.

In the placebo group 52 patients had adverse events. 4 had somnolence, 4 had vomiting, 11 had pyrexia, 7 had diarrhea.

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Lahat E;Goldman M;Barr J;Bistrizter T;Berkovitch M;

Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study.[see comment]

Ref ID 48

2000 Jul 8

Study Type Randomised Controlled Trial **Funding** None listed.

Number of participant A total of 44 patients of both sexes with a total of 52 seizure episodes were evaluated. In midazolam was given for 26 episodes of febrile seizures in 21 children and IV diazepam for 26 episodes in 23 children.

Inclusion/Exclusion Criteria All children aged 6 months to 5 years who presented with febrile seizures lasting for at least 10 minutes were included. Children who had received an anticonvulsant or had an intravenous line sited by paramedics prior to hospital attendance were excluded from the study.

Patient Characteristics Children aged 6 months to 5 years. This study evaluates a specific sub-group of children with prolonged convulsive febrile seizures.

Recruitment From a paediatric emergency department at a General Hospital.

Setting paediatric emergency department, Israel.

Interventions/ Test/ Factor being investigated intranasal midazolam (0.2mg/kg) and intra-venous diazepam (0.3mg/kg) in the treatment of prolonged febrile seizure (a seizure of at least 10 minutes duration). Treatment was successful if the clinical features of the seizure stopped within 5 minutes. If the seizure stopped between 5 and 10 minutes this was identified as a delayed but successful treatment. Treatment failures (continued seizure activity after 10 minutes) received intravenous diazepam and then phenobarbital as per local guidelines.

Comparisons intranasal midazolam and intra-venous diazepam

Length of Study/ Follow-up Children were observed up to 24 hours after cessation of seizures.

Outcome measures studied	Cessation of seizures within a given time frame (7-10 minutes), and seizure-recurrence at 1 hour.
Results	<p>Treatment was successful if the seizure stopped within 5 minutes. Seizures that stopped between 5 and 10 minutes after treatment were defined as successful but delayed control of seizure. Seizures that did not stop within 10 minutes after treatment were defined as treatment failures, and IV diazepam 0.3 mg/kg was given.</p> <p>Intranasal midazolam and intravenous diazepam were found to be equally effective in prolonged febrile convulsions. 23/26 (88%) in the midazolam group and 24/26 (92%) in the diazepam group, RR 0.96 (95 % CI 0.8 - 1.14). Mean time from arrival in hospital to seizure cessation was shorter in the midazolam group (6.1 minutes [6.3-6.7] versus 8.0minutes [7.9-8.3]). Time of cessation of seizure from drug administration was shorter in the diazepam group (2.5 [2.4-2.6] versus 3.1 [2.9-3.3]). No children in either group had clinical signs of respiratory depression (as assessed by continuous pulse oximetry and 15 minute- blood pressure measurements) during or in the 60 minutes following the seizure.</p>
Safety and adverse effects	No adverse events, including respiratory depression were identified in either group.
Does the study answer the question?	the study showed that time from hospital admission to seizure cessation was significantly faster despite the fact that intravenous diazepam was faster acting when drug administration to seizure cessation was measured. Although not stated in the paper, this presumably reflects the time to obtain intravenous access.
Effect due to factor in study?	Randomisation was allocated in advance by way of a random number table and investigators received an opaque envelope with each allocation at the time of administration. Randomisation is adequate with similar patient demographics in both groups. In addition this study evaluates a specific sub-group of children with prolonged convulsive febrile seizures. This is important as the aetiology of seizures varies across the age ranges during childhood thereby potentially affecting results. The study was unblinded.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct study
Internal Validity	

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Eriksson AS;Nergardh A;Hoppu K;

The efficacy of lamotrigine in children and adolescents with refractory generalized epilepsy: a randomized, double-blind, crossover study

Ref ID 4612

1998

Study Type Randomised Controlled Trial **Funding** Funded with grants from the voluntary sector.

Number of participant Thirty participants of whom 20 had Lennox Gastaut Syndrome. Each patient acted as his or her own control during the double-blind cross-over phase.

Inclusion/Exclusion Criteria Exclusion criteria: presence of liver, renal or progressive neurologic disease, or the diagnosis of focal epilepsy.

Patient Characteristics Children and adolescents aged older than 2 years with refractory (defined as not seizure free despite attempts with at least 3 conventional AEDs) or intractable generalised epilepsy.
Thirty consecutive patients of whom 20 had Lennox Gastaut Syndrome., 15 boys and 15 girls took place in the study. The median age was 9.9 years (range 2.5-22 years). The median duration of epilepsy was 8.3 years (range 1.4-19.1 years).

Recruitment Referred to the Department of Child Neurology, Karolinska Hospital if they had more than 2 seizures per month.

Setting Secondary Care

Interventions/ Test/ Factor being investigated Lamotrigine and placebo were randomly added to existing AEDs.

Comparisons Lamotrigine compared to placebo

Length of Study/ Follow-up

Outcome measures studied Reduction rates of all seizures

Results The trial consisted of six phases: an 8 week baseline phase during which each child was observed on pre study medication. An open phase during which an attempt was made to find the optimal lamotrigine dose for each child. A double-blind phase of two 12-week periods during which, for each child, lamotrigine and placebo tablets were administered in random order. The treatment periods were separated by a 3-week washout phase. Results were given for 13 patients.

At the end of the open phase, 7 out of 27 children showed a $\geq 50\%$ seizure reduction, and 2 had $>75\%$ seizure reduction. Ten children were classified as non-responders.

The authors reported that 9 out of 15 children who completed the double-blind phase of the trial showed a $>50\%$ seizure reduction during the Lamotrigine phase, compared with the placebo phase. One child showed a 100% reduction and another child showed $>75\%$ reduction in seizure frequency.

The effect of treatment on the reduction in number of tonic, atonic, myoclonic and partial seizures was not reported.

Safety and adverse effects From the non-responders group (10 children), one child had ataxia and double vision. This symptom disappeared when carbamazepine dose was reduced by 100mg in patient 29 to 600mg/day and when the LTG dose was decreased by 50mg to 200mg/day in patient 10.
No adverse events were reported during the Lamotrigine phase in the double-blind period. When receiving placebo, 10 children complained of fatigue, and four children had more intense seizures.

Does the study answer the question?

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity ITT not performed. Cross-over trial

The Felbamate Study Group in Lennox Gastaut syndrome;

Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome).

Ref ID 4676

1993

Study Type Randomised Controlled Trial

Funding Wallace Laboratories, Division of Carter-Wallace, Inc and Public health services grant

Number of participant 73 patients in total
Felbamate: 37; Placebo: 36

Inclusion/Exclusion Criteria
Inclusion: history of multiple types of seizures, minimum of 90 atonic seizures or atypical absence seizures per month during the previous 8 weeks, not taking more than 2 antiepileptic drugs, no evidence of progressive central nervous system lesions on MRI or CT, weighed over 11.3 kg, slow spike-wave complex (greater than or equal to 2.5 Hz) on electroencephalography
Exclusion: history of identifiable neurological disorders, anoxic episodes within the last year, poor compliance with past antiepileptic therapy, recent drug or alcohol abuse, a major medical illness or previous suicide attempts, received corticotrophin on ketogenic diet, inadequate supervision by parents or guardians, females who were pregnant or not using adequate contraception

Patient Characteristics
51 out of 73 were male, 22 out of 73 were female
In the Felbamate group (37 in total) the mean age was 12 years, range 4 to 24 years, the mean weight was 37 kg, range 18 to 99.5kg, 27 were male, 33 were white, 2 were black and 2 were of other race. The baseline seizure frequency in 28 days was 370 atonic seizures, 1617 in total, 9 tonic-clonic. The mean number of antiepileptic drugs previous taken was 8, range 3 to 16.
In the placebo group (36 in total) the mean age was 14 years, range 4 to 36 years, the mean weight was 40 kg, range 14.2 to 86.4kg, 24 were male, 33 were white, 1 was black and 2 were of other race. The baseline seizure frequency in 28 days was 228 atonic seizures, 716 in total, 6 tonic-clonic. The mean number of antiepileptic drugs previous taken was 8, range 4 to 12.

Recruitment Not reported

Setting Not reported

Interventions/ Test/ Factor being investigated Felbamate (200mg)

Comparisons between Felbamate and placebo.

Length of Study/ Follow-up 14 day titration period and 56 day maintenance period.
No follow up reported

Outcome measures studied Number who were seizure free; adverse events

Results

The trial consisted of a 14 day titration period and a 56 day maintenance period. The first dose of 15mg per kg was given which was increase to 30 mg per kg after 7 days and to 45 mg per kg or 3600mg per day after 14 days. Patients were monitored by close circuit television and electroencephalography on days 42, 49, 70 and 98.

Number who were seizure free:

During the treatment phase in the Felbamate 3 out of 37 were seizure free as recorded by close circuit television and electroencephalography compared to 1 out of 36 in the placebo group. During the maintenance phase 6 of 37 were seizure free in the Felbamate group compared to 1 out of 35 in the placebo group.

During the treatment phase in the Felbamate 3 out of 28 were seizure free of atonic seizures compared to 0 out of 22 in the placebo group. During the maintenance phase 5 of 28 were seizure free in the Felbamate group compared to 0 out of 22 in the placebo group.

During the treatment phase in the Felbamate 0 out of 37 were seizure free of total seizures compared to 0 out of 36 in the placebo group. During the maintenance phase 4 of 37 were seizure free in the Felbamate group compared to 1 out of 36 in the placebo group.

During the treatment phase in the Felbamate 2 out of 16 were seizure free of generalized tonic-clonic seizures compared to 1 out of 13 in the placebo group. During the maintenance phase 7 of 16 were seizure free in the Felbamate group compared to 1 out of 13 in the placebo group.

Adverse events:

In the Felbamate group 14 patients had upper respiratory tract infections, 18 had anorexia, 15 had vomiting, 16 had somnolence, 6 had injury, 8 had fever, 6 had insomnia, 5 had nervousness, 4 had headaches, 1 had diarrhoea, 6 had fatigue, 4 had pruritis, 5 had abnormal gait, 4 had ataxia and 1 had rhinitis.

In the placebo group 10 patients had upper respiratory tract infections, 5 had anorexia, 5 had vomiting, 3 had somnolence, 10 had injury, 5 had fever, 5 had insomnia, 5 had nervousness, 5 had headaches, 8 had diarrhoea, 2 had fatigue, 3 had purpura, 0 had abnormal gait, 1 had ataxia and 4 had rhinitis.

Safety and adverse effects

In the Felbamate group 14 patients had upper respiratory tract infections, 18 had anorexia, 15 had vomiting, 16 had somnolence, 6 had injury, 8 had fever, 6 had insomnia, 5 had nervousness, 4 had headaches, 1 had diarrhoea, 6 had fatigue, 4 had purpura, 5 had abnormal gait, 4 had ataxia and 1 had rhinitis.

In the placebo group 10 patients had upper respiratory tract infections, 5 had anorexia, 5 had vomiting, 3 had somnolence, 10 had injury, 5 had fever, 5 had insomnia, 5 had nervousness, 5 had headaches, 8 had diarrhoea, 2 had fatigue, 3 had purpura, 0 had abnormal gait, 1 had ataxia and 4 had rhinitis.

Does the study answer the question?

During the treatment phase in the Felbamate 0 out of 37 were seizure free of total seizures compared to 0 out of 36 in the placebo group. During the maintenance phase 4 of 37 were seizure free in the Felbamate group compared to 1 out of 36 in the placebo group.

During the treatment phase in the Felbamate 2 out of 16 were seizure free of generalized tonic-clonic seizures compared to 1 out of 13 in the placebo group. During the maintenance phase 7 of 16 were seizure free in the Felbamate group compared to 1 out of 13 in the placebo group.

Adverse events:

In the Felbamate group 14 patients had upper respiratory tract infections, 18 had anorexia, 15 had vomiting, 16 had somnolence, 6 had injury, 8 had fever, 6 had insomnia, 5 had nervousness, 4 had headaches, 1 had diarrhoea, 6 had fatigue, 4 had purpura, 5 had abnormal gait, 4 had ataxia and 1 had rhinitis.

In the placebo group 10 patients had upper respiratory tract infections, 5 had anorexia, 5 had vomiting, 3 had somnolence, 10 had injury, 5 had fever, 5 had insomnia, 5 had nervousness, 5 had headaches, 8 had diarrhoea, 2 had fatigue, 3 had purpura, 0 had abnormal gait, 1 had ataxia and 4 had rhinitis.

Effect due to factor in study?

Uncertain due to high risk of selection bias (absence of allocation concealment).

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Question: How effective and cost-effective are anti-epileptic drugs for Severe myoclonic epilepsy of infancy (SMEI)

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Chiron C;Marchand MC;Tran A;Rey E;d'Athis P;Vincent J;Dulac O;Pons G;

Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group

Ref ID 4631

2000

Study Type Randomised Controlled Trial **Funding** Biocodex, France.

Number of participant N=21, n stiripentol=21 and n placebo=20

Inclusion/Exclusion Criteria Inclusion criteria: children 3 years and older, SMEI, defined as onset of the epilepsy in the first year of life with clonic (or tonic-clonic) generalized seizures but normal psychomotor development and normal EEG, appearance of myoclonia after 1 year of age, atypical absences, generalised spikes and waves on EEG, mental delay, at least four clonic (or tonic-clonic) generalized seizures a month, valproate and clobazam as ongoing antiepileptic drugs. Exclusion criteria: patients receiving other drugs (except progabide) and those whose parents were unable to comply regularly with drug delivery and daily seizure diary.

Patient Characteristics Mean age was 9.4 years and 9.3 years for stiripentol and placebo groups respectively. 6/21 were males in stiripentol and 11/20 were males in placebo. The two groups had similar mean weights (32 kg for the stiripentol and 21 kg for the placebo). The mean dose valproate was 23.7 and 24 mg/kg daily for the stiripentol and placebo groups respectively, and the mean dose of clobazam was 0.53 and 0.55 mg/kg a day for the stiripentol and placebo groups respectively. 5/21 patients in stiripentol group and 2/20 in placebo were on progabide.

Recruitment Not reported.

Setting 15 French centres.

Interventions/ Test/ Factor being investigated Stiripentol as add-on therapy of epilepsy for children with SMEI.

Comparisons Comparison are made between patients received stiripentol and the placebo group.

Length of Study/ Follow-up 1 month baseline (no treatment), 2 months follow up (double blind treatment phase) and 1 month open treatment. Results are reported for the assessment of outcomes at the end of 2 months follow up.

Outcome measures studied
1) >50% reduction in seizure frequency
2) seizure freedom
3) experience of adverse events (>10%)

Results
1) 5/21 in stiripentol group and 1/20 on placebo were responders (>50% reduction in seizure frequency).
2) 9/21 patients in stiripentol and 0/20 in placebo became free of clonic (or tonic-clonic) seizures.
3) experience of adverse events (above 10%):
- drowsiness: 15/21 in stiripentol group and 2/10 in placebo
- hyperexcitability: 5/21 in stiripentol and 0/20 in placebo
- aggressiveness: 3/21 in Stiripentol and 0/20 in placebo
- ataxia: 3/21 in stiripentol and 1/20 in placebo
- tremor: 3/21 in stiripentol and 0/20 in placebo
- loss of appetite: 7/21 in stiripentol and 1/20 in placebo
- loss of weight: 6/21 in stiripentol and 0/20 in placebo
- weight gain: 5/21 in stiripentol and 4/20 in placebo
- neutropenia (1000-1500/MI): 3/21 in stiripentol and 0/20 in placebo

Safety and adverse effects See Q2-9 in adverse events.

Does the study answer the question?

Yes. More patients in stiripentol were responders and seizure free compared to placebo group. However, more participants in stiripentol experienced adverse events compared to placebo.

Effect due to factor in study?

The study was a well conducted randomized double blind trial, however the absence of allocation concealment may have an impact on the results observed. The study may be underpowered, limited number of events (wide confidence intervals).

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Question: How effective and cost-effective are anti-epileptic drugs for Benign rolandic epilepsy/benign epilepsy with centrotemporal spikes (BECTS)

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Rating D;Wolf C;Bast T;

Sulthiame as monotherapy in children with benign childhood epilepsy with centrotemporal spikes: a 6-month randomized, double-blind, placebo-controlled study. Sulthiame Study Group

Ref ID 4663

2000

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant N=66, n sulthiame group=31, n placebo=35.

Inclusion/Exclusion Criteria Inclusion criteria: children with a diagnosis of BECTS who had two or more seizure during the past 6 months, between 3 and 10 years of age and weighted between 10-50 kgr. Exclusion criteria: patients with severe organic diseases, acute porphyria, a history of mental illness, relevant hypersensitivity, somatic signs of puberty, or relevant renal, thyroid, or hepatic dysfunction, patients pre-treated with AEDs after the sixth month of life (an exception was made for those who received acute AED intervention of less than 1 week).

Patient Characteristics The mean age and the weight of the two groups was comparable (for the sulthiame group, median (range) age was 8.2 (3.9-10.7) years and for the placebo 8.4 (3.1-10.3) (for the sulthiame group, median (range) weight was 28 (16.6-56.6) kgr and for the placebo 26 (15-40.1). However, a higher proportion of males were included in the placebo group (68.6%) compared to sulthiame treated group (51.6%).

Recruitment Patients were recruited in 26 centres in Europe from 1996-1999.

Setting Not reported.

Interventions/ Test/ Factor being investigated Sulthiame (STM).

Comparisons Between sulthiame monotherapy versus placebo.

Length of Study/ Follow-up 6 month historic baseline period and a 6 month double blind treatment phase.

Outcome measures studied Primary outcome measure: rate of treatment failure events (TFEs) in each group. Patients had a TFE if they experienced first seizure after a 7 day run in period, had intolerable AEs, developed another epileptic syndrome or were terminated from the trial.

Results 25/31 in STM group and 10/35 in placebo group completed the trial without any treatment failure events.
The treatment failure events in sulthiame group were: 4/31 seizures after study admission, 2/31 were taken out of the study when results of the interim analysis available.
The treatment failure events for the placebo group were: 21/31 had seizures after a 7 day study admission, 2/35 were taken out of the study when results of the interim analysis available and 2/35 had seizures in the 7 day run in period and requested termination (drop outs).
Time to first seizure: 0/31 in STM group and 2/35 in placebo had seizures in the 7 day run in period.
25/31 (80.6%) in STM group and 10/35 (28.6%) in placebo were seizure free.
0/31 in STM group and 0/35 in placebo group had withdraws due to adverse events.

Safety and adverse effects No intolerable adverse events were noticed. Leukopenia occurred in two placebo treated patients, and loss of strength and fatigue were each observed in two STM treated patients.

Does the study answer the question? Yes. Sulthiame was found to be more effective than placebo in seizure prevention in patients with BECTS aged 3-11 years.

Effect due to factor in study?

This was a well conducted double blind randomized clinical trial. However, the sample size in this trial (N=66) was lower than the minimum sample size calculated for this study (N=140), therefore the study was underpowered.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Coppola G;Franzoni E;Verrotti A;Garone C;Sarajlija J;Operto FF;Pascotto A;

Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign epilepsy of childhood with centrotemporal spikes (BECTS): an open-label, parallel group trial

Ref ID 271

2007 Jun

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant N=38, n LEV =21, n OXC=18.

Inclusion/Exclusion Criteria Inclusion criteria: age comprised between 3-12 years, newly diagnosis of BECTS according to the International League Against Epilepsy (ILAE) classification, frequent seizures and/ or seizures that recur during wakefulness in the last 6 months, partial motor seizures, typically hemifacial or hemiclonic, with or without generalization, EEG features consisting of peculiar focal or multifocal centrotemporal spikes (CTS), increasing in frequency during sleep, on a normal background activity and sleep organization, MRI disclosing normal or slight abnormal findings, absence of neurological and mental deficits, no previous therapy, informed consent by parents or carers. Exclusion criteria were: poor compliance by parents/caregivers to fill in the diary of seizure frequency and adverse events and to undergo the requested clinical controls, progressive neurological and/or systemic disease, patients with pseudoseizures (as diagnosed by MRI scans).

Patient Characteristics The participants were aged between 3.3 and 14 years (mean 10.7 years) with 21 of them males and 18 females. Mean seizure frequency before starting therapy was 1.6/month during the last 6 months and seizure type was secondary generalised tonic-clonic in about 80% of children.

Recruitment From the outpatient clinics of Child Neuropsychiatry (Second University of Naples, University of Bologna, University of Chieti, Italy).

Setting The outpatient clinics of Child Neuropsychiatry.

Interventions/ Test/ Factor being investigated levetiracetam (LEV) monotherapy versus oxcarbazepine (OXC) monotherapy.

Comparisons Between levetiracetam and oxcarbazepine.

Length of Study/ Follow-up Mean follow up period of 18.5 months (range 12-24 months).

Outcome measures studied Primary outcome: seizure freedom, proportion of participants having treatment withdrawn, incidence of adverse events, withdrawal due to adverse events.

Results 19/21 (90.5%) in the LEV group and 13/18 (72.2%) in OXC group were seizure free. 2/21 ((9.5%) in LEV group and 1/18 (5%) in OXC group had treatment withdrawn due to adverse events. 1/21(4.8%) in LEV group and 5/18 in OXC (27.7%) had treatment withdrawn due to lack of efficacy. The proportion of adverse side effects was 3/21 (14.3%) in LEV (two participants had decreased appetite, one moderate decreased appetite combined with daily frontal cephalagia) and 2/18 (11.1%) in OXC group respectively (one patient with headache and the other with sedation).

Safety and adverse effects See Q2 on adverse events.

Does the study answer the question? Within the limitations of an open trial, both levetiracetam and oxcarbazepine were effective in seizure prevention. However, more participants in LEV group compared to OXC had treatment withdrawn due to adverse events and a higher proportion of children in OXC withdrawn due to lack of efficacy compared to LEV.

Effect due to factor in study? The study was unblinded, and there was no reconsideration of minimum sample size required to test the efficacy of the two interventions. The study may be underpowered.

Consistency of results with other studies?

Directly applicable to guideline population? Serious indirectness. Maximum dose for both levetiracetam and oxcarbamazepine was 20 mg/kg daily (recommendations by BNF for children; maximum dose for levetiracetam is 30mg/kg twice daily and for oxcarbamazepine 23mg/kg twice daily).

Internal Validity

Kang H;Eun B;Wu LC;Ku MH;Kim J;Wook KD;Soo LJ;Young CK;Ho CB;Sook SE;Chae PJ;Lim K;Hye HE;Ho SD;Dong KH;

The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign rolandic epilepsy

Ref ID 1556

2007

Study Type Randomised Controlled Trial

Funding By a grant of JANSSEN, KOREA LIMITED, a Johnson & Johnson company.

Number of participant N=112 patients, n Topiramate =58, n carbamazepine= 54.

Inclusion/Exclusion Criteria Inclusion criteria: 5-15 years old with normal intelligence and had at least two partial onset seizures during 6 months at baseline, parent and/or patient wanted to take AEDs, daytime seizures, at least 1 episode of a convulsive seizure during 6 months, absence of a progressive cerebral lesion. Exclusion criteria: evidence of a progressive cerebral lesion or neurodegenerative metabolic disorder, cognitive impairment that could interfere with cognitive testing procedure, history of psychiatric disorder requiring major tranquilizers in the past 6 months, regular treatment with antihistamines, CNS active compounds during the past 30 days, history of poor compliance with antiepileptic treatment or inability to maintain a seizure calendar independently or with assistance, history of nephrolithiasis and patients who have taken any medication associated with nephrolithiasis. Patients previously treated with TPM or CBZ were also excluded.

Patient Characteristics The mean age was similar to both groups (mean (sd) was 8.7 (1.9) and 8.7 (2.0) for the TPM and CBZ groups respectively). 32/58 in TPM and 32/54 in CBZ were males and participants in both groups had similar baseline weights (mean weight was 30.6 and 31 kgr for the TPM and CBZ groups respectively).

Recruitment Not reported.

Setting The study was conducted at 12 centres. No more inf

Interventions/ Test/ Factor being investigated Topiramate versus carbamazepine.

Comparisons Comparison between Topiramate and carbamazepine.

Length of Study/ Follow-up 1st week: screening phase, 2nd- 7th week: dose escalation phase, additional escalation was allowed up to the maximum tolerated until the 22th week (from the screening phase), maintenance period between 22th-28th weeks (from the screening phase).

Outcome measures studied seizure freedom, incidence of adverse events.

Results 40/58 (69.6%) of patients in TPM and 38/54 (70%) in CBZ were seizure free during the trial.

6/58 (10.3%) in TPM group and 5/54 (9%) in CBZ group withdrawn due to adverse

events.

Incidence of adverse events (above 10%):
somnolence: 7/58 (12.1%) in TPM and 5/54 (9%) in CBZ group
rash: 1/58 (1.7%) in TPM and 8/54 (14.8%) in CBZ group

Safety and adverse effects

See adverse events in Q2.

Does the study answer the question?

Almost similar high proportions of TPM and CBZ groups were seizure free during the trial.
Almost similar proportions of patients in both groups, TPM and CBZ, withdrawn due to adverse events.

Effect due to factor in study?

The sample size of this study was larger than the minimum required to detect a difference in the effect between the two groups (however the calculation of sample size as it is stated is incomplete in relation to size of effect). The study was a single blinded trial with no information on allocation concealment. Uncertain about the overall effect of the intervention.

Consistency of results with other studies?

Directly applicable to guideline population?

Serious indirectness. Maximum dose for Topiramate was 4mg/kg daily and for carbamazepine was 30mg/kg daily (recommendations by BNF for children; maximum dose for Topiramate is 7.5mg/kg twice daily and for carbamazepine 20mg/kg twice daily).

Internal Validity

Question: What is the clinical effectiveness and cost-effectiveness of a ketogenic diet?

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Neal EG;Chaffe H;Schwartz RH;Lawson MS;Edwards N;Fitzsimmons G;Whitney A;Cross JH;

The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial.[see comment]

Ref ID 135

2008 Jun

Study Type Randomised Controlled Trial **Funding** HAS, Smiths Charity, Scientific Hospital Supplies, and the Milk Development Council.

Number of participant Seventy-three randomised to the diet group and 72 randomised to control group.

Inclusion/Exclusion Criteria Inclusion: children aged between 2 and 16 years who had seizures at least daily or more than 7 seizures per week, had not responded to at least two antiepileptic drugs, and had not previously been treated with the ketogenic diet.
Exclusion: history of hyperlipidaemia, renal stones, or organic-acid-deficiency syndromes: which did not apply to any referred children.

Patient Characteristics Epilepsy syndrome were combined into 2 categories: those with generalised symptoms and those that had focal symptoms.
78 children had generalised epilepsy and 57 children had focal epilepsy. Children had a mean of 11.6 seizures per day (13.3 in the diet group and 10.1 in the control group).

Recruitment Recruited from referrals from epilepsy clinics and from paediatric neurologists and paediatricians around the UK.

Setting Secondary Care.

Interventions/ Test/ Factor being investigated Ketogenic diets, either the classical or Medium-chain tryglycerides (MCT), compared to normal diet until 3 months, then KD versus MCT (at additional 3, 6 and 12 months results).

Comparisons Ketogenic diet compared to normal diet with no dietetic input until 3 months
Ketogenic diet compared to MCT (at3, 6 and 12 months results).

Length of Study/ Follow-up Up to 12 months.

Outcome measures studied Decrease in seizure frequency.

Results All ketogenic diets were calculated on an individual basis by a dietitian after a telephone consultation with the parents or carers with regard to the child's current food preferences. The children's pre-study calorific intake was calculated with a computer program from a 4-day food record. The initial calorie prescription for the ketogenic diets was based on an average between their pre-diet intake and the recommendations for energy requirements on the ketogenic diet and taking into account current and previous weight and height, UK recommended calorific requirements, levels of physical activity, seizure activity, and medications.

(Neal et al 2008) KD group (n=73) vs control group at 3 months (n=72):
>90% reduction 5 (7%) vs 0 (0%) p =0.0582.
>50% reduction (already includes >90%) 28 (38%) vs 4 (6%) p<0.001.

At 3 months, freedom from seizures was attained in 1 child in the KD group and none in the control group.

Side effects reported at 3 months on the KD diet:

Vomiting 13 (24%).
Diarrhoea 7 (13%).
abdominal pain 5 (9%).

Constipation 18 (33%).
Medication for constipation needed 13 (24%).
Lack of energy 13 (24%).
Hunger 12 (22%).

Results from Neal et al (2009) (Classical Ketogenic Diet versus MCT diet- patients had been on the previous phase KD versus control)

At 3 months:

Classical group (n=73) vs MCT diet group (n=72):
>90% reduction 5 (6.8%) vs 2 (2.7%) p=0.442.
>50% reduction 18 (24.7%) vs 21 (29.2%) p=0.578.

At 6 months:

Classical group (n=73) vs MCT diet group (n=72):
>90% reduction 6 (8.2%) vs 4 (5.6%) p=0.745.
>50% reduction (already includes >90%) 18 (24.7%) vs 14 (19.4%) p=0.549.

At 12 months:

Classical group (n=73) vs MCT group (n=72)
>90% reduction 7 (9.6 %) vs 7 (9.7%) p =1.000.
>50% reduction (already includes >90%) 13 (17.8 %) vs 16 (22.2%) p=0.539.

There was no significant differences between the 2 types of diet, except increased reports of lack of energy after months and vomiting after 12 months of classical diet.

The mean beta-hydroxybutyrate level was higher in the classical diet group after 3, 6 and 12 months of treatment; this was significant at 3 and 6 months only.

Adverse events from (n=55) who continued the KD for 3 months:

Classical

Vomiting 13 (28%).
Diarrhoea 7 (15%).
abdominal pain 5 (11%).
Constipation 21 (45%).
Lack of energy 17 (36%).
Hunger 12 (26 %).
Taste problems 10 (21%).

MCT

Vomiting 11 (26 %).
Diarrhoea 6 (14%).
abdominal pain 8 (19%).
Constipation 14 (33 %).
Lack of energy 6 (14 %).
Hunger 14 (33 %).
Taste problems 7 (17%).

Adverse events from those who continued the classical and MCT diets for 6 months:

Classical

Vomiting 9 (36%).
Constipation 12 (48%).
Hunger 6 (24%).
Taste problems 4 (16%).

MCT

Vomiting 7 (22%).
Diarrhoea 4 (13 %).
abdominal pain 4 (13%).
Constipation 13 (41%).
Lack of energy 5 (16%).
Hunger 6 (19 %).
Taste problems 11 (34%).

Adverse events from those who continued the classical and MCT diets for 12 months

Classical

Vomiting 9 (45 %).

Diarrhoea 2 (10 %).
abdominal pain 2 (10 %).
Constipation 9 (45 %).
Lack of energy 2 (10 %).
Hunger 5 (25 %).
Taste problems 3 (15 %).

MCT
Vomiting 3 (13%).
Diarrhoea 4 (17 %).
abdominal pain 4 (17 %).
Constipation 9 (39 %).
Lack of energy 3 (13%).
Hunger 4 (17 %).
Taste problems 5 (22%).

Safety and adverse effects

Of the 45 children on the classical diet and 49 on the MCT diet, 9 and 11 respectively discontinued at 3 months. This was due to limited efficacy, the psychosocial costs of following the strict dietary regimen outweighing the benefit seen in terms of seizure reduction. After the 6 months follow-up, an additional 12 children (6 on each diet) discontinued. By 12 months, 57 of the 125 who had started a dietary treatment had discontinued dietary treatment.

Does the study answer the question?

The findings support the use of ketogenic diet in children with intractable epilepsy.

Effect due to factor in study?

Study is not blinded, however a good quality study.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct population.

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Freeman JM;Vining EP;Kossoff EH;Pyzik PL;Ye X;Goodman SN;

A blinded, crossover study of the efficacy of the ketogenic diet.[see comment]

Ref ID 4832

2009 Feb

Study Type Randomised Controlled Trial **Funding** Supported by the NIH and by the Paediatric Clinical Research Unit.

Number of participant Twenty children were enrolled. Eleven given glucose first.

Inclusion/Exclusion Criteria Inclusion: children aged 1 to 10 years, prior exposure to at least 2 anticonvulsants, electroencephalography (EEG) evidence within 6 months of the typical LGS patterns of 2-2.5 Hz spike and slow wave discharges, and an average of at least 15 atonic-myoclonic seizures per day by parental records over the prior month. Exclusions: evidence for a metabolic disorder, treatment with steroids or adrenocorticotropic hormone (ACTH) in the prior month (which would theoretically negate ketosis), or previous KD treatment.

Patient Characteristics Mean age of 3.9 years (range 1.0-7.4 years), and eleven (55%) were male.

Recruitment Not specified.

Setting Secondary Care.

Interventions/ Test/ Factor being investigated Ketogenic Diet. 60g of glucose solution as placebo and artificial sweetener (saccharin) as treatment arm. During each day of the study, the child was given a solution of sweetened, flavored water that replaced an equivalent portion of the typical carbohydrate-free fluid allotment. Children were randomised to either receive a solution containing 60g of glucose or a similar saccharin solution.

Comparisons Ketogenic diet versus placebo.

Length of Study/ Follow-up Up to 12 months after discharge.

Outcome measures studied >50% reduction in seizures, median change of seizures, urinary ketones, EEG-identified events.

Results Other seizures, including absence, tonic, and generalised tonic-clonic seizures were not recorded by the parents.

Between the ends of the saccharin and glucose arms, 6 children showed both >50% seizure reduction with saccharin in addition to <50% improvement in glucose, compared to 3 children who demonstrated to opposite response ($p=0.50$). The sequence of treatment arms did not make a difference in EEG-identified events ($p=0.32$).

At day 6, 65% of patients experienced a >50% reduction in seizures.

At 6 months after discharge, 80% had a >50% decrease in reported seizures, and at 12 months 65% had a >50% decrease.

On the final days of each saccharin arm of the study, urinary ketones were uniformly large (80-160mg/dL); however even during the glucose arm, ketones were still typically trace to moderate (15-60mg/dL). There was a significant difference between the serum BOH of children during the glucose arm compared to the saccharin arm (2.7 versus 6.0mmol/L, $p<0.001$).

Safety and adverse effects Six children had emesis, during the fasting period or after, one of which required 1 day glucose free intravenous fluids. Three additional children were fatigued. Hypoglycaemia occurred in 25% of children.

Does the study answer the question?

Moderate evidence of reduction of parent reported seizures.

Effect due to factor in study?

No ITT analysis, lack of detail on blinding and randomisation concealment. Medium risk of Bias.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct intervention and population.

Internal Validity

Question: Which AEDs are clinically effective and cost-effective for people with Convulsive status epilepticus?

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Ahmad S;Ellis JC;Kamwendo H;Molyneux E;

Efficacy and safety of intranasal lorazepam versus intramuscular paraldehyde for protracted convulsions in children: an open randomised trial.[see comment]

Ref ID 4590

2006

Study Type	Randomised Controlled Trial	Funding	Supported by an academic grant from the College of Emergency Medicine (UK). Mucosal administration devices were supplied at no cost by Wolfetory Medical, Salt lake City.
Number of participant	N= 80 in the Lorazepam group and n=80 in the paraldehyde group.		
Inclusion/Exclusion Criteria	Children with features of hepatic or hypertensive encephalopathy or organophosphate poisoning were excluded as were children who had received an anticonvulsant agent within one hour of presentation.		
Patient Characteristics	<p>Children of both sexes and aged 2 months to 12 years children presenting to a paediatric emergency centre with a generalised convulsion continuing for a minimum of 5 minutes.</p> <p>Because of the geographical location of this study the majority of the children had acute symptomatic seizures mainly due to acute brain infection (cerebral malaria or bacterial meningitis in 2/3 of each of the two study groups). For children in whom clinical seizure activity continued after 10 minutes, investigator followed a locally agreed protocol.</p> <p>In the intranasal Lorazepam group seizure were exclusively due to acute brain infection secondary to cerebral malaria or bacterial meningitis in 51 (64%) of 80 children, and 53 (66%) of 80 children in the intramuscular paraldehyde group.</p>		
Recruitment	Patients entering the paediatric emergency department within the Blantyre region in Malawi.		
Setting	Resuscitation room.		
Interventions/ Test/ Factor being investigated	Intranasal lorazepam versus intramuscular paraldehyde.		
Comparisons	Intranasal lorazepam versus intramuscular paraldehyde.		
Length of Study/ Follow-up	Not clear.		
Outcome measures studied	Seizure cessation, incidence of cardio respiratory depression, need for further anti-convulsant/s.		
Results	<p>Intranasal lorazepam and intramuscular paraldehyde were equally effective in the management of prolonged seizures, with 60/80(75%) in the lorazepam group and 49/80(61%) in the intramuscular paraldehyde group successfully terminating (RR 1.9, 95% CI 0.96-3.74). 8/80 (10%) children in the lorazepam group and 21/80 (26%) in the paraldehyde group required 2 or more further anticonvulsant doses to terminate the seizures (RR 0.38, 95%CI 0.18 - 0.81).</p> <p>The median time for the presenting seizure to stop after drug administration did not differ between groups.</p> <p>No significant difference was found between either treatment in terms of seizure recurrence within 24 hours.</p> <p>No difference was found between either treatment group in terms of clinically important cardiorespiratory events.</p>		

IN Lorazepam group: 15 children whose SBP fell by at least 5mm Hg, with a median reduction of 7mm Hg (range 5-20 mm Hg) and 12 children whose DBP fell by at least 5 mm Hg with a median of 7.5 mm Hg (5-16 mm Hg)

IM Paraldehyde group: 16 children with SBP reduction of at least 5 mm Hg with a median of 6.5 mm Hg (5-10 mm Hg) and 4 children with a DBP reduction of at least 5 mm Hg, median 6.5 mm Hg (5-20 mm Hg)

Safety and adverse effects

Seventy-five children had a pre-treatment-seizure duration of less than 2 hours, 8 of whom died (absolute risk 0.1, 95% 0.04-0.2). Of the 85 patients with a pre-treatment-seizure duration of greater than 2h, 20 died (absolute risk 0.23, 95% CI 0.15-0.34; RR 0.45, 95% CI 0.21-0.86, p=0.03). Proportion of deaths was greater in those with HIV infection. Seven deaths occurred in the 19 HIV infected children compared to 21 of the 141 non infected (RR 2.51, 95% CI 1.23-5.10, p=0.02).

Does the study answer the question?

Relevant study.

Effect due to factor in study?

Overall well conducted study, with appropriate power calculations.

Consistency of results with other studies?

Directly applicable to guideline population?

Sub-Saharan population, otherwise direct comparisons.

Internal Validity

Allredge BK;Gelb AM;Isaacs SM;Corry MD;Allen F;Ulrich S;Gottwald MD;O'Neil N;Neuhaus JM;Segal MR;Lowenstein DH;

A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus

Ref ID 4792

2001

Study Type

Randomised Controlled Trial

Funding

Supported by a grant from the National Institutes of Health.

Number of participant

Total randomised: 258. Some patients were enrolled more than once. Report data from the first enrolment of each patient. Total patients: 205: Lorazepam group: 66 patients; Placebo group: 71 patients; Diazepam group: 68 patients.

Inclusion/Exclusion Criteria

Inclusion criteria:

1. Meets clinical diagnosis of status epilepticus
 - A. Paramedics or reliable witnesses verify continuous or repeated convulsive seizure activity of more than 5 minutes.
 - B. Patient does not regain consciousness (operationally defined as meaningful speech or obeying commands) between seizures.
2. Patient is still seizing on paramedic arrival; or, if not, patient was unresponsive on paramedic arrival and has a qualifying generalised seizure without regaining consciousness (as defined in 1b)
3. Adult patient (18 years or older).

Exclusion criteria:

1. Pulse <60bpm
2. Systolic blood pressure <100mm Hg
3. Second or third degree atrioventricular block
4. Sustained ventricular tachyarrhythmia
5. Asthma or chronic obstructive pulmonary disease
6. Known history of chronic benzodiazepine use
7. Known sensitivity to benzodiazepines
8. Known pregnancy
9. No IV access
10. Transport to no participating emergency department
11. Patient in custody

12. Responding ambulance from private company
13. Telecommunications failure

Patient Characteristics

Lorazepam vs diazepam vs placebo:
Age (years): 49.9+/-20.1 vs 50.4+/-19.1 vs 52.0+/-18.2;
Male sex: 69.7% vs 60.3% vs 59.1%.
Race or ethnic group (%):
American Indian or Alaskan: 1.5 vs 1.5 vs 4.2.
Asian or Pacific Islander: 21.2 vs 7.4 vs 9.9.
Black: 18.2 vs 16.2 vs 29.6.
Hispanic 9.1 vs 20.6 vs 8.5.
White 48.5 vs 54.4 vs 46.5.
Other 1.5 vs 0 vs 0
Unknown 0 vs 0 vs 1.4.

History of seizures: 54.6% vs 69.1% vs 66.2%.

Cause of status epilepticus (%):
Low blood levels of antiepileptic drugs: 16.7% vs 25 vs 23.9.
Refractory epilepsy: 13.6 vs 13.2 vs 8.5.
Alcohol abuse: 9.1 vs 11.8 vs 9.9.
Metabolic derangement: 3 vs 2.9 vs 7.
Toxic effects of drugs (recreational or prescribed): 10.6 vs 7.4 vs 7.
Anoxia or cardiopulmonary arrest: 1.5 vs 0 vs 0.
Infection in the central nervous system: 7.6 vs 7.4 vs 5.6.
Trauma: 6.1 vs 8.8 vs 4.2.
Tumour in central nervous system: 6.1 vs 4.4 vs 9.9.
Stroke: 16.7 vs 13.2 vs 9.9.
Nonepileptic seizures: 3 vs 4.4 vs 7.
Other 0 vs 0 vs 1.4.
Unknown: 6.1 vs 1.5 vs 5.6.
Duration of SE before study treatment (min) 34+/-17.8 vs 31.3+/-14.5 vs 46.7+/-38.8.
Interval from study treatment to arrival at emergency department (min): 16.2+/-9.3 vs 15.9+/-9.3; 16.5+/-8.2.

Recruitment

If attended by a paramedic ambulance.

Setting

San Francisco.

Interventions/ Test/ Factor being investigated

Ongoing training given to affiliated personnel; Paramedics instructed to call the base hospital to confirm suspected status epilepticus (SE). Base Hospital radio contact logs reviewed for quality assessment and population details. Drug kits prepared by drug pharmacist and labelled with unique identifying number (study drug number) from a master list of computer-generated randomised numbers which were prepared at the study start.

Each kit had two 2 mL glass syringes with 1 mL each of identical study medication: diazepam 5mg, Lorazepam 2mg or placebo propylene glycol 20% v/v in 0.9% sodium chloride. The drugs were administered during general tonic-clonic seizures. If seizures recurred or continued four minutes or more after then a 2nd identical injection was given.

Comparisons

Intravenous Diazepam versus intravenous Lorazepam versus placebo.

Length of Study/ Follow-up

Not reported.

Outcome measures studied

Primary outcome: termination of SE by time of arrival at the ED. Secondary outcomes: out-of-hospital complications; complications at transfer; duration of SE before arriving at hospital; neurological outcome at discharge; disposition of patient from ED.

Results

Status epilepticus at the time of arrival at the emergency department:

SE terminated:

Lorazepam 39 (59.1) vs diazepam 29 (42.6) vs placebo 15 (21.1). P=0.001.

Ongoing SE:

Lorazepam 27 (40.9) vs diazepam 39 (57.4) vs placebo 56 (78.9).

Safety and adverse effects Interim safety analyses performed. O'Brien-Fleming procedure applied to each of comparisons of treatments. Data and monitoring board and external advisory committed concluded data as whole did not support early termination of study.

Does the study answer the question? It has one outcome of interest. The authors concluded that benzodiazepines are safe and effective when administered by paramedics for out-of-hospital status epilepticus in adults. Lorazepam is likely to be a better therapy than diazepam.

Effect due to factor in study? Yes. 80% power with 5% significance level with target sample size of 210 patients, 208 patients included in study so slightly underpowered. Good methodology.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Leppik IE;Derivan AT;Homan RW;Walker J;Ramsay RE;Patrick B;

Double-blind study of lorazepam and diazepam in status epilepticus

Ref ID 4782

1983

Study Type Randomised Controlled Trial **Funding** Not clear.

Number of participant N=37 in the Lorazepam group and n=33 in the Diazepam group.

Inclusion/Exclusion Criteria Exclusion: presence of illness, cardiac arrhythmia, hypotension, any acute metabolic disorder causing SE, a history of sensitivity to benzodiazepines, or childbearing potential. Persons who had received diazepam or other drug treatment for status before referral to the study were not included.

Patient Characteristics Definition of SE- Generalised tonic-clonic status: three or more generalised tonic-clonic seizures in one hour; two or more generalised seizures in rapid succession without recovery of consciousness; (b) absence status: confusional state with generalised 3 Hz spike wave pattern on EEG; (c) complex partial status: confusional state, clinical seizure or both with focal EEG abnormality; (d) elementary status: partial seizures without loss of consciousness.

Mean age of the Diazepam group was 56 years and 50 years for the Lorazepam group.

Recruitment Not clear.

Setting USA

Interventions/ Test/ Factor being investigated Arm 1 = lorazepam
Arm 2 = diazepam

After an IV infusion and all the emergency measures to ensure patient airway and safety were initiated, 2 mL of the study drug (10mg of diazepam or 4mg of lorazepam) was injected over a period of two minutes. The 2nd 2mL dose of the same drug was administered at the discretion of the treating physician if seizures continued or recurred after 10 minutes. Because the know duration of action of diazepam is 20-30 minutes, most patients were given a loading dose of phenytoin even if seizures had not recurred 30 minutes after administration of study drug.

Comparisons IV Lorazepam versus IV diazepam

Length of Study/ Follow-up Not clear.

Outcome measures studied Cessation of seizures.
Recovery at discharge.
Mortality.

Requirement for ventilatory support.
Complications.
Adverse effects.

Results

Seizure activity was terminated by a single injection of diazepam in 19 (58%) of 33 episodes, as compared with 29 of 37 terminating after lorazepam administration. A second dose of diazepam was given to 13 of the 14 persons not responding initially; seizures ceased to 6. For Lorazepam, a second dose was given to 8 persons; seizures ceased to four.

One or two doses (10 or 20mg) of diazepam terminated seizure activity in 25 (76%) of 33 episodes, and lorazepam (4 or 8 mg) was effective in 33 (89%) of 37 cases (p =non significant).

Latency for action ranged from immediate effectiveness to 10 minutes (median, two minutes) for diazepam in all patients whose seizures were controlled. For lorazepam, the range was immediate to 15 minutes (median, 3 minutes) (p =non significant).

Adverse effects occurred in 5 of the 41(12%) treatments with diazepam and 5 of the 40 (13%) treatments with lorazepam.

Safety and adverse effects

Adverse effects occurred in 5 of the 41(12%) treatments with diazepam and 5 of the 40 (13%) treatments with lorazepam.

Does the study answer the question?

Relevant study to the clinical question.

Effect due to factor in study?

Uncertain. No details on randomisation nor allocation concealment.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct population.

Internal Validity

Mehta V;Singhi P;Singhi S;

Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial

Ref ID 202

2007 Oct

Study Type Randomised Controlled Trial

Funding Not reported.

Number of participant N=20 VPA and n=20 in DIA

Inclusion/Exclusion Criteria

Children aged 5 months to 12 years, with refractory convulsive SE. SE was defined as 30 minutes of continuous seizure activity or 2 or more sequential seizures without full recovery of consciousness between seizures.
Neonates and infants up to 3 months of age as well as known or suspected cases of mitochondrial disorders were excluded.

Patient Characteristics

Most common cause of SE was central nervous system infection.

Recruitment

Children admitted to an Emergency and Neurology Ward.

Setting

India. Emergency Care Unit.

Interventions/ Test/ Factor being investigated

Sodium Valproate initial bolus of 30mg/kg diluted 1:1 in normal saline from 2 to 5 min. If SE not controlled within 10 min after the bolus dose, a repeat bolus dose of 10mg/kg was given. Followed by infusion at a rate of 5mg/kg/hr continued until a seizure-free period of 6 hours and then reduced at a rate of 1mg/kg/hr every 2 hours. After discontinuation of IV infusion, a maintenance dose of 10mg/kg IV every 8 hours was continued until the child could take oral anticonvulsants.

In the DIA group, infusion was 10 microg/kg/min and was increased every 5 minutes by 10microg/kg/min until SE was controlled or a maximum dose of 100microg/kg/min was reached.

If seizures were not controlled within 30 min of giving IV sodium valproate, DIA was given as the next line of treatment. If there was no response to the maximum dose of DIA, thiopental infusion was given.

Comparisons

IV Sodium Valproate versus DIA infusion

**Length of Study/
Follow-up**

Not clear.

**Outcome measures
studied**

1) proportion of patients whose SE was controlled within 30 minutes; 2) time taken for control of SE. Adverse events.

Results

Refractory SE controlled within 30 min
VPA group 16/20 (80%)
DIA group 17/20 (85%) (p=1.0)

Time interval for control of RSE after giving study drug (min) (mean±SD)
VPA group: 8.8±7.4
DIA group: 26.6±26.7 (p=0.001)

Four children in the VPA group, whose SE was not controlled were given DIZ infusion. SE was controlled in 3, whilst 1 required thiopental.

**Safety and adverse
effects**

Respiratory Depression
VPA group: 0
DIA group: 12/20 (60%)

Deaths
VPA group: 4/20
DIA group: 3/20
5 had meningoencephalitis with raised intracranial pressure and 1 each had uremic encephalopathy and intractable epilepsy.

Hypotension after drug administration
VPA group: 0
DIA group: 10/20 (50%)

Breakthrough seizures
VPA group: 8/20 (40%)
DIA group: 8/20 (40%)

**Does the study
answer the question?**

Relevant study to the clinical question.

**Effect due to factor in
study?**

Overall well conducted study, however open-label.

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?**

Direct population.

Internal Validity

Singhi S;Murthy A;Singhi P;Jayashree M;

Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus

Ref ID 4784

2002

Study Type

Randomised Controlled Trial

Funding

Not reported.

Number of participant

N=21 continuous Midazolam and 19 diazepam infusion.

Inclusion/Exclusion Criteria	Children 2 months to 12 years of age in refractory convulsive status epilepticus who were consecutively admitted over a period of 1.5 years to the Emergency and Intensive Care Services of the Advance Pediatric Centre. Neonates and children with primary cardiac or respiratory diseases or any other chronic illness were excluded.
Patient Characteristics	Status Epilepticus was defined as 30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures. Patients whose seizures were not controlled after 2 bolus doses of diazepam (0.3mg/kg) and phenytoin infusion (20mg/kg in normal saline infusion over 20 minutes) followed by a repeat dose of benzodiazepine were considered to have refractory SE.
Recruitment	Patients admitted to the Emergency and Intensive Care Services of the Advance Pediatric centre, Postgraduate Institute of Medical Education and Research.
Setting	Chandigarh, India.
Interventions/ Test/ Factor being investigated	Arm 1 = midazolam Arm 2 = diazepam in both groups, infusion was continued for at least 6 hours after control of the last seizure and then was gradually tapered over 12 to 24 hours under clinical monitoring. If the seizures were not controlled with the maximum dose of the study drug, thiopental (loading dose of 3mg/kg followed by a continuous infusion of 0.2mg/kg/min) was used.
Comparisons	IV Midazolam versus IV Diazepam.
Length of Study/ Follow-up	Appears to be at 24 hours.
Outcome measures studied	Cessation of seizures. Recovery at discharge. Mortality. Complications. Adverse effects
Results	Refractory SE was controlled successfully in 18/21 (85.7%) of patients in the midazolam group and 17/19 (89.5%) of patients in the diazepam group (p=non significant). The mean time interval between starting the infusion and initial control of seizure activity was about 16 minutes in both groups (p=non significant) 13 patients on midazolam and 16 on diazepam required intubation either for protection of the airway, poor respiratory efforts requiring ventilation, or both. 11 of 21 in the midazolam group and 9/19 in the diazepam group required ventilation (p= non significant). Hypotension occurred in 8 patients in the Midazolam group and 8 in the diazepam group. 2 patients in each group had hypotension even before diazepam or midazolam infusion was started, whereas 13 (32.5%) of patients developed hypotension on the drug infusion.
Safety and adverse effects	Eight patients died in the Midazolam group, compared to 2 in the diazepam group (p< 0.1 > 0.05), 5 because of meningoencephalitis and one each from acute hyponatremia (caused by diarrhoea) and hepatic encephalopathy.
Does the study answer the question?	Relevant study
Effect due to factor in study?	Yes.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct population

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Agarwal P;Kumar N;Chandra R;Gupta G;Antony AR;Garg N;

Randomized study of intravenous valproate and phenytoin in status epilepticus

Ref ID 220

2007 Sep

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant VPA group: n=50; PHT n=50.

Inclusion/Exclusion Criteria
Inclusion criteria:
Patients with status epilepticus which was refractory to IV diazepam.
Definition of SE: continuous or repeated seizure activity for more than 5 minutes without recovery of consciousness.
Exclusion criteria:
Pregnant women.
Children less than 2 years of age.
Patients with: hepatic encephalopathy, myoclonic status epilepticus, neurological emergency requiring immediate surgical intervention, or contraindication to therapy with hydantoin, benzodiazepine or barbiturates.
Only first episode included if patient enrolled more than once by mistake.

Patient Characteristics VPA vs PHT:

Mean age (years): 27.4+/-16.8 vs 27+/-15.1.
Male sex: 35 (70%) vs 32 (64%).
Below 18 years: 22 vs 16.
Most common etiology of SE:
- AED non-compliance or withdrawal: 12 (24%) vs 14 (28%).
- Inflammatory granuloma 12 (24%) vs 12 (24%).
- CNS infections 10 (20%) vs 12 (24%).
- Primary generalised epilepsy 8 (16%) vs 6 (12%).
- Stroke 2 (4%) vs 2 (4%).
- Head injury with extradural hematoma 2 (4%).
Duration of SE at time of presentation:
<2 hours: 30/50 (60%) vs 26/50 (52%).
>3 hours: 20/50 (40%) vs 24/50 (48%).

Recruitment Those admitted to the emergency ward and ICU.

Setting Emergency ward and intensive care unit.

Interventions/ Test/ Factor being investigated Patients were switched to other group if seizures not controlled or recurred within 12 hours of the treatment.

Comparisons Intravenous sodium valproate versus intravenous phenytoin.

Length of Study/ Follow-up 7 days.

Outcome measures studied Treatment success: success was defined as all motor/EEG seizure activity ceasing within 20 mins after beginning drug infusion & no return of seizure activity during the next 12 hrs; Secondary: in-hospital complications & neurological outcome at discharge.

Results
Response to treatment:
VPA vs PHT:

SE controlled: 44/50 (88%) vs 42/50 (84%) p>0.05.

SE < 2 hours: 30/30 (100%) vs 25/26 (96%) p<0.05.
SE > 2 hours: 14/20 (70%) vs 17/24 (71%) p<0.05.

Treated with both drugs: 4/7 (57%) vs 2/5 (40%).

< 18 years of age responding to treatment: 20/22 vs 12/16.

Safety and adverse effects

Mortality rate in both groups was 8% (4/50) in group A and 4/50 in group B. One patient in group A and one in group B left against medical advice due to the cost of total treatment.

Hypotension was found in 0/50 in group A and 6/50 in group B;
Total adverse events 4/50 in group A and 8/50 in group B.

Does the study answer the question?

IV sodium valproate was found to be as effective as IV phenytoin, with better tolerability compared to IV phenytoin. IV sodium valproate can be used to treat all types of status including myoclonic status, where, this is the only drug which is effective. It can be used as first line treatment of SE after benzodiazepines as an alternative to phenytoin, especially in patients of cardio-respiratory disease. The response to treatment was better in patients of SE over 2 hours than under 2 hours reflecting need of immediate treatment.

Effect due to factor in study?

No. Small population and no power calculation made. Methodology not explained clearly.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Appleton R;Sweeney A;Choonara I;Robson J;Molyneux E;

Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus

Ref ID 85

1995 Aug

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant N=53 received diazepam (34 IV) and n=33 (27 IV).

Inclusion/Exclusion Criteria Not reported.

Patient Characteristics Mean age in both groups who received the drug rectally was lower than in those who received the drug via IV, as IV access is harder in younger children.
Mean age (years): DIA (IV: 5.2; REC: 3.8) LOR (IV: 6.6; REC: 3.3)

Recruitment Patients presenting to the A&E department of the Alder Hey hospital.

Setting UK. Emergency Care.

Interventions/ Test/ Factor being investigated DIA versus LOR. When IV access was not possible, the same dose of DIA or LOR was given rectally.

Comparisons IV Diazepam versus IV lorazepam.

Length of Study/ Follow-up Appears to be up to 24 hours.

Outcome measures studied Cessation of seizures.
Requirement for ventilatory support.
ICU admission.
Adverse effects.

Results	<p>Mean time for initial seizure to stop (sec) (IV) DIA: 26 LOR: 29</p> <p>Additional drugs required to terminate presenting seizures (IV) DIA: 5/34 LOR: 1/27</p> <p>Seizure stopped: (IV) DIA: 22/34 LOR: 19/27</p> <p>(rectal) DIA: 6/19 LOR: 6/6</p>
Safety and adverse effects	<p>Respiratory depression: (IV) DIA: 7/34 LOR: 1/27</p> <p>Patients requiring Intensive care (IV) DIA: 8/34 LOR: 0/27</p>
Does the study answer the question?	Relevant study to the clinical question.
Effect due to factor in study?	Quasi-randomised study. Unblinded. High risk of bias, however authors state that randomisation would have delayed treatment for acute seizures, which are a medical emergency. Also no clear inclusion/exclusion criteria.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct Population.
Internal Validity	
Baysun S;Aydin OF;Atmaca E;Gurer YK;	
A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures	
Ref ID 460	2005 Nov
Study Type	Randomised Controlled Trial
Funding	Not reported.
Number of participant	Total n= 43. Midazolam n=23; Diazepam n=20.
Inclusion/Exclusion Criteria	<p>Inclusion criteria: Aged 2 months to 12 years. All patients who were seen at ER room of hospital included in study.</p>
Patient Characteristics	<p>Midazolam versus diazepam: Sex: female: 12 (52%) vs 9 (45%); male: 11 (48%) vs 11 (55%); Age (mean): 3.87+/-3.39 years (range 2 months - 12 years) vs 2.85+/-3.13 years (range 4 months to 9 years). Most common type of convulsive episode in both groups was generalised tonic-clonic seizures.</p>
Recruitment	ER of Dr Sami Ulus Children's hospital.

Setting	Turkey.
Interventions/ Test/ Factor being investigated	<p>Nasal oxygen given to all patients. ECG closely monitored and IV access established. BP and oxygen saturation monitored.</p> <p>Midazolam (dormicum 15mg midazolam/dmL ampul) given on even days by squirting around buccal mucosa. Diazepam (desitin rectal tube 10mg) given on odd days.</p> <p>If first drugs did not stop seizures in 10 minutes after first drug, the second drug (midazolam or diazepam) was administered then observed after 5 and 10 minutes and then observed after one hour after seizures. Only one episode of each patient was enrolled into the study.</p>
Comparisons	Buccal midazolam versus rectal diazepam.
Length of Study/ Follow-up	5 and 10 minutes after the second drug recordings observed. Observed one hour after seizures.
Outcome measures studied	Percentage of those whose seizure was stopped; duration of time to cessation of seizure; incidence of adverse events;
Results	<p>Midazolam versus diazepam:</p> <p>% of those whose seizure was stopped (in the first 10 minutes): 18 (78%) vs 17 (85%).</p> <p>Time to cessation of seizure:</p> <p>Midazolam: 3 minutes: 12 (67%); 3 to 5 minutes: 3 (17%); 5 to 10 minutes: 3 (17%);</p> <p>Diazepam: 3 minutes: 10 (59%); 3 to 5 minutes: 4 (23.5%); 5 to 10 minutes: 3 (18%);</p> <p>Anticonvulsant effect: midazolam was found to be as effective as diazepam ($p>0.05$). Response periods of the 2 drugs showed no significant difference ($p>0.05$).</p> <p>Non-responders (5) crossed over to diazepam: 2 responded in 1 to 3 minutes; 1 responded in 3 to 5 minutes; 1 responded in 5 to 10 minutes; 1 did not respond.</p> <p>Non-responders (3) crossed over to midazolam: 1 responded in 3 to 5 minutes; 1 responded in 5 to 10 minutes; 1 did not respond.</p> <p>The need for a second drug for seizures not stopped with first was equal in the 2 groups, the difference was not statistically significant ($p<0.05$). The 2 nonresponders for both drugs had midazolam infusion in 1 and phenytoin infusion in the other.</p>
Safety and adverse effects	Diazepam group: 1 had bradypnea and oxygen saturation of 84% at 5 minutes; respiration pattern returned to normal at 10 minutes spontaneously. In the midazolam group 1 patient coughed nonparoxysmally for 1-2 minutes and then stopped spontaneously. There was no statistically significant difference for adverse events between the two groups $p=0.09$.
Does the study answer the question?	The authors concluded that buccal midazolam is safe and as effective as rectal diazepam for treating seizures.
Effect due to factor in study?	No. No power calculation and no allocation concealment and quasi-randomised.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Cereghino JJ;Mitchell WG;Murphy J;Kriel RL;Rosenfeld WE;Trevathan E;

Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group

Ref ID 4776

1998

Study Type	Randomised Controlled Trial	Funding	Athena. One of authors has been a paid consultant to provide expert testimony to the FDA Advisory Board for Diastat. Another author has owned stocks in the company (Athena) that sponsored the study.
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Number of participant	Total randomised=158. 33 excluded as did not have an ARS episode during study period. The others were excluded as they were randomised but not treated due to withdrawal of consent (1), protocol violation (1), loss to follow-up (3) or other life event (1) and 5 placebo randomised because they were not treated because of protocol violation (1) or other life event (4). Of those not treated non were due to adverse events, change in medical condition or death. Total n=114. Diazepam (diastat) n=56 vs placebo n=58.
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Inclusion/Exclusion Criteria	<p>Inclusion criteria:</p> <p>Outpatients or institutionalised patients aged 2 years or older with documented history of Acute repetitive seizures (ARS);</p> <p>Epileptic seizure type within the episode of ARS: primary generalised, complex partial with or without secondarily generalised or simple partial with a motor component epileptic seizure;</p> <p>At least 2 episodes of ARS had to have occurred within 1 year and one episode within 6 months of study entry;</p> <p>Maximal weight 111kg.</p> <p>Postmenarcheal women had to used a standard form of birth control, or abstinence, if capable of becoming pregnant.</p> <p>Normal results on rectal examination and a negative result for blood in stool at study entry.</p> <p>Availability of a caregiver to administer drug accurately and to monitor the patient during treatment and to complete the data collection forms.</p> <p>Written consent from parent or legal guardian.</p>
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Exclusion criteria:

Patients who progressed habitually to status epilepticus despite therapeutic intervention.

All AEDS had to remain at the same dosage for 2 weeks before study entry and could not be increased during the study. Initially, patients could not receive other benzodiazepine, CNS depressant or drugs that are known to alter diazepam pharmacokinetics or pharmacodynamics. This criterion was later relaxed to allow use of oral benzodiazepines if stable and chronic at a low dose. Barbiturates were allowed at a constant dosage if the steady-state plasma concentration did not exceed 30ug/mL. Patients who had received another investigational medication or device within 30 days of study entry were excluded.

Not have a clinically significant baseline laboratory abnormality.

Had to have a documented epileptiform EEG abnormality and a CT or MRI excluding a treatable lesion.

Patient Characteristics	<p>ARS - various definitions of ARS given.</p> <p>Diastat versus placebo:</p> <p>Sex: male: 31 (55%) vs 26 (45%) female: 25 (45%) vs 32 (55%).</p>
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Age group (years):
 >=2 to <6: 9 (16%) vs 16 (28%).
 >=6 to <12: 13 (23%) vs 12 (21%).
 >=12: 34 (61%) vs 30 (52%).
 Race: white 45 (80%) vs 51 (88%); black 6 (11%) vs 2 (3%) vs other 5 (9%) vs 5 (9%).
 Residence: with family at home: 42 (75%) vs 48 (83%); residential facility 8 (14%) vs 5 (8%), other 6 (11%) vs 5 (9%).
 Duration of illness (years):
 <5: 12 (21%) vs 21 (36%).
 >=5: 44 (79%) vs 36 (62%).
 ARS episode frequency/m:
 mean: 13.8 vs 6.5.
 median: 2 vs 2.
 Minimum: 0.2 vs 0.2.
 Maximum: 150 vs 90.

Recruitment

Not reported.

Setting

29 centres in North America?

**Interventions/ Test/
Factor being
investigated**

Single administration of Diastat (diazepam gel) versus matching placebo.

Characteristics of each patients' individual ARS episode defined in writing at beginning of study by caregivers, nurse coordinator and investigator. Caregivers were instructed by use of video-tape and illustrated written material on the proper methods of rectal administration and monitoring of patient respiration and response. Nurse coordinators maintained telephone contact every 2 weeks with a caregiver (to review recognition, treatment and documentation of the event) until an ARS episode occurred. When the caregivers identified an ARS they were to administer treatment and call the investigator immediately. 24 hour phone coverage available. Seizures were counted at 15 minutes after treatment then observed for 12 hours. If they continued to seize, or increase in severity or frequency or adverse event occurred the caregivers were to contact the study centre. The patients were seen within 72 hours after treatment. Caregivers and investigators completed a global assessment each.

Comparisons

Diazepam versus placebo.

**Length of Study/
Follow-up**

Patients exited the study after treatment of one ARS episode.

**Outcome measures
studied**

Primary: seizure count. Secondary: time to the next seizure, the time elapsed between administration plus 15 minutes to the occurrence of the next seizure within the 12-hour observation period and the caregiver and global assessments.

Results

Seizure free at 12-hour observation period after treatment: diastat group (55%) vs placebo group (34%), p=0.031.

At least one adverse event: diastat group (46%) vs placebo (28%), p=0.0518.
 Somnolence in all of the population: diastat 7 (13%) vs placebo 2(3).
 Somnolence in those judged by the investigator to be related to the study treatment: 7 (13% vs 2 (3).

**Safety and adverse
effects**

A concern in the study design was that placebo-treated patients, or event the Diastat-treated patients may continue to have uncontrollable seizures. Caregivers were instructed in first aid procedures and some received cardiopulmonary resuscitation training, although not required by protocol. They were to call the study site after administering the study medication to site personnel could monitor the patients response. 3 of 56 diastat-treated patients (5%) required additional treatment in an ER or hospital compared with 7 out of 58 (13%) in the placebo group.

**Does the study
answer the question?**

The authors conclude that administration of a single rectal dose of Diastat was significantly more effective than placebo in reducing the number of seizures following an episode of ARS. Also that diastat increased the probability that patients would remain seizure free for the 12 hours after Diastat treatment compared with those who received placebo. Caregivers could administer treatment safely and effectively in a no medical setting.

**Effect due to factor in
study?**

To detect a significant treatment difference of 0.30, at a power of 80% 56 patients were needed in each group. For a treatment difference of 0.25 there would need to be 39 patients per group for 80% power. Therefore the power of the study was

adequate.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Chamberlain JM;Altieri MA;Futterman C;Young GM;Ochsenschlager DW;Waisman Y;

A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children.[see comment]

Ref ID 74

1997 Apr

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total randomised: n=28. 3 randomised to diazepam were excluded because seizures did not persist for 10 minutes and did not receive medication. 1 child was randomised to receive diazepam but received midazolam after 25 minutes of unsuccessful attempts at IV access, so was excluded. One child was enrolled twice so is represented in both groups.

Total included n=24. Midazolam group n=13. Diazepam group n=11.

Inclusion/Exclusion Criteria

Inclusion criteria:
Children with motor seizures of at least 10 minutes duration.
Aged between birth and 18 years.

Exclusion criteria:
Already had an IV line established or had received anticonvulsants for the current seizure episode.

Patient Characteristics

Midazolam versus diazepam:
Age (months) median (range):42 (9-165) vs 39 (3-112).
Sex (male/total): 8/13 vs 9/11.
Prior seizure disorder: 9/13 vs 8/11.
Generalised tonic-clonic: 10/13 vs 5/11, p=0.12.

Recruitment

Presenting at the ED.

Setting

ED of children and general hospitals (3), USA.

Interventions/ Test/ Factor being investigated

Intramuscular midazolam versus intravenous diazepam.
Recorded times of: arrival, administration of medication, IV access, seizure cessation and seizure recurrence (if they had any).
Treatment successful: If patients' seizures ended in five minutes after administration.
Seizure cessation: between 5 and 10 minutes after medication was successful, but delayed seizure control.
Treatment failure: If seizures were not stopped within 10 minutes.
Recurrent seizures: if seizures stopped then recurred within 60 minutes.
Early recurrence: seizures that stopped but recurred within 15 minutes.

Comparisons

IM midazolam versus IV diazepam.

Length of Study/ Follow-up

Not reported.

Outcome measures studied

Time to cessation of seizures.

Results

Midazolam versus diazepam:

One treatment failure in each group has been excluded from the analysis. All times are in minutes (mean+/- SD):

Time to cessation after medication: 4.5+/- 3 vs 3.4 +/- 2, p=0.32.

22/24 patients responded to initial treatment with diazepam or midazolam. There was a treatment failure in each group.

All 23 patients had cessation for seizures within 15 minutes after arrival except for one patient who was started on diazepam but after 25 minutes of unsuccessfully attempts at IV access was given midazolam and the seizures stopped 6 minutes after administration.

4 patients in each group had recurrent seizures which required additional anticonvulsants within 60 minutes after medication. One case of early recurrence in each group. Phenytoin was used successfully when seizures recurred.

Safety and adverse effects

No respiratory depression and no complications in the study.

Does the study answer the question?

The authors concluded that IM midazolam is an effective anticonvulsant for children with motor seizures. Compared to IV diazepam there was more rapid cessation of seizures due to more rapid administration. The IM route of administration may be particularly useful in physicians' offices, in the prehospital setting and for children with difficult IV access.

Effect due to factor in study?

No. No power calculation given and small sample size.

Consistency of results with other studies?**Directly applicable to guideline population?**

Direct.

Internal Validity

Dreifuss FE;Rosman NP;Cloyd JC;Pellock JM;Kuzniecky RI;Lo WD;Matsuo F;Sharp GB;Conry JA;Bergen DC;Bell WE;

A comparison of rectal diazepam gel and placebo for acute repetitive seizures

Ref ID 4777

1998

Study Type

Randomised Controlled Trial

Funding

Supported by contracts with then national institute of neurological disorders and stroke and athena neurosciences. Some of the authors consulted for Athena Neurosciences and Upsher-Smith Laboratories, which market and develop rectal diazepam gel.

Number of participant

Randomised n=125. Treated patients n=91. For those randomised, diazepam n=64 vs placebo n=61. For those treated diazepam n=45 vs placebo n=46.

Inclusion/Exclusion Criteria

Inclusion criteria: boys and girls aged 2 to 14 years; adults aged 15 to 60 years; Maximal weight 100kg; At least 4 episodes of acute repetitive seizures (ARS) during the preceding year and at least one in the preceding 3 months; ARS defined as an episode of multiple complex partial or generalised (tonic, clonic, tonic-clonic, atypical absence or myoclonic) seizures occurring with a 24-hour period in adults or a 12-hour period in children, with a pattern distinguishable from the patient's usual seizure pattern, and with onset readily recognisable by a caregiver,

such as a parent;
On a stable AED regimen for at least 4 weeks before enrolling;
Brain computed tomography or MRI and lab screening had shown no evidence of a treatable cause of seizures;
Women of childbearing potential were eligible if used contraception and had a negative pregnancy test;

Exclusion criteria:
Plasma phenobarbital concentrations greater than 30mg per litre;
Current treatment with drugs other than anticonvulsants, long-term use of benzodiazepines, use of CNS depressants or drugs interacting with diazepam, more than one previous treatment with rectal diazepam, nonepileptic seizures within the preceding five years, habitual progression to status epilepticus, clinically significant psychiatric disorder, lack of a suitable caregiver, or use of an investigational drug or device within the preceding 5 months.

Patient Characteristics Diazepam versus placebo

Randomised patients:
sex (number) male: 38 vs 32; female 26 vs 29.
race (number): white 44 vs 53; black 14 vs 7; other 6 vs 1;
age group (number): 36 vs 31;
median age (year): child 8 vs 8; adult 28 vs 30;
median body weight (kg) child: 23.6 vs 22.4; adult 57.1 vs 60.2;

Treated patients:
sex (number) male: 29 vs 22;
race (number): white 29 vs 40; black 12 vs 5; other 4 vs 1;
age group (number): child 25 vs 22;
median age (year) child 7 vs 7; adult 18.5 vs 23;
median body weight (kg): child 23 vs 21.9; adult 55.6 vs 56.8;

Recruitment Not reported.

Setting Not reported.

**Interventions/ Test/
Factor being
investigated** Diastat rectal gel versus placebo.
An instructional videotape taught caregivers how to identify ARS, give medication and record respiration, skin color, seizures, adverse event and global assessment of treatment outcome in a booklet.

Study nurses maintained telephone contact with caregivers during episodes of ARS to review the procedures, monitor patients and intervene if patients needed additional treatment.

Comparisons Diazepam versus placebo.

**Length of Study/
Follow-up** Caregivers and patients returned to the clinic 72 hours after treatment review the recorded data.

**Outcome measures
studied** Seizure frequency and global assessment of treatment outcome by caregiver. Two outcome variables were retrospectively defined: time to first recurrence of seizures after initial treatment and number of patients remaining seizure-free (in 1st 12 hours).

Results Somnolence n=15 patients vs 5.

**Safety and adverse
effects** Adverse effects over 10%:
See results section.

**Does the study
answer the question?** The authors conclude that rectal diazepam gel, administered at home by trained caregivers, is an effective and well-tolerated treatment for acute repetitive seizures.

**Effect due to factor in
study?** Calculated that a sample size of 144 patients was planned on the basis of estimates of the sample size for a 2-sided test to detect a 50% reduction in seizure frequency with diazepam and a significance level of 0.05 and a power of 0.80.

**Consistency of
results with other
studies?**

Directly applicable to guideline population?

ARS not status epilepticus.

Internal Validity

Fallah R;Gofrani M;

Comparison of intravenous lidocaine and midazolam infusion for refractory convulsive status epilepticus in children

Ref ID 608

2007

Study Type Randomised Controlled Trial

Funding Grant for the Shaheed Beheshti University of Medical Sciences and Health Services, Tehran, Iran.

Number of participant Total n=20. Lidocaine group: n=10; midazolam group n=10.

Inclusion/Exclusion Criteria

Inclusion:
Children aged 1 month to 12 years.

Exclusion criteria:
Liver or kidney dysfunction, hypotension, cardiac arrhythmia or block and electrolyte abnormalities;
Second admission with status epilepticus.

Patient Characteristics

Sex: male: 9; female: 11;
Aged 1 month to 12 years.
Mean age: group 1: 3.4+/-2.9 years; group 2: 4.2+/-4.4 years, not stat sig diff p=0.6.
Females more in both groups: group 1: 50% vs group 2: 60%.
Neurodevelopmental delay occurred in: group 1: 4/10 (40%) vs group 2: 6/10 (60%);
Neuroimaging abnormality: in both groups 50%.
EEG abnormalities: group 1: 40%; group 2: 80%;
No sig diff seen regards age, sex, concomitant fever, EEG and neuroimaging abnormalities and neurodevelopmental delay.
Etiology of status epilepticus:
Lidocaine vs midazolam group:
- symptomatic epilepsy: 8 vs 9;
- idiopathic epilepsy: 2 vs 1;

Recruitment

Patients admitted in the ICU of children's hospital.

Setting

Mofid children's hospital, Iran.

Interventions/ Test/ Factor being investigated

Blood samples drawn at admission to measure serum sodium, potassium, total calcium and glucose levels.

All patients received: Intravenous diazepam (0.2-0.3mg/kg) which was repeated after 5 minutes if seizures recurred. Followed by phenytoin (15-20mg/kg) infused intravenously over 20 minutes. If seizures recurred, midazolam drip or intravenous lidocaine was administered as second line anticonvulsant.

Group 2 received: midazolam 0.15mg/kg followed by continuous intravenous infusion of 1microgram/kg/min with increase of 1 microgram/kg/min every 15 minutes until control of seizures or maximum dose of 6micrograms/kg/min reached.

If drug effective infused with same dose for 24 hours then decreased by 1 microgram/kg/min every 2 hours until cessation.

Group 1 lidocaine given at 1mg/kg intravenously at 25mg/min. A second dose of 1mg/kg infused if no response occurred or recurrent seizures. If did not stop in 15 minutes continuous lidocaine infusion of 1mg/kg/hour used and increased at 1mg/kg/h every 15 minutes until control of seizures or max dose of 5mg/kg/h. If effective then infused for 12 hours then decreased by 0.5mg/kg/h until cessation. If seizures did not cease with full dose of drugs then discontinued and pentobarbital coma induced.

Comparisons	IV lidocaine vs IV midazolam as second line treatment.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Cessation of seizures; safety of drugs;
Results	Lidocaine vs midazolam infusion group: Cessation of seizures: 5/10 (50%) vs 2/10 (20%), p=0.17. In lidocaine group: 2 stopped seizing with initial dose of 1mg/kg and in other 2 with 2nd dose of 1mg/kg and 1 with infusion of 1mg/kg/h. In midazolam group: 2micrograms/kg/min stopped 2 seizing.
Safety and adverse effects	No electrolyte imbalance or elevated liver enzymes or rise in blood urea nitrogen and creatine seen. Hypothermia and acidosis seen in 3 patients (30%) with midazolam and one lidocaine (10%) patient showed transient bradycardia. Intubation needed less in lidocaine than midazolam group (2 vs 7, p=0.03);
Does the study answer the question?	The authors concluded that lidocaine can be used in refractory status epilepticus treatment especially when respiratory care and intubation facilities are not present.
Effect due to factor in study?	No. No power calculation. Poor methodology.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.
Internal Validity	

Fisgin T;Gurer Y;Tezic T;Senbil N;Zorlu P;Okuyaz C;Akgun D;

Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study

Ref ID 4780

2002

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total n=45. diazepam group n=22; midazolam group: n=23.

**Inclusion/Exclusion
Criteria** Infants and children aged 1 month to 13 years;
Admitted to ER;
Informed consent obtained from a parent;
Seizure started at least 5 minutes previously;

Patient Characteristics Diazepam vs midazolam
Sex n (%): female: 11 (50) vs 15 (65.2); male: 11 (50) vs 8 (34.8);
Age: 0-24 months 16 (72.7) vs 12 (52.1); 25 months to 7 years: 4 (18.1) vs 7 (30.4);
7+ years: 2 (9) vs 4 (17.3);
Fever:
febrile: 5 (22.7) vs 5 (21.7);
nonfebrile: 17 (77.3) vs 18 (78.3);
Type of seizures:
Simple focal 3 vs 7;
After focal secondarily generalised: 8 vs 1;
Generalised tonic-clonic: 14 vs 14;
Generalised tonic: 1 vs 0;
Myoclonic: 1 vs 1;

Recruitment Those admitted to ER room at Dr Sami Ulus Children's Hospital.

Setting	Turkey.
Interventions/ Test/ Factor being investigated	<p>Nasal oxygen given to all patients. Electrocardiogram closely monitored and IV access established. Biochemical tests and arterial blood gas measurements evaluated.</p> <p>Rectal diazepam was given on the odd days of the month and midazolam was given (by an injector via the nasal route as nasal drop and spray forms are not available in Turkey) on the even days of the month.</p> <p>Heart rate, respiratory rate and bp were monitored after 5 and 10 minutes.</p> <p>Second drug administered if seizures did not stop in 10 minutes after the first drug. Observed after 5 to 10 minutes on second drug. Observed 1 hour after seizures. A bolus IV midazolam injection of 0.15mg/kg was administered if the convulsions persisted and infusion increased by 1ug/kg/min every 15 minutes until the seizures terminated.</p>
Comparisons	Rectal diazepam versus intranasal midazolam.
Length of Study/ Follow-up	After 5 and 10 minutes monitored. Given 2nd drug if did not stop in 10 minutes after 1st and then observed after 5 and 10 minutes again. Observed for 1 hour after seizures.
Outcome measures studied	% of those whose seizure stopped; duration of time to cessation of seizure;
Results	<p>% of those whose seizure stopped within 10 minutes: diazepam 13/22 (60%) vs midazolam 20/23 (87%);</p> <p>Seizures termination time: Diazepam versus midazolam: 0-1 min: 1/22 (4.5) vs 5/23 (22%); 1-2 min: 4/22 (18%) vs 9/23 (39%)*; 2-5 min: 7/22 (32%) vs 5/23 (22%); 5-10 min: 1/22 (4.5%) vs 1/23 (4%); Stopped (0-10 min): 13 (60%) vs 20 (87%)*; Not stopped: 9/22 (41%) vs 3/23 (12%)*;</p> <p>Termination periods: highest ratio diazepam 2 to 5 minutes in 7 (32%) and midazolam 1 to 2 minutes in 9 (39%).</p> <p>Non-responders: Original diazepam group non-responders administered midazolam after 10 minutes: 5/9 (55%) responded. Original midazolam group non-responders administered diazepam after 10 minutes: 2/3 (6%) responded.</p> <p>Time to response in the non-responder groups: original diazepam, now receiving midazolam: 1-2 minutes: 1 responded. 2 to 5 minutes: 2 responded. 5 to 10 minutes: 5 responded.</p> <p>Original midazolam, now receiving diazepam: 1 minute: 1. 1 to 2 minutes: 1.</p> <p>original midazolam, now receiving diazepam:</p>
Safety and adverse effects	In the midazolam group one patient had tachypnea at 5 minutes and another patient had tachycardia at 10 minutes, but was not statistically significant.
Does the study answer the question?	The authors conclude that intranasal midazolam is more effective than rectal diazepam. They did not observe any serious complications. But further investigations are necessary. Intranasal administration is easy.
Effect due to factor in study?	No. No power calculation and small sample (45 patients). Randomisation done by odds and even days. No mention of allocation concealment.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Mahmoudian T;Zadeh MM;

Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children

Ref ID 696

2004 Apr

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total n=70. Midazolam group n=35; Diazepam group n=35.

Inclusion/Exclusion Criteria Inclusion criteria:
2 months and 15 years age;
Acute seizures (febrile or afebrile);

Exclusion criteria:
Children who had received anticonvulsants before admission;

Patient Characteristics Midazolam versus diazepam:

Etiology of seizures:
hypocalcemia:2 vs 8.
hypoglycemia:0 vs 2.
febrile convulsions: 14 vs 1.
epilepsy: 14 vs 13.
head trauma: 0 vs 1.
CNS infection: 4 vs 10.
hyponatremia:1 vs 0.

Types of seizures:
GTC: 25 vs 25.
SPS: 3 vs 3.
CPS: 4 vs 8.
Myoclonic: 3 vs 2.

Recruitment Patients admitted to the pediatric emergency department of the medical university.

Setting ER Alzahra Hospital, Isfahan, Iran.

Interventions/ Test/ Factor being investigated Intranasal midazolam vs Intravenous diazepam.

Diazepam was given intravenously to patients with odd numbers after an intravenous line was introduced. Midazolam solution dropped into syringe into both nostrils in equal doses with even numbers and an intravenous line immediately introduced.

If seizures did not stop within 10 minutes of treatment IV diazepam was given to the midazolam group and phenobarbital to the diazepam group.

High flow oxygen by mask and routine life support provided.

Comparisons IN midazolam vs IV diazepam.

Length of Study/ Follow-up Not reported.

Outcome measures studied Time from treatment to cessation of seizures.

Results	All patients in both groups had seizure control within 10 minutes, and no significant difference in effectiveness between IN midazolam and IV diazepam $p>0.05$. Mean interval between drug administration and seizure control: midazolam 3.58 (sd 1.68) vs diazepam 2.94 (sd 2.62) minutes, $p=0.007$. This did not include time to get IV line.
Safety and adverse effects	No significant side effects in either group. No patient had to be intubated or mechanically ventilated.
Does the study answer the question?	The authors concluded that although intranasal midazolam was as safe and effective as diazepam, seizures were controlled more quickly with intravenous diazepam than with intranasal midazolam. Intranasal midazolam can possibly be used not only in medical centres but in general practice and at home after appropriate instructions given to families of children with recurrent seizures.
Effect due to factor in study?	No. No power calculation and quasi-randomised study.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Mahvelati F; Tonekaboni H; Javadzade M; Ghofrani M;

The efficacy of propofol and midazolam in treatment of refractory status epilepticus in children

Ref ID 1372

2007

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant N=16 to the MID group and n=16 to the PROP group.

Inclusion/Exclusion Criteria Criteria for Refractory SE: a) acute seizures persisting more than 60 min despite being treated with first-line antiepileptic drugs including IV diazepam, phenytoin and phenobarbital and b) seizures recurring at a rate of at least 2 times per hour without any recovery of the consciousness between attacks.

Patient Characteristics All patients had generalized tonic-clonic seizures. Sixteen patients had a mean \pm SD age of 3.83 ± 3.79 years and received Midazolam. Another 16 patients with a mean \pm SD age of 5.08 ± 4.82 were treated with Propofol.

Recruitment Patients being treated at an Intensive Care Unit.

Setting Iran. ICU

Interventions/ Test/ Factor being investigated Propofol versus Midazolam.

Comparisons IV Propofol versus IV Midazolam.

Length of Study/ Follow-up Appears to be up to 48 hours.

Outcome measures studied Complete seizure control, seizure recurrence and side effects.

Results Complete seizure control was achieved in 6/16 (38%) in the MID group and 10/16 (63%) in the PROP group.

Safety and adverse effects MID group: Bradycardia followed by cardiac arrest in 1 patient (successfully resuscitated) and elevated serum creatine phosphokinase in another patient. PROP group: rise in serum creatine phosphokinase in 5 patients (31%) and increase in

serum triglyceride and cholesterol in 5 patients (31%). Both alteration were significant (p=0.04). Apnea was present in 9 patients in the MID group and 11 patients in the PROP group (p=0.71)

Does the study answer the question?

Relevant to the clinical question.

Effect due to factor in study?

No details on randomisation nor allocation concealment. Unblinded study. Risk of bias in this study.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct Population.

Internal Validity

McIntyre J;Robertson S;Norris E;Appleton R;Whitehouse WP;Phillips B;Martland T;Berry K;Collier J;Smith S;Choonara I;

Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial.[see comment]

Ref ID 4591

2005

Study Type

Randomised Controlled Trial

Funding

By SEARCH, Derbyshire Children's Research Fund, and Alder Hey Children's Hospital Research Fund.

Number of participant

The study evaluated 219 seizure episodes in 177 children of both sexes. Buccal Midazolam group (109 episodes, 92 initial episodes) and Rectal Diazepam (110 episodes, 85 initial episodes). AHCH: 133 episodes, 106 patients; DCH: 37 episodes, 26 patients; QMC: 15 episodes, 15 patients; BCH: 34 Episodes, 30 patients.

Inclusion/Exclusion Criteria

Children aged 6 months to 16 years brought to an emergency department with active generalised tonic-clonic seizures including established convulsive status epilepticus. Patients with partial seizures or non-convulsive status epilepticus were excluded from the trial.

Patient Characteristics

Most children were aged between 1 and 4 years (109 [62%] and 135 [62%], respectively). 14 infants (6%) were aged between 6 and 12 months, 50 children (23%) between 5 and 9 years and the remaining 20 (9%) were 10 years and older. In 157 (72%) episodes, patients had previously had seizures and 115 (53%) were receiving AED (102 [58%] and 98 [55%]).

Recruitment

Children brought to an emergency room of one of the 4 participating hospitals: Alder Hey Children's Hospital, Derbyshire Children's Hospital, QMC and Birminham Children's Hospital).

Setting

UK. Emergency care.

Interventions/ Test/ Factor being investigated

Buccal midazolam compared to rectal diazepam as the first line treatment of children aged 6 months to 15 years presenting to a paediatric accident and emergency department with active seizures. Weekly blocks of treatment of either buccal midazolam or rectal diazepam were randomly selected in each of the four participating centres. Locally agreed guidelines were followed in the event of continued seizure activity after the 10 minute period

Comparisons

Buccal midazolam compared to rectal diazepam

Length of Study/ Follow-up

Up until 24 hours.

Outcome measures studied

The primary outcome measure was clinical cessation of the seizure within 10 minutes of drug administration without seizure recurrence within 1 hour and without respiratory depression

Results

Randomisation of 2 drugs in weekly blocks.
Therapeutic success (all episodes): 61/109 episodes (56%) for Buccal Mid and 30/110 episodes (27%) for Rectal DIA.

Time (mins) to stop seizing after treatment (median IQR) (all episodes): 8 (5-20) for Buccal Mid and 15 (5-31) for Rectal DIA.

Stopped seizing within 10 min (all episodes): 71/109 episodes (65%) for Buccal MID and 45/110 episodes (41%) for Rectal DIA.

From Cochrane Review:

Buccal midazolam was more effective than rectal diazepam in the emergency treatment of seizures, 61/109 (56%) versus 30/110 (27%) respectively. Relative Risk (RR) was 2.05 and 95% confidence interval (CI) was 1.45 -2.91. Results were similar for the initial presenting seizure and for total number of seizures. Fewer children in the midazolam group required intravenous lorazepam to terminate the seizure 36/109 versus 63/110 , RR 0.58 (95% CI 0.42-0.79).

Safety and adverse effects

In the midazolam group 5/109 (5%) children had respiratory depression, 2 requiring intubation and ventilation in contrast to 7/110 (6%) children in the rectal diazepam group, 3 requiring intubation and ventilation.

Does the study answer the question?

Relevant study to the clinical question.

Effect due to factor in study?

Un-blinded study. However, the authors acknowledge this in the paper and it was felt to be inappropriate to administer both an active drug and placebo to each patient, in what is a medical emergency

Consistency of results with other studies?

Directly applicable to guideline population?

Direct Population.

Internal Validity

Misra UK;Kalita J;Patel R;

Sodium valproate vs phenytoin in status epilepticus: a pilot study

Ref ID 4655

2006

Study Type

Randomised Controlled Trial

Funding

Not reported.

Number of participant

VPA n=35 and PHT n=33.

Inclusion/Exclusion Criteria

Patients with SE defined as two or more convulsive seizures without full recovery of consciousness between seizures or continuous convulsive seizures lasting for more than 10 minutes. Patients with no convulsive and subtle SE, hypotension, cardiac arrhythmia, congestive heart failure, pregnancy, pancreatitis, and drug allergy and those requiring immediate neurosurgery were excluded.

Patient Characteristics

N=27 adults in the VPA group and n=29 adults in the PHT group (>15 years). N=8 children in the VPA group and n=4 children in the PHT group (<15 years). N=24 male in the VPA group and n=17 male in the PHT group. N=12 had associated medical illnesses in the VPA group and n=10 in the PHT group. Seizure duration (hours) 1.76 ± 0.49 for VPA group and 1.70 ± 0.47 for the PHT group. Etiology of SE was CNS infection in 38, stroke in 9, metabolic-toxic encephalopathy in 16, drug withdrawal in 2, and idiopathic in 3 patients.

Recruitment

Not reported.

Setting

Emergency care. India.

Interventions/ Test/ Factor being investigated Sodium Valproate versus IV Phenytoin. Subsequent failure was treated by diazepam or lorazepam.

Comparisons IV VPA vs IV PHT.

Length of Study/ Follow-up UP to 24 hours.

Outcome measures studied Seizure cessation after infusion and seizure freedom at 24 hours.

Results SE was aborted by VPA in 23 patients (66%) and by PHT in 14 (42%) ($p=0.046$). In refractory patients, as a second choice, VPA was effective in 15/19 patients (79%), whilst PHT was effective in 3/12 patients (25%) ($p=0.004$). Twenty-four hour seizure freedom was achieved in 29/55 patients, of whom 8 achieved control with PHT, 10 achieved control with VPA and 11 achieved control with a combination ($p=no$ significant).

Safety and adverse effects After therapy, hypotension occurred in 4, liver dysfunction occurred in 12 and respiratory depression occurred in 12 patients, 5 of which needed artificial ventilation. Nineteen patients died during the hospital stay: 11 in the 1st week, 6 in the 2nd week, and 2 in the 3rd week. Six of these patients had metabolic encephalopathy, 16 had CNS infection, and 3 had stroke.

Does the study answer the question? Relevant study to the clinical question.

Effect due to factor in study? No details on allocation concealment, nor blinding.

Consistency of results with other studies?

Directly applicable to guideline population? Direct population.

Internal Validity

Scott RC;Besag FM;Neville BG;

Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial

Ref ID 4778

1999

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant 42 - of whom 28 had episodes. Aged 5 to 19 years. 40 episodes randomised to midazolam and 39 to rectal diazepam.

Inclusion/Exclusion Criteria Individuals who had been previously treated with rectal diazepam for acute seizures.

Patient Characteristics No baseline differences.

Recruitment Enrolled from a residential school for children and young people with severe epilepsy and other needs, including learning difficulties.

Setting Residential school, UK

Interventions/ Test/ Factor being investigated buccal administration of liquid midazolam and rectal administration of liquid diazepam. Continuous seizures of more than 5 minutes duration were randomly treated with buccal midazolam or rectal diazepam. If the seizure did not stop within 10 minutes, additional medication chosen by the attending physician was administered. Oxygen saturation and blood pressure were monitored for 30 minutes after treatment.

Comparisons	buccal administration of liquid midazolam and rectal administration of liquid diazepam
Length of Study/ Follow-up	Emergency care
Outcome measures studied	Termination of seizures, Time to response, Seizure duration, Oxygen saturation and blood pressure.
Results	<p>Buccal midazolam was used to treat 40 seizures in 14 students, and rectal diazepam 39 seizures in 14 students. Midazolam stopped 30 (75%) of 40 seizures and diazepam 23 (59%) of 39 (p=0.16). The median time from administration of medication to end of seizure was 6 min (IQR 4-10) for midazolam and 8 min (4-12) for diazepam (p=0.31).</p> <p>Response to buccal midazolam within 10 min was seen in 8 of 12 episodes compared to 4/12 treated with rectal diazepam (p=0.10).</p> <p>Time from administration to end of seizure did not differ significantly between the two treatments.</p> <p>The median time from arrival of the nurse to administration of medication was 2 min.</p>
Safety and adverse effects	No clinically important adverse cardiorespiratory events were identified in the two groups.
Does the study answer the question?	Relevant study to the clinical question.
Effect due to factor in study?	Small study. Pragmatic trial. Lack of concealment of allocation.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Shaner DM;McCurdy SA;Herring MO;Gabor AJ;

Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin⁴⁸⁴

Ref ID 484

1988 Feb

Study Type Randomised Controlled Trial **Funding** Not reported.

Number of participant Total n=36. Diazepam and phenytoin n=18. Phenobarbital n=18.

In 6 patients they met at least one of the criteria but documented therapy did not conform closely enough to the treatment protocol and so were excluded from analysis. 2 patients were excluded due to retrospective diagnosis of pseudoseizures. One patient entered study twice.

**Inclusion/Exclusion
Criteria**

Inclusion:
 Older than 15 years of age.
 A history of 30 minutes of continuous generalised convulsive seizures, and witnessed generalised seizures in the ER.
 A history of 30 minutes of recurrent generalised convulsive seizures but failure to attain baseline mental status between seizures, and witnessed generalised seizures in the ER.
 A history of 3 or more generalised convulsive seizures in 1 hour in patients with obtundation prior to the onset of status epilepticus, and witnessed generalised convulsive seizures in the ER.
 Uncertain history of seizures but generalised convulsive seizures continuously for

more than 5 minutes as witnessed in the ER.

Exclusion criteria: if anticonvulsants given for the presenting convulsive episode before arrival in the ER.

Patient Characteristics	<p>Diazepam and phenytoin versus phenobarbital:</p> <p>Mean age +/- SD (*years): 43.8+/- 16.5 versus 55.9 +/-19.4. History of previous seizures (n): 14 vs 11. Sex ratio (M:F): 9:9 vs 13:5. Focal features (n):9 versus 10. Phenobarbital or phenytoin present in serum prior to treatment (n)*: 10 vs 7. Criterion for entrance into study (N): Criterion 1: 6 vs 4; Criterion 2: 11 vs 14. Criterion 3: 0 vs 0. Criterion 4: 1 vs 0.</p> <p>Presumed seizure etiologies (n): Alcohol withdrawal: 5 vs 5. Subtherapeutic anticonvulsants: 11 vs 7. Infections: 2 vs 0. Structural lesions: 5 vs 7. Toxic/metabolic: 2 vs 2. * One patient in the diazepam group and no patients in the phenobarbital group had pretreatment phenobarbital levels in the therapeutic range (15 to 40mg/l). 2 patients in the diazepam group and 1 in the phenobarbital group had pretreatment phenytoin levels in the therapeutic range (10 to 20mg/l).</p>
Recruitment	Presenting to the ER with status epilepticus.
Setting	USA?
Interventions/ Test/ Factor being investigated	Diazepam and phenytoin versus phenobarbital as initial therapy.
Comparisons	IV Diazepam and IV phenytoin versus IV phenobarbital as initial therapy.
Length of Study/ Follow-up	Not reported.
Outcome measures studied	Response latency; cumulative convulsion time; adverse events; death.
Results	<p>Convulsions were controlled within 7 hours in all patients. The median cumulative convulsion time for those on phenobarbital was shorter than the median cumulative convulsion time for those receiving diazepam (5 versus 9 minutes, $p<0.06$).</p> <p>The median response latency was shorter for the phenobarbital group compared to the diazepam group (5.5 vs 15 minutes, $p<0.10$).</p> <p>There was data on how many of the phenobarbital group were controlled with phenobarbital alone (11/18) and that five of the phenobarbital group ultimately received phenytoin for presumed additional clinical efficacy although no additional seizures were documented. No data given for the other group but assume from statement that convulsions were controlled within 7 hours in all patients that all patients seizures were controlled in this group.</p>
Safety and adverse effects	Arrhythmias $n = 0$ vs 1, not significant. Hypotension $n= 3$ vs 2, not significant.
Does the study answer the question?	<p>The authors conclude that the phenobarbital regime is rapidly effective and comparable in safety and has some practical advantages in comparison to the diazepam and phenytoin regime.</p> <p>This does not point out that some of the patients who were on phenobarbital (5) were then put on phenytoin.</p>
Effect due to factor in study?	No power calculation and small sample.

Consistency of results with other studies?

Directly applicable to guideline population?

Reports the no of events in each group rather than the number of participants having events.

Internal Validity

Sreenath TG;Gupta P;Sharma KK;Krishnamurthy S;

Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: A randomized controlled trial

Ref ID 582

2010

Study Type Randomised Controlled Trial **Funding** None

Number of participant N=178. 90 subjects in lorazepam group and 88 in diazepam-phenytoin group.

Inclusion/Exclusion Criteria Aged between 1-12 years and presenting with a clinical diagnosis of convulsive status epilepticus. Exclusion criteria: if children had received any antiepileptic medication in the preceding 4 weeks, sustained acute head trauma, jaundice, suspended renal failure or diarrhea presenting with seizures and history of poisoning.

Patient Characteristics The mean age (Sd) in months was 84 (36.8) and 78.8 (32.4) in lorazepam and in diazepam+ phenytoin groups respectively. The majority of children in both groups were boys (61.1% in lorazepam and 53.4% in diazepam+ phenytoin). The predominant type of seizures in both groups was generalised tonic clonic seizures (55.5% in lorazepam and 69.3% in diazepam and phenytoin).

Recruitment Invited when attended a tertiary centre attached to a medical college in North India.

Setting A tertiary centre attached to a medical college

Interventions/ Test/ Factor being investigated Comparison of efficacy between intravenous lorazepam and diazepam +phenytoin.

Comparisons Between iv/rectal lorazepam and iv/rectal diazepam + phenytoin.

Length of Study/ Follow-up Seizure freedom was assessed within 10 min of the first intervention and there was no recurrence of seizure for the next 18 hours.

Outcome measures studied 1)seizure freedom
2) recurrence of seizure
3) proportion of children with respiratory depression

Results a) seizure freedom: 100% in both groups
b) recurrence of seizures after 18 h: None in both groups
c) Incidence of respiratory depression: Lorazepam 4/90 (4.4%) and Diazepam +phenytoin 5/88 (5.6%)
d) number of patients requiring transfer to the ICU for mechanical ventilation: none in both groups.

Safety and adverse effects None adverse event.

Does the study answer the question? Yes. No significant difference was found between iv/rectal lorazepam and iv/rectal diazepam +phenytoin on the proportion of participant achieving seizure freedom, had another episode of seizures after 18 hours and on the incidence of respiratory depression.

Effect due to factor in study? The study was unblinded so even though the study used a randomization process with allocation concealment and achieved the minimum required sample size, the effect of intervention is uncertain.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Talukdar B;Chakrabarty B;

Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial

Ref ID 53

2009 Nov

Study Type Randomised Controlled Trial

Funding None.

Number of participant N=120, N buccal midazolam =60 and N iv diazepam=60

Inclusion/Exclusion Criteria Children with an episode of convulsion irrespective of cause and duration was enrolled in the study. In a child with recurrent convulsions, only the first episode was included in the study. Seizure types included were partial and generalized tonic, clonic and tonic clonic. Myoclonic, atonic and absence seizures were excluded.

Patient Characteristics out of 120 cases, 82 were males and 38 females. 53.3% were below 1 year of age, 20.2% were between 2-5 years and 26.7% between 6-12 years. None of the children received any pre hospital treatment.

Recruitment Children attending the pediatric emergency department.

Setting Department of pediatrics, Maulana Azad Medical sch

Interventions/ Test/ Factor being investigated Efficacy of buccal midazolam compared to iv diazepam in controlling convulsions in children.

Comparisons Comparison are made between buccal midazolam and iv diazepam.

Length of Study/ Follow-up for 48 hours.

Outcome measures studied
1)seizure freedom
2) time to first seizure
3) incidence of adverse events

Results
1) seizure freedom: Buccal midazolam 51/60 (85%) and iv diazepam 56/60 (93.3%) (p=0.14)
2)mean time (sd) in minutes to first seizure (after drug administration): buccal midazolam 1.69 (0.93) and iv diazepam 1.13 (0.5) (p<0.001)
3) adverse events (unusual CNS depression, respiratory depression, apnea or cardiac dysrhythmia): 0% in both groups.

Safety and adverse effects No issues. Neither adverse events not death experienced by any participant in the study.

Does the study answer the question? Yes. No difference in achieving seizure freedom between buccal midazolam and iv diazepam but iv diazepam needed significantly less time to cessation of seizures compared to buccal midazolam.

Effect due to factor in study? The uncertainty over the effect of this intervention comes from the unblinded type of the study and the lack of preconsideration of study's statistical power.

Consistency of results with other studies?

Directly applicable to guideline population? Direct.

Internal Validity

Treiman DM; Meyers PD; Walton NY; Collins JF; Colling C; Rowan AJ; Handforth A; Faught E; Calabrese VP; Uthman BM; Ramsay RE; Mamdani MB;

A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group

Ref ID 4783

1998

Study Type	Randomised Controlled Trial	Funding	Department of Veterans Affairs Medical Research Service Cooperative Studies Program. Lorazepam and dummy lorazepam Tubexes donated by Wyeth-Ayerst Laboratories. The authors have consulted for Parke-Davis; one to Hoffman-LaRoche & Wyeth-Ayerst.
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Number of participant	Total n= 570. Lorazepam n=146. Phenobarbital n=133. Diazepam and phenytoin n=146. Phenytoin n=145.
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Inclusion/Exclusion Criteria	Inclusion criteria: Evidence of overt or subtle generalised convulsive status epilepticus at time of evaluation, regardless of prior drug treatment. Definitions: overt generalised convulsive status epilepticus- 2 or more generalised convulsions, without full recovery of consciousness between seizures, or continuous convulsive activity for more than 10 minutes (treatment after 10 minutes of continuous seizure activity was considered essential to protect against neuronal and systemic damage from ongoing seizure activity). Subtle generalised convulsive status epilepticus - coma and ictal discharges on the EEG, with or without subtle convulsive movements (rhythmic twitching of the arms, legs, trunk, or facial muscles, tonic eye deviation, or nystagmoid eye jerking). Exclusion criteria: Previously received treatment and whose seizures had stopped. Status epilepticus of a type other than generalised convulsive. Aged less than 18 years. Pregnant. A neurologic emergency requiring immediate surgical intervention. Presence of a specific contraindication to therapy with hydantoin, benzodiazepine, or barbiturate drugs. If patients (with unrepeated episodes) were inadvertently enrolled more than once, on the first episode was included in analysis.
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Patient Characteristics	Population characteristics stated according to the type of generalised convulsive status epilepticus: Overt (n=384) vs Subtle (n=134): Age (years, sd): 58.6+/- 15.6 vs 62.0+/-15.1. Veteran (%): 70.1 vs 80.6. Male sex (%): 82.3 vs 85.1. Not previously treated for current episode (%): 51.3 vs 51.5. History of acute seizures (%): 54.2 vs 25.4. History of epilepsy (%): 42.4 vs 12.7. History of status epilepticus (%): 12.8 vs 4.5. Median duration of status epilepticus at enrolment (hr) 2.8 vs 5.8. Causal factors (%) (some patients had more than one causal factor): - remote neurologic cause: 69.5 vs 34.3. - acute neurologic cause: 27.3 vs 37.3. - Life-threatening medical condition: 32.0 vs 56.7. - Cardiopulmonary arrest: 6.3 vs 38.1.
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- Toxic effects of therapeutic or recreational drug: 6.3 vs 5.2.
- Alcohol withdrawal: 6.t vs 0.7.

Recruitment

Not reported.

Setting

16 Veterans medical centres & 6 uni hospitals USA

**Interventions/ Test/
Factor being
investigated**

IV lorazepam versus phenobarbital vs phenytoin vs diazepam.

Phenytoin and diazepam were in the identical vials at appropriate concentrations so each drug could be administered at 1ml per minute to produce maximal rates of drug infusion. Lorazepam was given by Tubex injection at maximal rate of 0.5ml per minute.

The drug treatment kits looked identical and all contained a first, second and third treatment box within it. The first treatment box held a tubex syringe and five vials labelled A to E. A nomogram (based on weight of patient) determined the volume of solution to be administered (to ensure blinding). The tubex and vial A were injected simultaneously. Tubexes and vials with active drug contained propylene glycol, as did dummy tubexes; dummy vials contained saline. Second and third treatment boxes provided for further treatment if needed without revealing the identity of the study drug.

Contents of 1st treatment box:

	Lorazepam	Phenobarbital	Diazepam & Phenytoin	
Phenytoin				
Tubex	Lorazepam	Dummy	Dummy	Dummy
Vial A	Dummy	Phenobarbital	Dummy	
Dummy				
Vial B	Dummy	Phenobarbital	Diazepam	
Phenytoin				
Vial C	Dummy	Phenobarbital	Phenytoin	
Phenytoin				
Vial D	Dummy	Dummy	Phenytoin	
Phenytoin				
Vial E	Dummy	Dummy	Phenytoin	
Dummy				

Active drug in second treatment box:

	Phenytoin	Phenytoin	Lorazepam
Lorazepam			

Active drug in third treatment box:

	Phenobarbital	Lorazepam	Phenobarbital
Phenobarbital			

Comparisons

Lorazepam versus phenobarbital versus phenytoin versus diazepam.

**Length of Study/
Follow-up**

30 days after treatment.

**Outcome measures
studied**

Rate of successful initial treatment.

Treatment successful if all clinical and electrical evidence of seizure activity stopped within 20 minutes from start of drug infusion and no recurrence from 20 to 60 minutes after starting treatment.

Results

Rates of successful initial treatment:

Lorazepam: overt gcse 67%; subtle gcse 26.1% [67/100; 12/46].

Phenobarbital: overt gcse 63%; subtle gcse 24.4% [58/92; 10/41].

Diazepam and Phenytoin: overt gcse 59.6%; subtle gcse 23.4% [59/99; 11/47].

Phenytoin: overt gcse 51\5; subtle gcse 19.5% [53/104; 8/41].

12 hour study period: 67 of the patients with over status epilepticus (17%) regained full consciousness before end of 12 hour study period, with no significant differences among the four treatment groups (p=0.59) [figures not given]. None of the patients with subtle status epilepticus completely regained consciousness during the 12-hour study period.

30 days after treatment:

50.1% of overt status epilepticus were discharged from hospital compared with 8.8% with subtle status epilepticus. 22.9% with overt status epilepticus were still in the hospital compared with 26.5% with subtle status epilepticus.

Mortality rates were 27% and 64.7% respectively.

There were no significant differences in outcome at 30 days among the four treatments for either over or subtle status epilepticus.

It does not give figures for those who regained consciousness at 12 hours or at 30 days apart from saying that there was no significant difference. It gives initial treatment effect data but separates overt from subtle generalised convulsive status epilepticus.

Safety and adverse effects

Incidence of adverse events:

lorazepam vs phenobarbital vs diazepam & phenytoin vs phenytoin
hypoventilation: 10.3% vs 13.2% vs 16.8% vs 9.9%.
Hypotension: 25.8% vs 34.1% vs 31.6% vs 27%.

Subtle:

Hyperventilation: 12.8% vs 15.2% vs 2.9% vs 7.7%.

Hypotension: 59% vs 48.5% vs 58.3% vs 57.7%.

Does the study answer the question?

The authors conclude that lorazepam is more effective than phenytoin for initial intravenous treatment for overt generalised convulsive status epilepticus. Although it is no more efficacious than phenobarbital or diazepam and phenytoin, it is easier to use.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Grading: 2++

High-quality systematic reviews of case-control or cohort studies
High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

Mahmoudian T;Najafian M;

Comparing the effect of intravenous midazolam with rectal sodium valproate in controlling of children with refractory status epilepticus⁷¹⁰

Ref ID 4886

2006

Study Type	Randomised Controlled Trial	Funding	Not reported.
Number of participant	N=18 in the odd group and n=18 in the even group.		
Inclusion/Exclusion Criteria	Children referred with seizures to pediatric emergency ward that continued despite IV DIA (0.3mg/kg) followed by IV bolus Phenytoin (20mg/kg) and then IV bolus Phenobarbitol (20mg/kg).		
Patient Characteristics	Children within the range of 2 months to 18 years of age. Seizures lasting 60-90 min were considered as refractory SE.		
Recruitment	Children referred with seizures to pediatric emergency ward.		
Setting	Iran. Pediatric Emergency ward.		
Interventions/ Test/ Factor being investigated	Sodium Valproate (20mg/kg) diluted with equal volume of water through rectal enema (IV SV was not available). If seizure stopped within 20 minutes of enema, oral SV would be continued 20mg/kg/24hours divided into 2 equal doses after 12 hours from first administration. IV bolus of Midazolam 400 microgram/kg. followed by 200microgram/kg through infusion up to 20 minutes. If seizure stopped, MID continued for extra 6 hours and was discontinued gradually. If there was no positive response after 20 minutes in both groups, then treatment was discontinued and treatment with barbiturates coma (sodium thiopental or Nesdonal) was started and the child was excluded from the study.		
Comparisons	IV Midazolam vs Sodium Valproate through rectal enema.		
Length of Study/ Follow-up	Appears to be up to 24 hours.		
Outcome measures studied	Response to treatment (cessation of seizures)		
Results	MID: 16/19 (84.2%) responded to treatment after 4.5±0.5 minutes (even group); SV: 12/19 (63%) responded to treatment within 16.5±0.8 minutes (odd group), (p<0.00001) between the 2 groups.		
Safety and adverse effects	No side effects reported during or after treatment.		
Does the study answer the question?	Relevant study to the clinical question.		
Effect due to factor in study?	High risk of bias as there is unadequate randomisation methods (odd, even method), no allocation concealment, nor blinding. Main outcome not clearly reported in the study. Baseline characteristics between groups not clear.		
Consistency of results with other studies?			
Directly applicable to guideline population?	Direct population.		

Internal Validity

Question: Which AEDs are clinically effective, cost-effective and safest for use in pregnancy?

Grading: 2+

Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

Adab N; Tudur SC; Vinten J; Williamson P; Winterbottom J;

Common antiepileptic drugs in pregnancy in women with epilepsy

Ref ID 5217

2004

Study Type Systematic Review

Funding not reported.

Number of participant cohort

**Inclusion/Exclusion
Criteria**

Patient Characteristics

Recruitment

Setting

**Interventions/ Test/
Factor being
investigated**

Comparisons

**Length of Study/
Follow-up**

**Outcome measures
studied**

Results

**Safety and adverse
effects**

**Does the study
answer the question?**

1) any monotherapy exposure in utero compared to non exposed in the general population; 6 studies were included. Neither study found a significant difference in neurodevelopmental scores between children exposed to monotherapy and normal population
2) carbamazepine exposure compared to non exposed in the general population; early years; only one out of 4 studies included found a significantly lower score in Bayle's mental index in children exposed to carbamazepine compared to non exposed. Early years to school years; two out of four studies found children exposed to CBZ have a significantly lower scores (using the McCarthy General cognitive index) than the general population.
3) phenytoin exposure in utero compared to the general population; early years; four out of five studies found no difference between those exposed to PHT in utero and the general population. Early years to school years; 1 study found no difference using the overall Bayle scale of development, but it was found that children exposed to phenytoin in utero scored significantly lower in the language domain compared to controls. Preschool to school years; unclear results due to studies limitations.
4) phenobarbitone exposure in utero compared to the general population; early years; no differences were found in three studies. Preschool to school years; one out of three studies found a higher proportion of children with delayed school career and impaired results in tests of spelling, arithmetic, and reading.
5) Any polytherapy exposure in utero compared to the general population. Early years; all 5 studies found lower scores in those children exposed to any polytherapy regime in utero compared to unexposed children of mothers without epilepsy. Preschool to school years; 4 studies found no difference. Two studies found a poorer

performance in those exposed to polytherapy in all areas tested using a variety of scales. (the group of polytherapy was a very heterogeneous group).

6) polytherapy compared to monotherapy exposure in utero; early years; one of two studies found significant difference in the neurodevelopmental scores between the two groups. Preschool to school years; one of the two studies found evidence for lower scores in verbal and motor categories of intelligence in those exposed to polytherapy compared to monotherapy.

7) Any AED exposure in utero with non exposed in the general population; early years; five out of six studies found that those exposed to AEDs in utero had significantly lower scores for development than controls from the general population. Preschool to school years; four out of seven studies found that exposed children scored significantly lower in general scores of IQ than control children.

8)Any AED exposure in utero compared to non exposed children of mothers with epilepsy; one out of three studies found a higher proportion of children with poor performance in arithmetic and school career in the exposed group (small numbers of non exposed children).

9) any monotherapy exposure in utero compared to non exposed children of mothers with epilepsy; no significant differences found (small numbers of non exposed children).

10) phenytoin compared to carbamazepine exposure in utero; 2 out of three studies showed significantly lower scores in the phenytoin exposed group.

11) phenytoin compared to phenobarbitone exposure in utero; no difference was found in all three studies

12) phenobarbitone compared to carbamazepine exposure in utero; in both studies, a higher proportion of children exposed to phenobarbitone had a lower mean developmental score and were poor achievers using the Dutch test for reading, spelling and arithmetic or in an inappropriate class for their age compared to children exposed to carbamazepine.

13) Valproate compared to carbamazepine exposure in utero; no difference between the two groups in developmental problems and mental delay.

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Banach R;Boskovic R;Einarson T;Koren G;

Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies.

Ref ID 5215

2010

Study Type Systematic Review

Funding No sources of funding were used for this study.

Number of participant cohort studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

**Interventions/ Test/
Factor being
investigated**

Comparisons

**Length of Study/
Follow-up**

**Outcome measures
studied**

Results

**Safety and adverse
effects**

**Does the study
answer the question?**

Valproic acid group: The mean verbal IQ, performance IQ and full scale IQ were significantly lower in the valproic acid group compared with the control group (comprising mothers with and without epilepsy). The mean VIQ, PIQ and FSIQ scores in children exposed to valproic acid in utero were 83.9 (64.2, 103.6), 93.7 (72.6, 114.7) and 88.3 (69.6, 106.9) respectively. The mean VIQ, PIQ and FSIQ in the control all group (mothers with epilepsy) were 98.6 (70.4, 126.8) and 98.7 (73.1, 124.3) respectively.

2 meta-analyses conducted for exposure to carbamazepine; in the first meta-analysis using the Wechsler scale, the mean VIQ and FSIQ of children exposed to carbamazepine were not statistically significantly different from the control all group ($p=0.097$ and $p=0.095$). The mean PIQ of children exposed to carbamazepine was significantly lower than the control all group (mothers with and without epilepsy) ($p<0.002$). The mean VIQ, PIQ and FSIQ of children exposed to carbamazepine was not statistically different from the control epilepsy group. In the second meta-analysis using the Bayley McCarthy scale, the mean FSIQ of children exposed to carbamazepine was not statistically different from the unexposed control group.

**Effect due to factor in
study?**

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?**

Internal Validity

D'Souza SW;Robertson IG;Donnai D;Mawer G;

Fetal phenytoin exposure, hypoplastic nails, and jitteriness

Ref ID 4937

1991 Mar

Study Type Cohort

Funding North Western Regional
Health Authority.

Number of participant N=123, group of epileptic mothers=61 and group of controls=62

**Inclusion/Exclusion
Criteria** Group of epileptic mothers= pregnant women with a history of grand mal epilepsy and were referred to out antenatal clinic from September 1980- August 1982. Control mothers were selected at the time of antenatal booking and were matched for age, parity and social class. Exclusion criteria: no heavy smokers (more than 20 cigarettes/day), medical complications (diabetes, hypertension). Drug use.

Patient Characteristics Pregnant women in both groups had similar ages (mean (sd) for epileptic mothers was 26.5 (4.9) and for control was 26.6 (4.8), and the majority of them gave a spontaneous vaginal birth delivery (37/61 in epileptic women and 40/62 in controls). Both groups attended the antenatal clinic in St Mary's Hospital, Manchester.

Recruitment	Not clearly described.
Setting	The antenatal clinic in St Mary's Hospital.
Interventions/ Test/ Factor being investigated	Epileptic mothers
Comparisons	Comparisons are made between the group of epileptic mothers and the control group. One comparison is made for the incidence of hypoplastic nails in infants with congenital anomalies within epileptic mothers.
Length of Study/ Follow-up	start date: September 1980-August 1982, end date:1986-89.
Outcome measures studied	1)proportion of children with congenital anomalies 2) proportion of children with neonatal conditions 3)proportion of neonatal deaths 4)developmental impairment
Results	<p>1) 26/61 children from epileptic mothers and 0/62 in controls had congenital anomalies. These anomalies occurred in 15/31 mothers with a monotherapy, 10/18 whose mothers had a mixture of drugs and 1/8 whose mothers had no drugs during pregnancy.</p> <p>2/61 children from epileptic mothers had congenital heart disease, 1/61 had ventricular septal defect, 1/61 had patent ductus arteriosus, 1/61 had hypoplastic left heart syndrome, 2/61 had cranial nerve palsy.</p> <p>Hypoplasia of nails affected 11/61 (18%) of children of epileptic mothers.</p> <p>2) neonatal conditions were diagnosed in 26/61 children in the study group (43%) and 6/62 (10%) in control group.</p> <p>3) 2/61 neonatal deaths among children of epileptic mothers.</p> <p>4) excluding one child with Down's syndrome, 0/61 children in the study group had a major developmental impairment. The median developmental quotients for children of epileptic mothers and of controls were 94 (75-134) and 98 (90-120) respectively.</p>
Safety and adverse effects	See outcomes of the study.
Does the study answer the question?	Yes. A higher proportion of children of epileptic mothers had congenital anomalies with the most frequent the hypoplasia of nails and neonatal conditions compared to controls. Two neonatal deaths observed in the study group. Developmental delay was not observed in either group, study or control.
Effect due to factor in study?	The study had a good methodological, however no estimation of statistical power was performed so uncertain about the effect of the exposure on the outcomes measures.
Consistency of results with other studies?	Not consistent.
Directly applicable to guideline population?	Direct.
Internal Validity	Adequately addressed

Gaily E;Kantola-Sorsa E;Granstrom ML;

Intelligence of children of epileptic mothers

Ref ID 4943

1988 Oct

Study Type Cohort **Funding** Not reported.

Number of participant N children of epileptic mothers=148, N control children=159.

Inclusion/Exclusion Criteria Inclusion criteria for children of epileptic mothers: having epileptic mother and born at the obstetric clinic of the Helsinki University Central Hospital from December 1975 to December 1979. Inclusion criteria for controls: absence of epilepsy or other chronic disorder in the mother, absence of intrauterine drug exposure (other than iron and vitamins), gestational period of at least 37 weeks and no major perinatal illness or

complication.

Patient Characteristics	The children were examined at 66+/-3 months of age.
Recruitment	The children of epileptic mothers were recruited from the obstetric clinic of the Helsinki University Central Hospital (HUCH). The controls were enrolled in the study from the same clinic and from 2 welfare centers in Helsinki.
Setting	The obstetric clinic of the HUCH.
Interventions/ Test/ Factor being investigated	Having epileptic mother.
Comparisons	Comparison are made between the case group (children of epileptic mothers) and the control (children of non epileptic mothers). Comparisons are also made within groups of different antiepileptic drugs and control (no medication)
Length of Study/ Follow-up	66+/-3 months.
Outcome measures studied	intelligence (measured by a verbal measure, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and a nonverbal measure of intelligence, the Leiter International Performance Scale (LIPS))
Results	<p>1) Any monotherapy (N=67) compared to general population (N=104): no statistically significant between the two groups (the mean WPPSI for the monotherapy was 109.7 (20.5) and for the general population 114.5 (13.3) (difference in means and 95% confidence interval was -4.8 (-10.3, 0.7), P=0.09. The mean LIPS for the monotherapy was 108.9 (16.4) and for the general population 113.2 (13.3) (difference in means and 95% confidence interval was -4.3 (-9.0, 0.4), P=0.07).</p> <p>2) Any polytherapy (N=38) compared to monotherapy (n=67): no statistically significant difference between the two groups; the mean (sd) WPPSI for the monotherapy and polytherapy groups were 109.7 (20.5) and 110.7 (13.6) respectively (difference in means was -1 (-7.5, 5.5), P=0.8. The mean LIPS for the monotherapy group was 108.9 (16.4) and for the polytherapy was 109.5 (14.2) (difference in means -0.6 (-6.6, 5.4), P=0.8.</p> <p>3)Any AED exposure in utero compared to the general population: borderline significance with lower scores in exposed group; the mean WPPSI for the exposed group was 110 (18.4) and for the general population 114.5 (13.3) (mean difference was -4.5 (-8.85, -0.15), P=0.04. The mean LIPS for the exposed group was 109.1(15.4) and for the general population was 113.2 (13.3) (mean difference -4.10 (-8, -0.2), P=0.06).</p> <p>4) Any AED exposure in uterao compared to non exposed children of mothers with epilepsy: no significant difference between the two groups; The mean WPPSI score for the study group was 110 (18.4) and for the control group was (116 (18.4) (the mean difference was -1.6 (-12.6, 9.4), P=0.08). The mean (sd) of LIPS was 109 (15.4) and 104.7 (13.2) for the study and control groups respectively (the mean difference was 4.40 (-3.6, 12.4), P=0.3.</p>
Safety and adverse effects	5 perinatal deaths in the epileptic group of mothers compared to controls. No other perinatal complications or premature deaths.
Does the study answer the question?	Yes. No significant differences were found on the prevalence of mental deficiency among children of epileptic mothers compared to the general population.
Effect due to factor in study?	Unknown. The sample size was not based on a preconsideration of statistical power. There was not a matched control group although there was an exploration of potential confounding factors.
Consistency of results with other studies?	Consistent.
Directly applicable to guideline population?	Direct.
Internal Validity	Adequately addressed

Study Type	Cohort	Funding	Not reported.
Number of participant	N=84, case group (children of mothers with epilepsy)= 43, control (children of non epileptic mothers)= 41		
Inclusion/Exclusion Criteria	Inclusion criteria for cases: children of epileptic mothers who were recruited at the Child Development and Mental Retardation Center of the University of Washington before conception or during their first trimester of pregnancy. Inclusion criteria for controls: children of mothers without epilepsy or other chronic illness who was also recruited in the first or second trimester of pregnancy.		
Patient Characteristics	The two groups of children had mothers well matched for age, parity and race. The mean educational level was higher in the control group than the case group, but the difference was not of statistical significance.		
Recruitment	Epileptic women were recruited before conception or during their first trimester of pregnancy whereas controls were recruited during pregnancy.		
Setting	Child Developmental and Mental Retardation Center.		
Interventions/ Test/ Factor being investigated	Antiepileptic drugs during pregnancy.		
Comparisons	Comparisons are made between the cases (children of epileptic mothers) and the controls (children of non epileptic mothers). Comparisons are made also within cases on the monotherapy versus polytherapy subgroups and between monotherapy and controls.		
Length of Study/ Follow-up	Children were followed for 12 months.		
Outcome measures studied	1)minor anomalies 2)mental development 3)psychomotor development		
Results	<p>1) There was a statistically significant difference on the mean number of minor anomalies between the two groups ($p=0.002$); in the case group the mean number of minor anomalies was 4.7 whereas in the control was 3.1. The features more frequently seen in the case group were a flat nasal bridge (33%) (for the control group was 15%), an epicantal folds (28%) (for the control group was 15%), a broad alveolar ridge (19%) (for the control group was 3%), a pigmented nevi (17%) (for the control group was 3%), a metopic suture ridging (14%) (for the control group was 9%), and hypoplastic toenails (14%) (for the control group was 6%). The only statistically significant difference was between the two groups on the broad alveolar ridge.</p> <p>2) The mean Mental Development Index was significantly higher in the control group (mean 119, range 97-137) than in the case (mean 113, range 86-134) ($P=0.017$).</p> <p>3) There was no statistically significant difference between the two groups on the Psychomotor Development Index.</p> <p>4) In the subgroup analysis; there was a statistically significant difference in the mean mental development index score between the monotherapy group (mean 116) and the polytherapy (mean 108) ($P=0.038$). The subgroup with the highest mean mental development index score was the carbamazepine (mean 122), that was higher than the polytherapy (mean 108) and the control (mean 119).</p>		
Safety and adverse effects	See Q2.		
Does the study answer the question?	Yes. There was a significantly higher mean number of minor anomalies in the case group compared to control. The mean mental development index was significantly lower in the case group compared to control. Among the subgroups, children having mothers taking carbamazepine during pregnancy had the higher mean mental development index. No differences were found on the psychomotor development between the two groups.		

Effect due to factor in study?	Uncertain. There was no prior calculation of the minimum required sample size and unknown if the study had the statistical power to detect an effect if there was.
Consistency of results with other studies?	Unclear.
Directly applicable to guideline population?	Direct.
Internal Validity	Adequately addressed

Meador K;Reynolds MW;Crean S;Fahrbach K;Probst C;

Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. [Review] [99 refs]3

Ref ID 5216

2008 Sep

Study Type Systematic Review **Funding** Shire Development Inc.

Number of participant Population cross sectional studies

Inclusion/Exclusion Criteria

Patient Characteristics

Recruitment

Setting

Interventions/ Test/ Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studied

Results

Safety and adverse effects

Does the study answer the question?

Incidence of individual congenital malformations:
 Children of women with epilepsy had significantly higher rates of hernia, ear/ neck/ face, cleft lip and spina bifida ($p < 0.05$) compared to healthy women. The polytherapy AED group had significantly higher rates of ear/neck/face and cleft lip compared to the monotherapy.

Incidence of congenital malformation by treatment. The AED with the highest incidence of congenital malformations was valproate, which was 10.73% (95% c.i. 8.16, 13.29) and phenytoin (7.36%, 95% c.i. 3.60, 11.11). Carbamazepine (4.62%, 95% c.i., 3.48, 5.76), phenobarbital (4.91%, 95% c.i. 3.22, 6.59) and lamotrigine (2.91%, 95% c.i. 2.00, 3.82) were slightly lower. The rate for valproate was significantly higher than the rate for healthy women. The highest rates of births with congenital malformations for polytherapy regimens including the individual drugs plus one other AED were seen for phenytoin (11.47%, 95% c.i. 6.65, 16.30), phenobarbital (9.19%, 95% c.i. 5.88, 12.50) and valproate (9.79%, 95% c.i. 7.57, 12.02). The highest rate for polytherapy regimens including the individual drugs plus any two or more other AEDs was valproate with 25% (95% c.i. 5.97, 44.03).

Effect due to factor in study?

Consistency of results with other studies?

Directly applicable to guideline population?

Internal Validity

Rovet JF; Cole S; Nulman I; Scolnik D; Altmann D; Koren G;

Effects of maternal epilepsy on children's neurodevelopment

Ref ID 4959

1995

Study Type Cohort **Funding** Not reported.

Number of participant N=116, n carbamazepine= 29, n phenytoin=29, n controls=58.

Inclusion/Exclusion Criteria Inclusion criteria for the epileptic group; having mothers who sought counselling in the first trimester of pregnancy following either phenytoin or carbamazepine therapy. The children were born between 1984 and 1992 and were studied when they were between 7 and 85 months of age. The control children had mothers who sought antenatal counselling from the Motherisk Programme for suspected exposure to an agent deemed non teratogenic (matched on a one to one basis with children of mothers with epilepsy). Matching criteria were: age at conception, parity, gravity, and SES.

Patient Characteristics The mean age of the controls matched with phenytoin exposed children and was 34.5 months and of carbamazepine exposed (29.2 months) which did not differ from their respective epilepsy groups.

Recruitment Mothers of both groups recruited from the Motherisk Programme at the Hospital of Sick Children.

Setting Hospital of Sick Children.

Interventions/ Test/ Factor being investigated Exposure to antiepileptic drugs, carbamazepine and phenytoin, during pregnancy.

Comparisons Comparisons are made between carbamazepine, phenytoin and their respective control groups.

Length of Study/ Follow-up Children were studied between 7 and 85 months of age (mean=29.8 months, sd=16.1 months)

Outcome measures studied 1) Bayles of Infant Development: Mental and Psychomotor Development Index, Bayles II (Cognitive, Language, Motor) 2) McCarthy: General Cognitive Index, T scores (Verbal, Perceptual, Quantitative, Memory, Motor) 3) Reynell scores (comprehension, expressive)

Results	PHT (n=16)	CBZ (n=24)	Difference in means (95%ci) (by Cochrane Review)
MDI	108.2 (17.8)	114.2 (17.8)	-6 (-17.26, 5.26) P=0.3
PDI	104.8 (14.6)	106.0 (12.1)	-1.2 (-9.84, 7.44) P=0.8
Cogn	-0.75 (3.4)	-0.96 (3.3)	0.21 (-1.92, 2.34) p=0.8
Lang	-3.13 (3.3)	-1.96 (3.0)	-1.17 (-3.18, 0.84) p=0.3
Mo	0.38 (4.1)	-0.29 (4.1)	0.67 (-1.92, 3.26) p=0.6
	PHT (n=13)	CBZ (n=5)	
T scor	99.3 (28)	93.5 (11.2)	5.80 (-12.31, 23.91) p=0.5
Verbal	50.3 (15.9)	46.0 (5.7)	4.30 (-5.68, 14.28) p=0.4
Perceptual	48.8 (14.6)	46.0 (7.1)	2.80 (-7.29, 12.89) p=0.6
Quantitat	45.9 (15.1)	45.8 (5.0)	0.10 (-9.21, 9.41) p=1.0

Memory	47.7 (14.5)	39.3 (3.8)	8.4 (-0.16, 16.96) p=0.05
Mortor	46.3 (13.7)	38.5 (7.9)	7.8 (-2.37, 17.97) p=0.13
PHT (n=26)		CBZ (n=28)	
Compreh	0.19 (1.62)	0.84 (1.44)	-0.65 (-1.47, 0.17)
Expres	-0.50 (1.28)	0.09 (0.95)	-0.59 (-1.19, 0.01) p=0.06

Safety and adverse effects

Not reported.

Does the study answer the question?

Yes. Lower scores in phenytoin exposed group.

Effect due to factor in study?

Unknown. The assessment of outcome measures were not available for all the participants in the study, therefore the statistical power of the study has been negotiated. However, the proportion of eligible mother child pairs in the clinic was 90%.

Consistency of results with other studies?

Unknown.

Directly applicable to guideline population?

Direct.

Internal Validity

Adequately addressed

Vanoverloop D;Schnell RR;Harvey EA;Holmes LB;

The effects of prenatal exposure to phenytoin and other anticonvulsants on intellectual function at 4 to 8 years of age

Ref ID 4935

1992 Sep

Study Type Cohort

Funding In part by NIH Grant no 10910 and the Easter Seal Research Fund.

Number of participant N study group (exposed to phenytoin)=20 and n controls (unexposed)=98.

Inclusion/Exclusion Criteria Inclusion criteria for the study group;exposure to phenytoin during pregnancy. Exclusion criteria for the study group: alcohol abuse during pregnancy, children's hearing and speech problems. Inclusion criteria for controls: children having three or more minor anomalies. Exclusion criteria for controls: major malformations, children's hearing problems.

Patient Characteristics The average age of exposed children was 60 months and of the matched controls was 62 months. All exposed children were the same sex as their assigned controls. All except one, the oldest girl, was the same parity as the control. For 12 out of 20 exposed children, the SES match was with the same Hollingshead category, and for 5 more, the socioeconomic status of the exposed child was in the same major category as that of the matched unexposed child.

Recruitment Children in the study group were recruited from a sample of 7085 children born at the Boston Hospital for Women, Lying in Division who were exposed during pregnancy to phenytoin. 38 (0.5%) mothers reported this exposure.

Setting Boston Hospital for Women, Lying-in Division.

Interventions/ Test/ Factor being investigated Maternal epilepsy.

Comparisons Comparisons were made between the study group (intrauterine exposure to phenytoin only or with additional anticonvulsants) and the controls (non epileptic mothers).

Length of Study/ Follow-up 4-8 years.

Outcome measures studied	1) intelligence (and two subtypes; verbal and performance intelligence) 2) visual motor integration 3) psycholinguistic abilities (two subtypes; grammatic closure and auditory association)
Results	<p>1) the intelligence full scale significantly differed between the two groups; the mean total intelligence score (sd) for the study group was 109.3 (10.9) and for the control was 118.16 (11.94) (difference in means given by the Cochrane review -8.86 (-14.19, -3.53), P=0.001). The mean performance score was significantly lower in the study group (105 (10.11)) compared to controls (115.64 (11.75)) (difference in means given by the Cochrane review -10.64 (-15.64, -5.64, P=0.00003). No significant differences were found between the two groups on the verbal intelligence scores (for the study group the mean (sd) verbal intelligence score was 111.4 (11.59) and for the control 117.14 (12.17) (difference in means given by the Cochrane review -5.74 (-11.36, -0.12, P=0.05).</p> <p>2)Significant differences were found on the mean scores of visual motor integration test between the two groups; for the study group the mean (sd) was 7.97 (4.37) and for the control group was 14.15 (8.23) (the difference in means given by the Cochrane review was 6.18 (-8.74, -3.62, P<0.00001).</p> <p>3)No significant differences were found in either the auditory association test or the grammatic closure). The mean (sd) for the auditory association test was 42.56 (7.54) and 43.80 (6.57) for the study and control groups respectively (the difference in means given by the Cochrane review was -1.24 (-5.17, 2.69, P=0.5). The mean (sd) for the grammatic closure test was 44.75 (9.12) and 44.94 (7.83) for the study and control groups respectively (the difference in means given by the Cochrane review was -0.19 (-4.51, 4.13, P=0.9).</p>
Safety and adverse effects	The 16 exposed children who were not evaluated included one with growth retardation at birth and 2 with a major malformation and 2 were dead at the date of evaluation.
Does the study answer the question?	Yes. The intelligence full scale and the performance subscale were significantly lower in the study group compared to controls. The average visual motor integration score was significantly lower in the exposed group compared to unexposed. No differences were found between the two groups on the verbal intelligence scale, on the auditroy association test or the grammatic closure.
Effect due to factor in study?	Uncertain. No priori calculation of minimum required sample size to detect a statistically significant difference if it exists. Study may have been underpowered.
Consistency of results with other studies?	With some but not all studies in the field.
Directly applicable to guideline population?	Direct.
Internal Validity	Adequately addressed

Wide K;Henning E;Tomson T;Winbladh B;

Psychomotor development in preschool children exposed to antiepileptic drugs in utero

Ref ID 4926

2002

Study Type	Cohort	Funding	Research grant K97-17z-12225-01A from the Swedish Medical Research Council, the Foundation of Samariten, the May Flower Foundation, the Research Foundation of Glaxo-Welcome company and the Research Foundation of Pediatric Research of the Freemasons.
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Number of participant N (exposed to any AED) =67, N(unexposed)=66, N (phenytoin)=15, N(carbamazepine)=35

Inclusion/Exclusion Criteria	Inclusion criteria for the exposed to any AEDs children were: giving birth during 1985-1995 and attending antenatal clinics in the south east region of Stocholm. For the non exposed children: baby matched for gestational age, gender and mode of delivery was recruited within +-2 days of the birth of a study child. Exclusion criteria: children were excluded if the birth examination was not performed by any of the participating paediatricians.
Patient Characteristics	The main characteristics for the whole exposed group (including several AEDs) compared to unexposed group; the number of families with only one child was significantly higher in the exposed group ($p<0.01$). Ten of the 67 exposed women had the lowest educational level, compared to only 2 women in the unexposed group ($p<0.001$).
Recruitment	They were recruited during early pregnancy from antenatal clinics and their epilepsy treatment was monitored carefully throughout pregnancy.
Setting	population study in the south east of Stockholm.
Interventions/ Test/ Factor being investigated	Exposure to any of the following antiepileptic drugs: carbamazepine, phenytoin, other antiepileptic drug and polytherapy.
Comparisons	Comparisons were made between exposed and unexposed groups and within the different subgroups of exposed group; phenytoin and carbamazepine.
Length of Study/ Follow-up	4.5-5 years.
Outcome measures studied	psychomotor development as assessed by the 6 subsets of Griffiths' test: locomotor function, personal and social behaviour, hearing and speech, eye and hand coordination, performance and practical reasoning.
Results	<ol style="list-style-type: none"> 1) Children exposed to carbamazepine had a higher mean score on locomotor function; 104 compared to phenytoin children; 98 2) Children exposed to carbamazepine had a higher mean score on personal and social behaviour; 107 compared to children exposed to phenytoin; 105 3) Children exposed to phenytoin had a higher mean(95%ci) scores on hearing and speech; 111 compared to carbamazepine group; 105 4) Almost similar mean scores had the both groups (carbamazepine; 100 and phenytoin; 101 on eye and hand coordination 5) A higher mean score had the phenytoin group on performance; 110 compared to carbamazepine 105 6)A higher mean score had the phenytoin group on practical reasoning;110 compared to carbamazepine 101. 7) The mean total score of psychomotor development was higher for the phenytoin group (635)compared to carbamazepine (618)
Safety and adverse effects	Not reported.
Does the study answer the question?	Unclear. The mean total scores of psychomotor development of exposed children to phenytoin was higher compared to carbamazepine group.
Effect due to factor in study?	The sample size calculation were based on comparison of an exposed group to various AEDs and to unexposed group. Therefore, the numbers in the groups of phenytoin and carbamazepine is unknown whether they have enough statistical power. No information on confidence intervals for the comparison of these two drugs.
Consistency of results with other studies?	Unclear.
Directly applicable to guideline population?	Direct.
Internal Validity	Adequately addressed

Grading: 2-	Case-control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
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Barqawi R;

Evaluation of antiepileptic drugs in pregnancy in a Jordanian army hospital

Ref ID 448

2005 Jul

Study Type	Cohort	Funding	Not mentioned.
Number of participant	N=50, Group A (carbamazepine)=16, Group B (carbamazepine and phenytoin)=16, group C(no medication)=18.		
Inclusion/Exclusion Criteria	Inclusion criteria:pregnant women aged 25-35 years, multiparous, with known past history of epilepsy fro the last 5 years and no obvious cause of the disease, attending regularly the internal medicine clinic at Kig Husein Medical Centre, Amman, Jordan.		
Patient Characteristics	They were recruited from the medicine clinic at Kig Husein Medical Centre, Amman, Jordan. See inclusion criteria.		
Recruitment	Women with a history of epilepsy being regular attenders of the internal medicine clinic at King Hussein Medical Centre were recruited in the study.		
Setting	The internal medical clinic at King Hussein Centre		
Interventions/ Test/ Factor being investigated	Being born by a mother treated on carbamazepine during pregnancy.		
Comparisons	Comparison are made between participants and their children on carbamazepine, on carbamazepine and phenytoin and on no medication.		
Length of Study/ Follow-up	throughout pregnancy until the delivery.		
Outcome measures studied	1) minor congenital anomalies 2)major congenital anomalies		
Results	<p>1) A statistically significant difference was found between the three groups on the proportions of minor congenital anomalies ($p=0.01$); n group A (carbamazepine), 4/16 children were born with minor congenital anomalies (25%) (distal digital hypoplasia and ear flap abnormalities), in group B (carbamazepine and phenytoin) 4/16 (25%) and in group C(no medication) 0/18.</p> <p>2) No statistically significant difference was found between the three groups on the proportions of major congenital anomalies ($p=0.07$); major congenital anomalies were detected only in group B (carbamazepine and phenytoin)p 2/16 (12.5%).</p>		
Safety and adverse effects	See results in Q2		
Does the study answer the question?	Unclear. 25% of children of mothers treated on carbamazepine during pregnancy and 25% of children born by mothers on carbamazepine and phenytoin were born with minor congenital anomalies. 12.5% of children born by mothers on carbamazepine and phenytoin had major congenital anomalies.		
Effect due to factor in study?	Unclear. The study had a small sample size and no information are given for the allocation of treatment to groups and any confounding factors on the outcome measure.		
Consistency of results with other studies?	Consistent.		
Directly applicable to guideline population?	Direct.		

Internal Validity Not addressed

Gaily E;Kantola-Sorsa E;Granstrom ML;

Specific cognitive dysfunction in children with epileptic mothers

Ref ID 4940

1990 May

Study Type Cohort

Funding Rinnekoti Research Foundation, Espoo, Finland, the Foundation of Paediatric Research and Orion Foundation.

Number of participant N=239, n children of epileptic mothers=134, n controls=105.

Inclusion/Exclusion Criteria Inclusion criteria for the study group (children of epileptic mothers): born to epileptic mothers from December 1955-December 1979 at Helsinki University Central Hospital. Exclusion criteria were: subnormal intelligence, born before 37 completed weeks of gestation or from a multiple pregnancy. Inclusion criteria for controls: born between December 1975 and December 1975, absence of epilepsy or other chronic disorder in the mother, absence of intrauterine drug exposure, other than iron and vitamins, gestation of at least 37 weeks, and no major perinatal illness or complication.

Patient Characteristics

Recruitment All pregnant with epilepsy whose babies were delivered at Helsinki University Central Hospital from December 1975 to December 1979 were enrolled in this study. The controls was sampled for the maternity hospital and child welfare centre records.

Setting Not clear.

Interventions/ Test/ Factor being investigated Any AED exposure in utero.

Comparisons Comparison was made between any AED exposure compared to the general population.

Length of Study/ Follow-up mean 5.5 years (range 5.2 to 5.8 years for both groups).

Outcome measures studied mental deficiency, borderline intelligence (defined as both scores for WIPPSI and LIPS<85, and at least one<70), proportion of children with specific cognitive dysfunction .

Results The proportion of children with mental deficiency in the study group (of epileptic mothers) was 1.4% (2/148), whereas 0% of control children had mental deficiency. The proportion of children with borderline intelligence was 1.7% (2/117) and 0% in the study and control groups respectively. The proportion of children with specific cognitive dysfunction (defined as performing below the 5th centile for one or more of: visuoconstructive score of Wechsler Preschool and Primary Scale, auditory phonemic score of Illinois Test of Psycholinguistic Abilities and/or comprehension score of Neuropsychological test battery NEPS) was 23% (22/94) and 7% (7/100) in the study and control groups respectively.

Safety and adverse effects See results (Q2-9).

Does the study answer the question? A higher proportion of children of epileptic mothers had specific cognitive dysfunction at the age of 5.5 years compared to controls. No significant differences were found on the neuropsychological impairment between study and control groups.

Effect due to factor in study? Uncertain. Due to absence of information the methodological rigour of the study couldn't be assessed. Uncertain about the statistical power of the study to detect a significant difference if it existed.

Consistency of results with other studies?	Consistent with some but not all studies.
Directly applicable to guideline population?	Direct.
Internal Validity	Adequately addressed
Hanson JW;Myriantopoulos NC;Harvey MA;Smith DW;	
Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome	
Ref ID 4958	1976 Oct
Study Type	Cohort
	Funding Not reported.
Number of participant	Unclear. Based on Cochrane Review information n study group=83 and n control=83
Inclusion/Exclusion Criteria	Inclusion criteria for exposed to AED group of children: born to mothers with a convulsive disorder treated with hydantoins continuously throughout pregnancy. Inclusion criteria for controls: born to mothers without seizures and who received no anticonvulsants during pregnancy. The controls were matched for maternal socioeconomic status, maternal age, race and institution of birth.
Patient Characteristics	Among the 104 women identified as receiving hydantoins, 62 were whites, 39 were black, and 3 were Puerto Rican. 24 women were treated with hydantoins alone, the remainder were treated with hydantoins and barbiturates, from whom 17 mothers also received other anticonvulsant drugs. Approximately 11% of infants exposed prenatally to hydantoins have enough unusual features to be clearly classified as having fetal hydantoin syndrome, while an additional 31% display some features compatible with the prenatal effects of hydantoins.
Recruitment	The exposed group was recruited from the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke.
Setting	Not reported.
Interventions/ Test/ Factor being investigated	Intrauterine exposure to AED.
Comparisons	Any AED exposure in utero compared to the general population.
Length of Study/ Follow-up	7 years.
Outcome measures studied	mental performance (measured by WISC full scale mental performance scores), intelligence (measured by IQ)
Results	The mental performance scores were significantly lower in the exposed group compared to controls; mean (sd) WISC full scale for the exposed group to AED was 91.7 (17.29) and for the general population 96.83 (15.5) (difference in means (95%ci) reported by the Cochrane Review was -5.13 (-10.3, -0.13), P=0.04). Data on IQ as reported by the Cochrane Review (extracted from graph); the proportion of children with IQ<70 was 7.5% in the exposed group and 5.8% for the general population respectively.
Safety and adverse effects	dysmorphic features?
Does the study answer the question?	The mental performance score was significantly lower in the exposed group compared to placebo.
Effect due to factor in study?	Poor methodology. Uncertain about the statistical power of the study and whether the effect observed was due to exposure to anticonvulsants.

Consistency of results with other studies? Unclear.

Directly applicable to guideline population? Direct.

Internal Validity Not addressed

Koch S;Titze K;Zimmermann RB;Schroder M;Lehmkuhl U;Rauh H;

Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for school-age children and adolescents

Ref ID 4929

1999 Sep

Study Type Cohort **Funding** Not reported.

Number of participant N=116, n monotherapy=31, n polytherapy=23, n no therapy (epileptic mothers)=13, controls (no epileptic mothers)=49.

Inclusion/Exclusion Criteria Inclusion criteria for the study groups: born between 1976 and 1984 and being members of the prospective longitudinal panel on "Epilepsy, pregnancy and development" (Steinhausen et al, 1994). The control mother(non epileptic)/child pairs were matched on five variables: socioeconomic status, age of the mother at delivery, birth order, cigarette consumption during pregnancy, and number of previous abortions.

Patient Characteristics The age of children ranged from 10-19 years. The children of mothers who received polytherapy during pregnancy were generally from older birth cohorts, and the children of mothers who received monotherapy during pregnancy were generally from younger birth cohorts. Many of the children in the control group entered the longitudinal study later, so were on average younger at the time of this examination.

Recruitment Both study and control participants were recruited from the obstetric departments where pregnant women with epilepsy were cared for during pregnancy and at delivery.

Setting Not reported.

Interventions/ Test/ Factor being investigated Intrauterine AED exposure.

Comparisons 1)any monotherapy exposure in utero compared to the general population, 2)any polytherapy compared to any monotherapy exposure in utero, 3)any monotherapy exposure in utero compared to non exposed children of mothers with epilepsy.

Length of Study/ Follow-up 10.9-19 years.

Outcome measures studied general intelligence; measurement of performance (non verbal) and verbal components.

Results 1)any monotherapy exposure in utero compared to the general population: study does not report significance of this comparison. Performance and total score of intelligence significantly lower in the monotherapy group. No significant difference between groups in terms of verbal scores. Mean (sd) score of verbal intelligence for the monotherapy group was 99.7 (14.2) and for the controls 103.1 (12.6) (difference in means by Cochrane review (95%ci): -3.40 (-9.52, 2.72), P=0.3). Mean (sd) score of performance intelligence for the monotherapy group was 100.0 (15.2) and for the controls 106.7 (11.0) (difference in means by Cochrane review (95%ci): -6.70 (-12.87, -0.53), P=0.03). Mean (sd) score of total intelligence for the monotherapy group was 99.7 (13.8) and for the controls 105.4 (11.5) (difference in means by Cochrane review (95%ci): -5.70 (-11.53, 0.13), P=0.06). 2)any polytherapy compared to any monotherapy exposure in utero: trend suggests that scores are lower on polytherapy although the differences are not statistically significant; mean (sd) score of verbal intelligence for the monotherapy group was

99.7 (14.2) and for the polytherapy 92.7 (14.3) (difference in means by Cochrane review (95%ci): 7.0 (-0.69, 14.69), P=0.07). Mean (sd) score of performance intelligence for the monotherapy group was 100.0 (15.2) and for the polytherapy 92.2 (17.69) (difference in means by Cochrane review (95%ci): 7.80 (-1.19, 16.79), P=0.09). Mean (sd) score of total intelligence for the monotherapy group was 99.7 (13.8) and for the polytherapy 92.2 (17.6) (difference in means by Cochrane review (95%ci): -7.50 (-1.18, 16.18), P=0.09).

3)any monotherapy exposure in utero compared to non exposed children of mothers with epilepsy: study does not specifically report this comparison. Scores do not differ significantly between groups. Mean (sd) score of verbal intelligence for the monotherapy group was 99.7 (14.2) and for the controls 100.8 (17.7) (difference in means by Cochrane review (95%ci): -1.10 (-11.94, 9.74), P=0.8). Mean (sd) score of performance intelligence for the monotherapy group was 100.0 (15.2) and for the controls 98.6 (21.6) (difference in means by Cochrane review (95%ci): 1.40 (-11.50, 14.3), P=0.8). Mean (sd) score of total intelligence for the monotherapy group was 99.7 (13.8) and for the controls 101.8 (18.4) (difference in means by Cochrane review (95%ci): -2.10 (-13.22, 9.02), P=0.7).

Safety and adverse effects

Not reported.

Does the study answer the question?

Yes. Performance and total score of intelligence were significantly lower in the monotherapy group compared to the general population. Trend suggests that all three intelligence scores were lower on polytherapy compared to monotherapy although the differences were not statistically significant. Intelligence scores did not differ significantly between the monotherapy group and the non exposed children of epileptic mothers.

Effect due to factor in study?

Uncertain, as only 41% of the original study has been followed up. Unclear the risk of attrition bias and its impact on the statistical power of the study.

Consistency of results with other studies?

Unclear.

Directly applicable to guideline population?

Direct.

Internal Validity

Adequately addressed

Mawer G;Clayton-Smith J;Coyle H;Kini U;

Outcome of pregnancy in women attending an outpatient epilepsy clinic: adverse features associated with higher doses of sodium valproate

Ref ID 4925

2002 Dec

Study Type Cohort

Funding No funding.

Number of participant

43 mothers and 56 children were assessed; 1 pregnancy had no drug, monotherapy: 23 pregnancies in 14 women had sodium valproate, 18 pregnancies in 13 women had carbamazepine, 7 pregnancies in 3 women had phenytoin, 4 pregnancies in 3 women had lamotrigine, 1 pregnancy had ethosuximide. Polytherapy: 15 pregnancies in 12 women had combined AEDs

Inclusion/Exclusion Criteria

Inclusion criteria: Pregnant women attending the Epilepsy Clinic at Manchester Royal Infirmary between January 1990 and December 1999. No exclusions were made.

Patient Characteristics

Pregnant women attending a hospital unit. 26/45 had focal epilepsy, 17 had idiopathic generalised epilepsy and in 2 the epilepsy was unclassified.

Recruitment

From the Epilepsy Clinic at Manchester Royal Infirmary. No further information are given.

Setting

the Epilepsy Clinic at Manchester Royal Infirmary.

Interventions/ Test/ Factor being investigated	Epilepsy.
Comparisons	Comparisons were made within the population of women with epilepsy between different treatment groups (sodium valproate monotherapy, carbamazepine monotherapy and polytherapy).
Length of Study/ Follow-up	10 years?? (4 pregnancies were assessed retrospectively)
Outcome measures studied	1) number of miscarriages 2) dysmorphic features 3) developmental delay 4) structural anomalies
Results	<p>1) 10/69 pregnancies were lost (miscarriages)</p> <p>2) dysmorphic features were found in more than half the children with some evidence of developmental delay in about one quarter. Structural anomalies were found in about one third of children.</p> <p>3) monotherapy with valproate: in each assessment, a positive association was found between adverse outcome and VPS dose (the significance was borderline for developmental delay but high for the other two areas). At higher doses above 1000mg/day moderate or severe features were found in one area of assessment at least, in half the children. (3/4 women who had adverse outcomes to earlier pregnancies on doses of 1400-2500 mg/day on VPS, after withdrawal of AED, reduction of VPS dose or transfer to CBZ, conceived again producing normal children.</p> <p>4) monotherapy with carbamazepine: no significant association with adverse outcome and CBZ dose in any assessment area.</p> <p>5) monotherapy with phenytoin and lamotrigine: adverse features were absent or mild.</p> <p>6) polytherapy (clobazam, ethosuximide, gabapentin, lamotrigine, phenytoin, topiramate or vigabatrin with CBZ or VPS): adverse events were absent or mild except one case (VPS 1200 mg/day with LTG 125 mg/day) that spinal bifida was seen on anomaly scan and the pregnancy was terminated.</p>
Safety and adverse effects	See Q2 9-10
Does the study answer the question?	The study has several limitations; VPS in pregnancy at doses above 1000 mg/day carries a particular risk of adverse outcomes.
Effect due to factor in study?	Uncertain, small sample size, some comparisons could not be made and several methodological limitations.
Consistency of results with other studies?	In some but not all studies.
Directly applicable to guideline population?	Not clear.
Internal Validity	Not reported
Ornoy A;Cohen E;	
Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy	
Ref ID 4930	1996 Dec
Study Type	Cohort
Funding	No mentioned.
Number of participant	47 children whose mothers were treated on carbamazepine during pregnancy (Group A) and 47 control children (Group B).
Inclusion/Exclusion Criteria	Inclusion criteria for children in Group A: aged 6 months to 6 years, having mothers with epilepsy who were treated on carbamazepine monotherapy during pregnancy and attending the Israeli Teratogen Information Service during 1988-1994. Exclusion criteria were; premature babies (born before 32 weeks of gestation). The children in control group were matched by birth weight, gestational age and parental socioeconomic status.

Patient Characteristics	Children were aged 6 months to 6 years. 19 children were Ashkenazi, 24 children were of Oriental origin and six children were of unknown ethnic origin. Their mothers were patients at the the Israeli Teratogen Information Service during 1988-1994.
Recruitment	Their mothers were patients at the the Israeli Teratogen Information Service during 1988-1994. Not reported how matched controls were recruited.
Setting	Not clearly stated.
Interventions/ Test/ Factor being investigated	Being born by mothers with epilepsy who were taking carbamazepine monotherapy during pregnancy.
Comparisons	Comparisons were made between the children whose mothers were epileptic and taking carbamazepine during pregnancy (Group A) and the matched control children (Group B).
Length of Study/ Follow-up	Not clear.
Outcome measures studied	1)proportion of children born with major anomalies 2) proportion of children with facial dysmorphic features 3)proportion of children with cognitive, motor and mental delay (scores were given based on Bayley and McCarthy tests).
Results	<p>1) 3/47 children in Group A had major anomalies (1 had hydrocephalus, 1 had ventricular septal defect, 1 had dilatation of the pelvis of the kidney and 2 had cleft plate. 3/47 in Group B had major anomalies (pulmnonic stenosis, hypospadias and a solitary cyst of the kidney)</p> <p>2) in Group A 6/47 children had typical facial dysmorphic features as described in carbamazepine syndrome (upslanting palpebral fissure, epicanthic folds, micrognathia, broad nasal bridge, high arched palate or cleft palate. 0/47 children in Group B had dysmorphic features.</p> <p>3) There was a lower average mental and cognitive score in children born to mothers treated with carbamazepine when compared with controls (mean (sd) mental score for Group A 101.1 (14.8) and for group B 112 (10), mean cognitive score for group A 99.4 (21.1) and for group B 113 (15)). There were no differences on motor scores (mean (sd) for group A 97.5 (18) and for group B 101 (11.6)). 4/41 children in Group A had mental or cognitive scores between 81 and 90 and 5/41 had scores of 80 or below. In group B there was no child with mental or cognitive scores below 81 and 2/47 had these scores below 90.</p> <p>4) All children with facial dysmorphic features (carbamazepine syndrome) had a development quotient or intelligence quotient below 90.</p>
Safety and adverse effects	8/48 women who were pregnant had spontaneous or induced abortions.
Does the study answer the question?	No difference was found on the incidence of major anomalies between children born to epileptic mothers who were on carbamazepine monotherapy and matched controls. However, 6/47 children of epileptic mothers had typical facial dysmorphic features (carbamazepine syndrome) whereas none of the control children had it. Children from epileptic mothers had a lower average mental and cognitive score compared to control children.
Effect due to factor in study?	Uncertain, the group of children of epileptic mothers who had major anomalies was too small (4) to be related to carbamazepine, especially as three control children had congenital anomalies.
Consistency of results with other studies?	Partly.
Directly applicable to guideline population?	Unclear.
Internal Validity	Adequately addressed

Shapiro S;Hartz SC;Siskind V;Mitchell AA;Slone D;Rosenberg L;Monson RR;Heinonen OP;

Anticonvulsants and parental epilepsy in the development of birth defects

Study Type	Cohort	Funding	NIH-NINDS-72-2322 and by National Institute of Neurological Diseases and Stroke, US Public Health Service and Food and Drug Administration contract 223-75-3036.
Number of participant	N=2784. Comparisons of the exposed and control children yield ratios of 2.5/1 for any phenytoin exposure, 3.5/1 for any phenobarbitone exposure and 2/1 for phenytoin together with phenobarbitone.		
Inclusion/Exclusion Criteria	Inclusion criteria for the study group: children whose mothers had used an anticonvulsant during pregnancy with central nervous system, skeletal and/ or craniofacial defects.		
Patient Characteristics	They mentioned that epileptic and non epileptic mothers and their children differed with respect to a number of characteristics but no further information were given.		
Recruitment	Not reported (part of the Collaborative Perinatal Project USA).		
Setting	Not reported.		
Interventions/ Test/ Factor being investigated	exposure to anticonvulsant during pregnancy.		
Comparisons	2 comparisons were made; 1) between phenobarbitone in utero and general population, 2) between phenytoin and phenobarbitone exposure in utero		
Length of Study/ Follow-up	8 months to 4 years.		
Outcome measures studied	mental development (mental, motor) at 8 months, intelligence (IQ) for 4 years.		
Results	<p>All results were adjusted for ethnic group, SES and hospital.</p> <p>1) comparison on the mental development between phenobarbitone exposure in utero (n= 35) compared to the general population (n=27,832) at 8 months: The mental score (sd) of the phenobarbitone group was 78.6 (7.10) compared to 79.5 (5) of the general population (the difference in means (95% ci) -0.90 (-3.25,1.45), P=0.5). The motor score (sd) of the phenobarbitone group was 32.3 (5.32) compared to 33.6 (5) of the general population (the difference in means (95% ci) -1.30 (-3.06,0.46), P=0.15).</p> <p>2) comparison on the intelligence between phenobarbitone exposure in utero (n=27) compared to the general population (n=28,273) at 4 years: The intelligence score (sd) of the phenobarbitone group was 96.4 (16.11) compared to 97.0 (15.13) of the general population (the difference in means (95% ci) -0.60 (-6.68,5.48), P=0.8).</p> <p>3) comparison on the intelligence between phenytoin (n= 35) compared to phenobarbitone exposure in utero (n=27): The IQ score (sd) of the group was 91.1 (15.97) compared to 96.4 (16.11) of the phenobarbitone group (the difference in means (95% ci) was -5.30 (-13.36, 2.76), P=0.2).</p>		
Safety and adverse effects	Malformations reported elsewhere (Hartz et al).		
Does the study answer the question?	No statistically significant differences were found on either the mental and motor development of children at 8 months or the intelligence of 4 years old between the group of children exposed to phenobarbitone in utero and to the general population. No differences were found on the intelligence scores between the children exposed to phenytoin and phenobarbitone in utero.		
Effect due to factor in study?	Unclear. Unable to assess study's methodology due to absence of information.		

Consistency of results with other studies? Uncertain.

Directly applicable to guideline population? Direct.

Internal Validity Poorly addressed

van der Pol MC;Hadders-Algra M;Huisjes HJ;Touwen BC;

Antiepileptic medication in pregnancy: late effects on the children's central nervous system development

Ref ID 4938

1991 Jan

Study Type Cohort **Funding** Not reported.

Number of participant N study group (children of epileptic mothers)=61, N children exposed to phenobarbital only=13, N children exposed to carbamazepine only=12, N children exposed to phenobarbital and carbamazepine=12 and children not exposed to any antiepileptic medication=24. N control children (non epileptic mothers)= 61.

Inclusion/Exclusion Criteria Inclusion criteria for the study group: documentation of maternal epilepsy by a neurologist, antiepileptic medication (none, phenobarbital and/or carbamazepine), absence of seizures during pregnancy and delivery, no evidence of intrauterine infection or chromosomal abnormalities and absence of additional drug exposure. Control children were selected from singletons born in the same period and they were matched for their mother's parity and for birth weight, gestational age, sex, age at follow up and social class.

Patient Characteristics The children were followed for 6 years.

Recruitment During the years 1973 to 1981, children of epileptic mothers who had received extensive ante and perinatal care were recruited in the study. Controls of non epileptic mothers were selected from singletons born in the same period.

Setting Groningen University Hospital.

Interventions/ Test/ Factor being investigated Having an epileptic mother (exposure to antiepileptic drug in utero or not).

Comparisons Comparisons were made between the study and the control groups. Comparisons were also made between the different groups of drugs used in the study group and the control group.

Length of Study/ Follow-up 7-13 years.

Outcome measures studied 1) Children's ability for reading, spelling and arithmetic (proportion with score < 10th centile) 2) school career (proportion of children in inappropriate class for age and learning disorders)

Results 1) Phenobarbitone exposure in utero compared to the general population: higher proportion of children in phenobarbitone group had spelling and arithmetic problems; a) 2/9 in phenobarbitone and 4/43 in controls had reading problems b) 5/7 and 7/37 had spelling problems in phenobarbitone and general population respectively c) 3/7 and 2/37 had arithmetic problems in phenobarbitone and general population respectively. 4/12 and 10/54 children in phenobarbitone and general population respectively were in inappropriate class for age and learning disorders. 2) Any AED exposure in utero compared to the general population: a higher proportion of children with poorer outcomes was found in the exposed group. 5/28 in the study group and 4/43 in the control had problems with reading, 7/24 and 7/37 in the study and control groups respectively had problems with spelling and 4/24 in the study group and 2/37 in the control groups had problems in arithmetic. The proportion in inappropriate class was 6/34 for the study group and 10/54 for the controls. 3) Any AED exposure in utero compared to non exposed children of mothers with epilepsy: a higher proportion of children were found with poor outcomes in the

exposed group for arithmetic and school career; 6/34 children in the group of any AED exposure had problems in reading compared to 5/22, 5/28 children in the study group had problems in spelling compared to 2/15 in the control and 7/24 children with any AED exposure in pregnancy had problems in arithmetic compared to 2/13 in the control. 4/24 of the study children were in inappropriate class for age and learning disorders and 1/1 of the controls.

4) Any monotherapy exposure in utero compared to non exposed children of mothers with epilepsy; 2/18 and 2/15 children in the study and control groups respectively had problems with reading, 5/15 and 2/13 in the two groups had problems with spelling and 3/15 in the study group and 5/22 had problems with arithmetic. 4/22 and 5/22 children in the exposed and non exposed groups were in inappropriate classes for age and learning disorders.

Safety and adverse effects

One child in the non medication group died of complications of spina bifida.

Does the study answer the question?

Yes. No significant differences were found in the occurrence of (minor) neurologic dysfunction either between the control and the study groups as a whole, or between the control and specific drug groups.

Effect due to factor in study?

Unclear. No a priori consideration of statistical power. Small numbers of groups of children being exposed to different groups thus making statistical analysis weak.

Consistency of results with other studies?

Consistent.

Directly applicable to guideline population?

Direct.

Internal Validity

Adequately addressed

Wide K;Winbladh B;Tomson T;Sars-Zimmer K;Berggren E;

Psychomotor development and minor anomalies in children exposed to antiepileptic drugs in utero: a prospective population-based study.[Erratum appears in Dev Med Child Neurol 2000 May;42(5):356]

Ref ID 4957

2000 Feb

Study Type

Cohort

Funding

Research Gran from the Swedish Medical Research Council (K97-17X-12225-01A), the Foundation of the First of May Flower, The Foundation of Samariten, the Orion, Pharma Research Foundation and the Holmia Insurance Company.

Number of participant

For phase I (birth) N=170, N study group (epileptic mothers)=87, N control group=83, for phase II (9months), N=162, N study group=81, N control group=81.

Inclusion/Exclusion Criteria

The inclusion criteria for the study group were; mothers were continuously treated with AEDs from conception throughout pregnancy, the mothers were identified during the first trimester, from which time they attended the outpatient clinic for pregnant women with epilepsy at the department of neurology, and followed the protocol at this clinic, parents gave permission for their children to participate in the follow up, the children were born at one of the two delivery wards in the departments of paediatrics and neurology at the South Hospital, one of the participating paediatricians was available to organize the examination of the newborn infant within 4 days of birth. No home deliveries were included. The controls were born in the same hospital within 2 days of the study subjects and matched for gestational age and mode of delivery and for sex.

Patient Characteristics

Children from epileptic mothers treated continuously with AEDs throughout pregnancy and attended the departments of neurology and paediatrics at a hospital. Controls were born in the same hospital within 2 days of the study subjects. 71 mothers (83%) of children in the study group were receiving monotherapy, carbamazepine and phenytoin were the most frequent used. The mean gestational

age was 39.3 weeks for the subjects and 39.5 for the control infants.

Recruitment

All children in the study were recruited from the departments of neurology and paediatrics at the Sodersjukhuset Hospital in the south east region of Stockholm.

Setting

The Sodersjukhuset Hospital of Stockholm.

**Interventions/ Test/
Factor being
investigated**

Comparisons

Comparisons are made between the group of subjects (having antiepileptic mothers under treatment during pregnancy with carbamazepine, phenytoin, others and polytherapy) and the control group (mothers non epileptic).

**Length of Study/
Follow-up**

9 months follow up.

**Outcome measures
studied**

1) minor anomalies 2) major anomalies 3) psychomotor development

Results

1) 15/39 (11 facial anomalies, 5 digital, 1 genital anomalies, 4 skin anomalies) children in carbamazepine and 5/37 in control group had minor anomalies (OR 11, 95% CI 1.42-85.2).
2) 5/21 children in phenytoin (2 facial anomalies, 1 digital anomalies, 4 skin anomalies) and 6/19 in control group had minor anomalies (OR 0.8, 95% CI 0.22-2.98)
3) For children exposed to AEDs (no separate information): 1/84 had ventricular septal defect and a nail hypoplasia, 1/84 had an isolated hypospadias and in the control group 1/83 had a ventricular septal defect and a simian crease.
4) No statistically significant difference between the study and control groups for the results from the five subscales of Griffith's scale (measure gross motor function, personal and social behaviour, hearing and speech, eye and hand coordination, and performance). Mean (range) of Griffith's scale for carbamazepine group (N=35) was 350 (324-435) and for controls 335 (307-396) (mean difference -0.59, 16.57). Mean (range) of Griffith's scale for phenytoin group (N=21) was 346 (307-385) and for controls 344 (318-378) (mean difference -7.13, 11.34).

**Safety and adverse
effects**

Listed in the outcomes.

**Does the study
answer the question?**

There was a significant difference on the proportions of children with minor anomalies born from mothers treated in carbamazepine compared to controls. No difference on the proportion of children with minor anomalies was found between children in phenytoin and controls.
Small numbers in major anomalies incidence to allow interpretations. No significant differences in the psychomotor development between carbamazepine and matched control groups and phenytoin and matched controls.

**Effect due to factor in
study?**

Uncertain. Unclear the selection and attrition bias. The study used a control group of children with non epileptic mothers.

**Consistency of
results with other
studies?**

No consistency. Authors have explained the main reasons in their discussion.

**Directly applicable to
guideline population?**

Direct.

Internal Validity

Adequately addressed

Question: Which AEDs are most tolerable for people with learning disabilities?

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Kerr MP;Baker GA;Brodie MJ;

A randomized, double-blind, placebo-controlled trial of topiramate in adults with epilepsy and intellectual disability: impact on seizures, severity, and quality of life

Ref ID 367

2005

Study Type Randomised Controlled Trial **Funding** Janssen-Cilag Ltd.

Number of participant 88 enrolled but 14 withdrew before randomisation.
Total 74 patients randomised: 37 topiramate vs 37 placebo.

Inclusion/Exclusion Criteria

Inclusion criteria:
12 years or older;
Weigh at least 45kg;
Diagnosis of epilepsy with a documented 6-month history of at least 4 seizures per month and intellectual disability (defined as significant subaverage general intellectual functioning and an IQ of ≤ 70);
Had to be on treatment with one to three other anticonvulsants;
Have an identified carer;

Exclusion criteria:
Patients with absence seizures only or nonepileptic seizures;
A history of psychosis;
Psychiatric problems with in the last year;
Nephrolithiasis or renal impairment; Previous treatment with topiramate or treatment in the last 3 months with acetazolamide, zonisamide, triamterene, more than 2g/day vitamin C, or chronic use of antacids or calcium supplements;
Women who were pregnant, lactating, or without adequate contraception.

Patient Characteristics Topiramate (n=37) vs placebo (n=35):

Majority were caucasian (95.8%).
Age in years, mean (s.d): 29.9 (12.1) vs 31.9 (10.3);
Gender: males: 20 vs 19; females: 17 vs 16;
Epileptic seizure history, number (%):
-generalised tonic-clonic 17 (45.9) vs 19 (54.3);
-partial seizures only 28 (75.7) vs 26 (74.3);
-partial seizures with generalisation 16 (43.2) vs 18 (51.4);
-other seizure types: 15 (40.5) vs 18 (51.4);

Seizure and general medical histories were similar for the groups; patients in the topiramate group had on average more seizures of all types in the last 6 months, but the variation was wide; half of all patients had a history of status epilepticus; all patients had abnormal neurological history and 38 (52.85) had an abnormal psychological history; antiepileptics were taken by all patients before the start of the study;

Recruitment Not reported.

Setting 24 sites in the UK.

Interventions/ Test/ Factor being investigated

Maximum 400mg/day topiramate (adults) or 9mg/kg/day topiramate (children); Study medication was administered twice daily. For adults (16 years or over) treatment was initiated at 25mg daily for 1 week, and increased in 25 to 50mg increments at one to two weekly intervals, to recommended daily dose of 200 to 400mg daily according to each individual's response.
For children (12-16 years) treatment as initiated at 25mg nightly for 1 week, and increased in 1 to 3mg/kg/day increments at one to two weekly intervals to a recommended daily dose of 5 to 9 mg/kg/day according to individual's response. Subjects were withdrawn at investigators discretion if seizure control inadequate, any serious adverse events occurred or consent was withdrawn.

Participants were assessed in the clinic at weeks -4 and 0 (baseline) at weeks 4, 8, 12, and 18 (titration) at weeks 24 and 30 (maintenance) at early termination and at additional and final visits during the taper period.

Medical history, vital signs, body weights were recorded and physical and neurological examinations and hematology and biochemistry parameters were assessed.

Records of medication use and adverse events were reviewed.

Subjects recorded seizures on diary cards.

Comparisons

Topiramate vs placebo.

Length of Study/ Follow-up

4 week baseline period: routine AEDs remained constant;
18 week titration period to achieve optimum dose of study drug.
12 week maintenance period - doses remained constant.
Option to stop study medication over 4 -8 week taper phase or crossover to TPM.

Outcome measures studied

Response: 50% reduction in seizure frequency; seizure severity during the treatment phase;

National hospital severity scale; various scales for behaviour and quality of life.

Results

17 withdrew from the study (9 topiramate and 8 placebo), 12 due to adverse events (7 topiramate and 5 placebo): 7/37 vs 5/37.

11/37 in the topiramate and 9/25 in the placebo groups had >59% reduction in seizure frequency. There was no statistical difference between the two groups in the number of responders. However the % change from baseline indicated that topiramate provided a beneficial effect by reducing seizure frequency by 32% (compared to 1% for placebo).

Adverse events (>10%) : topiramate group; somnolence (32.4%), abnormal gait (10.8%), weight loss (21.6%), anorexia (24.3%), infection (24.3%), hostility (13.5%), asthesia (10.8%)

placebo group: somnolence (10.8%), abnormal gait (5.4%), weight loss (8.1%), anorexia (2.7%), infection (16.2%), hostility (8.1%), asthesia (8.1%).

There was no significant difference between the groups in the mean total of Epilepsy Outcome Scale, Aberrant Behaviour Checklist, Epilepsy and Learning Disabilities Quality of Life during the on drug phase. However, there was a trend toward significance for improvement of the mean Epilepsy and Learning Disabilities Quality of Life behaviour subscale score for patients treated with topiramate (P=0.080).

Only 34 patients (16 in topiramate and 18 in placebo groups) gave a global assessment of their treatment and of these 22 were better or much better. No significant differences were found between the groups in the global assessments of patients made by patients themselves, or by their carers.

Safety and adverse effects

Adverse events:

Topiramate vs placebo:

accidental injury: 1/37 (2.7%) vs 6/35 (16.2%);

asthesia: 4/37 (10.8%) vs 3/35 (8.1%);

hostility: 5/37 (13.5%) vs 3/35 (8.1%);

infection: 9/37 (24.3%) vs 5/35 (16.2%);

anorexia: 9/37 (24.3%) vs 1/35 (2.7%);

weight loss: 8/37 (21.6%) vs 3/35 (8.1%);

abnormal gait: 4/37 (10.8%) vs 2/35 (5.4%);

convulsion: 2/37 (5.4%) vs 4/35 (10.8%);

nervousness: 1/37 (2.7%) vs 5/35 (13.5%);

somnolence: 12/37 (32.4%) vs 4/35 (10.8%);

Does the study answer the question?

The author concludes that there was no significant differences between groups in mean seizure severity and other outcome measures. Topiramate was well tolerated and blood pressure reduced. Suggests that topiramate reduces seizure frequency in patients with epilepsy and intellectual disability without the added burden of behaviour effects, and was potentially advantageous to physical well-being.

Effect due to factor in study?

Uncertain, the study was underpowered as the minimum sample size of 120 patients was not achieved thus the observed treatment effect may be overestimated. In addition, unclear is the risk of selection bias due to absence of allocation concealment.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Crawford P;Brown S;Kerr M;

A randomized open-label study of gabapentin and lamotrigine in adults with learning disability and resistant epilepsy

Ref ID 4729

2001

Study Type	Randomised Controlled Trial	Funding	Parke-Davis Research and Development.
Number of participant	109 patients were screened, 83 patients were randomised; 39 patients entered the titration phase of gabapentin and 44 patients entered the titration phase of lamotrigine.		
Inclusion/Exclusion Criteria	Inclusion criteria: aged 12 years and over, either sex, had to have a degree of learning disability and to meet any level of the DSM-IV criteria for mental retardation, had a localization-related epilepsy which was not satisfactorily controlled by their existing antiepileptic medication, taking one, two or three standard AEDs (not including gabapentin or lamotrigine) but still achieving satisfactory seizure control. A minimum of four seizures in each 28 day period and no seizure free 29 day period in the preceding 3 month was required for entry. Exclusion criteria: primary generalized seizures, symptomatic generalized epilepsy or a history of non epileptic seizures. Concurrent therapy with antacids or a recent participation in any clinical trial, women if they were pregnant or lactating or of child bearing potential and sexually active and not practising a reliable method of contraception. A known hypersensitivity to gabapentin or lamotrigine, or significant renal or hepatic dysfunction.		
Patient Characteristics	All patients had a learning disability with a mean age of 38 years (sd 11.1) in the gabapentin group and a mean age of 33 years (sd 11.5) in lamotrigine group. 61.5% and 65.9% of patients were male in the gabapentin and lamotrigine groups respectively. The number of AEDs started before enrolment for each treatment group were very similar (41% and 50% in the gabapentin and lamotrigine groups respectively), with approximately the same numbers taking one or three.		
Recruitment	The study population comprised either outpatients or inpatients of specialist hospitals with an identified key worker/carer who was available for the trial, able to keep a record of seizures.		
Setting	multicentre study in 44 UK sites.		
Interventions/ Test/ Factor being investigated	gabapentin or lamotrigine as add on therapy to their existing AED therapy.		
Comparisons	Comparison are made between gabapentin and lamotrigine.		
Length of Study/ Follow-up	There was an initial baseline period of a 8 weeks, followed by a maximum 14 weeks titration period, and a minimum 10 weeks add on evaluation period (gabapentin or lamotrigine).		
Outcome measures studied	> 50% reduction in seizures frequency, % of seizure free patients, withdrawal due to adverse events, mood, behaviour and dependency.		
Results	- No statistically significant difference on the proportion of reduction in seizure frequency between gabapentin and lamotrigine. 50% of patients in gabapentin group experience >50% reduction in seizure frequency, compared to 48.6% of patients in lamotrigine groups. Three patients (7.7%) on gabapentin and 5 patients (11.4%) on lamotrigine were seizure free during the evaluation phase. -3 patients (8%) in the gabapentin group and four (9%) in the lamotrigine group were withdrawn due to adverse events. The most commonly occurring adverse event was convulsions in two patients (one in each group). Two patients on lamotrigine group reported cases of respiratory infection and a further two reported urinary tract infections. Four patients experienced serious adverse events on gabapentin, and five		

suffered serious adverse events on lamotrigine. 1 patient in gabapentin experienced drowsiness.

-Results showed a significantly greater improvement on gabapentin than on lamotrigine ($P < 0.05$) in the measurement of co-operation, communication and restlessness. There was a significant improvement in general health from gabapentin $P < 0.01$.

Safety and adverse effects

4 patients (11%) in gabapentin and 10 (26%) patients in lamotrigine experienced adverse events during evaluation period.

Does the study answer the question?

Yes. Main conclusions:

-50% of patients in gabapentin group experience $>50\%$ reduction in seizure frequency, compared to 48.6% of patients in lamotrigine groups.

Three patients (7.7%) on gabapentin and 5 patients (11.4%) on lamotrigine were seizure free during the evaluation phase.

-3 patients (8%) in the gabapentin group and four (9%) in the lamotrigine group were withdrawn due to adverse events.

- a significantly greater improvement on gabapentin than on lamotrigine ($P < 0.05$) in the measurement of co-operation, communication and restlessness. There was a significant improvement in general health from gabapentin $P < 0.01$.

Effect due to factor in study?

Uncertain. The sample size was smaller than the one calculated a priori of the study. Thus the study may lack some statistical power. In addition, unclear the risk of selection bias due to absence of randomization and allocation concealment.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Grading: 2-

Case-control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*

Losche G;Steinhausen HC;Koch S;Helge H;

The psychological development of children of epileptic parents. II. The differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors

Ref ID 4932

1994 Sep

Study Type Cohort **Funding** German Reseach Council.

Number of participant Not reported. Different sample sizes for different outcomes measures. Not clear.

Inclusion/Exclusion Criteria Inclusion criteria for the exposed children; having epileptic mothers treated with anticonvulsants during pregnanc. The controls were matched for socioeconomic status, age of the mother of deliver, parity, amount of smoking during pregnancy and number of abortions previous to the subject's birth.

Patient Characteristics No information on the main characteristics of the population was given.

Recruitment Randomly recruited from five obstetric departments with the city of Berlin, from the Department of Neurology, Free University of Berlin, during 1976 and 1983.

Setting Not reported.

Interventions/ Test/ Factor being investigated Exposure to one or more anticonvulsant during pregnancy.

Comparisons 1)any monotherapy exposure in utero compared to the general population 2) any polytherapy exposure in utero comapred to monotherapy exposure.

Length of Study/ Follow-up up to preschool years.

Outcome measures studied At 15 months: Bayley mental and motor scale, home inventory. At preschool years: verbal IQ (WPPSI), intelligence (CMMS), Psycholinguistic Abilities (ITPA), Frostig Test of Visual Perception (FTVP), motor performance (LOS), motor McCarthy scale (McC).

Results A) Any monotherapy exposure in utero compared to the general population.
15 months:
No significant difference was found between the two groups but scores were slightly lower in monotherapy group. The mean motor score (sd) for monotherapy group and general population was 56.3 (4.3) and 57.2 (7.2) respectively (n monotherapy= 24, n general population=42) (difference in means (95% c.i) given by the Cochrance Review was -0.90 (-3.68, 1.88), P=0.5). The mean mental score (sd) for monotherapy group and general population was 127.1 (12.8) and 129.2 (12.9) respectively (n monotherapy= 44, n general population=67) (difference in means (95% c.i) given by the Cochrance Review was -2.10 (-6.98, 2.78), P=0.4). No data for the home inventory.
Preschool years:
No significant difference was found between the two groups on the WIPPSI, CMMS, ITPA, FTVP and LOS scales, but scores were slightly lower in monotherapy exposed group compared to the general population. The mean verbal score (sd) for monotherapy group and general population was 50.9 (9.2) and 53.2 (8.8) respectively (n monotherapy= 52, n general population=67) (difference in means (95% c.i) given by the Cochrance Review was -2.30 (-5.57, 0.97), P=0.17). The mean performance score (sd) for monotherapy group and general population was 52.1 (9.9) and 53.8 (9.3) respectively (n monotherapy= 52, n general population=67) (difference in means (95% c.i) given by the Cochrance Review was -1.70 (-5.19, 1.79), P=0.3).
The mean CMMS score (sd) for monotherapy group and general population was 53.3 (9.8) and 53.8 (8.0) respectively (n monotherapy= 50, n general population=66)

(difference in means (95% c.i) given by the Cochrance Review was -0.50 (-3.83, 2.83), P=0.8). The mean ITPA score (sd) for monotherapy group and general population was 51 (6.3) and 52.1 (7.1) respectively (n monotherapy= 51, n general population=61) (difference in means (95% c.i) given by the Cochrance Review was -1.10 (-3.58, 1.38), P=0.4). The mean FTVP score (sd) for monotherapy group and general population was 52.7 (8.8) and 53.9 (8.5) respectively (n monotherapy= 45, n general population=66) (difference in means (95% c.i) given by the Cochrance Review was -1.20 (-4.49, 2.09), P=0.5). The mean LOS score (sd) for monotherapy group and general population was 48.7 (9.1) and 51.9 (7.7) respectively (n monotherapy= 49, n general population=64) (difference in means (95% c.i) given by the Cochrance Review was -3.20 (-6.37, -0.03), P=0.05). The mean McC score (sd) for monotherapy group and general population was 50.8 (9.8) and 51.9 (10.1) respectively (n monotherapy= 48, n general population=64) (difference in means (95% c.i) given by the Cochrance Review was -1.10 (-4.82, 2.62), P=0.6).

2) Any polytherapy compared to any monotherapy exposure in utero.

At 15 months:

Paper reports that there were no significant differences in motor and mental scales between the polytherapy and monotherapy groups, however results from the Cochrance review are contradictory; the mean motor score (sd) for monotherapy group and polytherapy was 56.3 (4.3) and 51.2 (3.3) respectively (n monotherapy= 24, n polytherapy=10) (difference in means (95% c.i) given by the Cochrance Review was 5.10 (2.43, 7.77), P=0.002). The mean mental score (sd) for monotherapy group and general polytherapy was 127.1 (12.8) and 121.7 (7.3) respectively (n monotherapy= 44, n general population=15) (difference in means (95% c.i) given by the Cochrance Review was 5.40 (0.11, 10.69), P=0.05).

Safety and adverse effects

Not reported.

Does the study answer the question?

Yes. No significant differences were found on any scale between the monotherapy and the general population for both the 15 months and the preschool years assessment. However, the scores were slightly lower in monotherapy group. The monotherapy groups scored significantly higher for both the mental and the motor scores when compared to polytherapy group.

Effect due to factor in study?

Uncertain, as no information were given regarding the original sample size, the drop outs and the minimum sample size required to detect a statistically significant difference if it exists in the study.

Consistency of results with other studies?

Unclear.

Directly applicable to guideline population?

Direct.

Internal Validity

Adequately addressed

Steinhausen HC; Losche G; Koch S; Helge H;

The psychological development of children of epileptic parents. I. Study design and comparative findings

Ref ID 4933

1994 Sep

Study Type Cohort

Funding German Research Council.

Number of participant N children exposed to anticonvulsants=73, N controls=65.

Inclusion/Exclusion Criteria Inclusion criteria for the exposed children; having epileptic mothers treated with anticonvulsants during pregnancy or without any anticonvulsant treatment or having epileptic fathers. The controls were matched for socioeconomic status, age of the mother of deliver, parity, amount of smoking during pregnancy and number of abortions previous to the subject's birth.

Patient Characteristics No information on the main characteristics of the population was given.

Recruitment Randomly recruited from five obstetric departments with the city of Berlin, from the Department of Neurology, Free University of Berlin, during 1976 and 1983.

Setting	Not reported.
Interventions/ Test/ Factor being investigated	Exposure to anticonvulsant during pregnancy, born to epileptic mother (without treatment during pregnancy), having epileptic fathers.
Comparisons	1) any AED exposure in utero compared to the general population 2) any AED exposure in utero compared to non exposed children of mothers with epilepsy.
Length of Study/ Follow-up	4-6 years.
Outcome measures studied	Mental development, motor abilities, quality and quantity of home support, intelligence, mental maturity, visual perception, motor performance.
Results	<p>1) any AED exposure in utero compared to the general population: at 15 months children exposed to AED scored significantly less in Bayle motor scales but no significant differences in mental development and home inventory; the mean (sd) of mental development index was 128 (12) and 130 (12) for the study group (children of mothers taking AED during pregnancy) and the controls respectively (the difference in means (95%ci) given by the Cochrane Review was -2 (-6.2, 2.2) P=0.4). The mean (sd) of motor scale for the study group was 55(4) and for the controls was 57(4) (the difference in means (95%ci) given by the Cochrane Review was -2 (-3.81, -0.19) P=0.03). The mean(sd) of home inventory was 34.5 (6.5) and 35.5 (6.5) for the exposed group to AED and the controls respectively (the difference in means (95%ci) given by the Cochrane Review was -1 (-3.47, 1.47) P=0.4).</p> <p>At 4-6 years, exposed children to AED scored significantly lower in verbal and performance intelligence scores, in mental maturity scale, in visual perception and in motor performance. The mean(sd) of verbal intelligence was 48 (9.5) and 52.5 (10) for study and controls groups respectively (mean difference by Cochrane -4.5 (-7.69, -1.31), P=0.006). The mean(sd) of performance intelligence was 51 (9) and 55 (8) for study and controls groups respectively (mean difference by Cochrane -4 (-6.77, -1.23), P=0.005). The mean(sd) of mental maturity scale was 51 (8) and 54 (9) for study and controls groups respectively (mean difference by Cochrane -3 (-5.82, -0.18), P=0.04). The mean(sd) of psycholinguistic abilities scale was 50 (7) and 52 (7) for study and controls groups respectively (mean difference by Cochrane -2 (-4.37, 0.37), P=0.10). The mean(sd) of visual perception scale was 52 (9) and 55 (8) for study and controls groups respectively (mean difference by Cochrane -3 (-5.88, -0.12), P=0.04). The mean(sd) of motor performance scale was 49 (8) and 52.5 (8.5) for study and controls groups respectively (mean difference by Cochrane -3.5 (-6.28, -0.72), P=0.01). The mean(sd) of motor scale was 50 (10) and 52.5 (10) for study and controls groups respectively (mean difference by Cochrane -2.5 (-5.91, 0.91), P=0.15).</p> <p>2) any AED exposure in utero compared to non exposed children of mothers with epilepsy: at 15 months children exposed to AED did not score significantly in Bayle motor scales, in mental development and home inventory compared to non exposed children; the mean (sd) of mental development index was 128 (12) and 124 (15) for the study group (children of mothers taking AED during pregnancy) and then non exposed children (of epileptic mothers) respectively (the difference in means (95%ci) given by the Cochrane Review was 4 (-5.02, 13.02) P=0.4). The mean (sd) of motor scale for the study group was 55(4) and for the non exposed children was 51(7) (the difference in means (95%ci) given by the Cochrane Review was 4 (-1.76, 9.76) P=0.17). The mean(sd) of home inventory was 34.5 (6.5) and 31.5 (8.5) for the exposed group to AED and the non exposed respectively (the difference in means (95%ci) given by the Cochrane Review was 3 (-2.59, 8.54) P=0.3).</p> <p>At 4-6 years, exposed children to AED scored generally similar with borderline or non significant differences in all scales compared to non exposed children. The mean(sd) of verbal intelligence was 48 (9.5) and 47.5 (7.5) for exposed and non exposed groups respectively (mean difference by Cochrane 0.5 (-3.84, 4.84), P=0.8). The mean(sd) of performance intelligence was 51 (9) and 47 (7) for exposed and non exposed groups respectively (mean difference by Cochrane 4 (0.12, 7.88), P=0.04). The mean(sd) of mental maturity scale was 51 (8) and 51 (8) for exposed and non exposed groups respectively (mean difference by Cochrane 0 (-4.21, 4.21), P=1). The mean(sd) of psycholinguistic abilities scale was 50 (7) and 52.5 (3.5) for exposed and non exposed groups respectively (mean difference by Cochrane -2.5 (-5.04, 0.04), P=0.05). The mean(sd) of visual perception scale was 52 (9) and 50 (5) for study and controls groups respectively (mean difference by Cochrane 2 (-1.38, 5.38), P=0.2). The mean(sd) of motor performance scale was 49 (8) and 45 (7.5) for exposed and non exposed groups respectively (mean difference by Cochrane 4 (-0.34, 8.34),</p>

P=0.07).The mean(sd) of motor scale was 50 (10) and 47(5.5) for study and controls groups respectively (mean difference by Cochrane 3 (-0.73, 6.73), P=0.12).

Safety and adverse effects

The only significant differences in safety issues between children exposed to anticonvulsants and controls were the speech disorders and sensory/motor disorders.

Does the study answer the question?

When the group of children exposed to any AED was compared to the general population, 15 months children exposed to AED scored significantly less in Bayle motor scales compared to controls and 4-6 years exposed children scored significantly lower in verbal and performance intelligence scores, in mental maturity scale, in visual perception and in motor performance.

When the group of children exposed to any AED was compared to non exposed children of epileptic mothers, no significant differences were found on any scale at children 15 months, and, only borderline or non significant differences in intelligence, mental maturity, visual perception and motor performance scales compared to non exposed children.

Effect due to factor in study?

Uncertain, as no information were given regarding the original sample size, the drop outs and the minimum sample size required to detect a statistically significant difference if it exists in the study.

Consistency of results with other studies?

Unknown.

Directly applicable to guideline population?

Direct.

Internal Validity

Not reported

Question: Which AEDs are the most tolerable for older people

Grading: 1+

Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Brodie MJ;Overstall PW;Giorgi L;

Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group

Ref ID 4722

1999

Study Type Randomised Controlled Trial**Funding** Glaxo Wellcome**Number of participant** 150 total: 102 in lamotrigine group (LTG) and 48 in carbamazepine group (CBZ)**Inclusion/Exclusion Criteria** Inclusion: Age 65 years or greater with newly diagnosed epilepsy with two or more seizures in previous year with at least one event during the past 6 months

Patient Characteristics	LTG	CBZ
Mean age (yrs)	77	76
Age range (yrs)	65-94	66-88
Male/female (%)	54/46	58/42
Wt (kg)	68	68
Ht (cm)	164	164
Baseline seizures (mean)	4	5

Recruitment Unknown**Setting** Multi centre UK**Interventions/ Test/ Factor being investigated** Treatment with lamotrigine or carbamazepine**Comparisons** LTG and CBZ are compared**Length of Study/ Follow-up** After a brief titration period, patients were followed for 24 weeks**Outcome measures studied** Primary: withdrawal from the study and proportion of patients remaining seizure free during the last 16 weeks of treatment.
Secondary: time to first seizure**Results** Drop out due to adverse events - LTG 18% versus CBZ 42%
40 patients on LTG (39%) remained seizure free during the final 16 weeks and did not discontinue compared with 10 (21%) taking CBZ (p=0.027)
Time to first seizure: No significant difference
The hazard ratio of withdrawal rates was 2.4 (95% CI 1.4-4.0) indicating that at any time a patient treated with CBZ was more than twice as likely to withdraw than on taking LTG (p<0.001).

Safety and adverse effects	LTG(n=102)	CBZ (n=48)	95%CI
Poor coordination	13	17	NS
Somnolence	12	29	4-30
Dizziness	10	17	NS
Rash	9	25	4-28
Headache	9	17	NS
Constipation	9	6	NS
Vomiting	9	6	NS
Diarrhoea	7	8	NS

Does the study answer the question? LTG is an acceptable choice as initial treatment for elderly patients with newly diagnosed epilepsy**Effect due to factor in study?** Yes

Consistency of results with other studies?

Directly applicable to guideline population? See GRADE

Internal Validity

Rowan AJ;Ramsay RE;Collins JF;Pryor F;Boardman KD;Uthman BM;Spitz M;Frederick T;Towne A;Carter GS;Marks W;Felicetta J;Tomyanovich ML;VA CS;

New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine.[see comment]

Ref ID 534

2005 Jun 14

Study Type	Randomised Controlled Trial	Funding	Research Grants and consultancy to one of authors from Pfizer, GSK, Novartis. Supported by Department of Veterans Affairs, Cooperative Studies Program. GSK and Pfizer provided study medications, placebos and drug plasma levels.
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Number of participant Total randomised: 593; CBZ n=198; GBP n=195; LTG n=200.

Inclusion/Exclusion Criteria Initial inclusion criteria was 65 years and older and newly diagnosed seizures of any type;
Changed this after the first year to 60 years and older to improve enrollment.

Inclusion criteria: newly diagnosed with epileptic seizures and were untreated, treated only acutely (<4 weeks), or treated but with subtherapeutic levels; a minimum of one seizure during the 3 months preceding enrollment was required; no restriction regarding concomitant diseases was imposed excepting those conditions likely to lead to a life expectancy of less than 12 months, progressive neurologic disease, or conditions that would significantly affect the response to treatment; all comedications were allowed save chronic AEDs; additional exclusion criteria included those with severe psychiatric conditions; current alcoholism; illicit drug use; history of noncompliance.

Patient Characteristics LTG vs GBP vs CBZ:

Age: 71.9 (s.d 7.4) vs 72.9 (s.d 7.5) vs 71.9 (s.d 7.7)
Males: 195 (97.5%) vs 192 (96.7%) vs 183 (93.8%);
Race:
white 139/200 (69.5%) vs 137/195 (70.3%) vs 133/198 (67.2%);
african american 47/200 (23.5%) vs 44/195 (22.6%) vs 52/198 (26.3%);
hispanic 11/200 (5.5%) vs 10/195 (5.1%) vs 5/198 (2.5%);
other 3/200 (1.5%) vs 4/195 (2.1%) vs 8/198 (4%);

Pre-study seizure types:
GTC only 48/200 (24.5%) vs 43/195 (22.4%) vs 56/198 (29%);
CPS 89/200 (45.4%) vs 81/195 (42.2%) vs 81/198 (42%);
SPS 28/200 (14.3%) vs 22/195 (11.5%) vs 26/198 (13.5%);
GTC and partial 23/200 (11.7%) vs 33/195 (17.2%) vs 21/198 (10.9%);
Mixed partial seizures 8/200 (4.1%) vs 13/195 (6.8%); 9/198 (4.7%);

Primary etiology:
cerebral infraction 69/200 (34.5%) vs 52/195 (26.7%) vs 56/198 (28.4%);
unknown 46/200 (23%) vs 43/195 (22.1%) vs 53/198 (26.9%);
cerebral arteriosclerosis 26/200 (13%) vs 37/195 (19%) vs 30/198 (15.2%);
head trauma 13/200 (6.5%) vs 13/195 (6.7%) vs 16/198 (8.1%);
all others 46/200 (23%) vs 50/195 (25.6%) vs 42/198 (21.3%);

Baseline medical problems:
 hypertension 138/200 (69%) vs 116/195 (59.5%) vs 137/198 (69.2%);
 stroke 103/200 (51.5%) vs 104/195 (53.3%) vs 95/198 (48%);
 cardiac disease 93/200 (46.55) vs 91/195 (46.7%) vs 102/198 (51.5%);
 mild cognitive decline 72/200 (36%) vs 66/195 (33.8%) vs 69/198 (35%);
 diabetes 49/200 (24.5%) vs 62/195 (31.8%) vs 57/198 (28.9%);
 cancer 47/200 (23.5%) vs 46/195 (23.6%) VS 48/198 (24.2%);
 psychiatric condition 39/200 (11.5%) vs 43/195 (22.1%) vs 47/198 (23.7%);
 renal 23/200 (11.5%) vs 26/195 (13.3%) vs 24/198 (12.1%);
 liver 5/200 (2.5%) vs 5/195 (2.26%) vs 6/198 (3%);

Baseline neurologic problems:
 gait disturbance 108/200 (54%) vs 107/195 (54.9%) vs 97/198 (49%);
 sensor abnormality 62/200 931%) vs 65/195 (33.3%) vs 56/195 (28.9%);
 memory problems 46/200 (23%) vs 56/195 (28.7%) vs 51/198 (25.8%);
 station, abnormal 42/200 (21%) vs 48/195 (24.6%) vs 50/198 (25.3%);
 motor power abnormal 39/200 (19.5%) vs 44/195 (22.6%) vs 49/198 (24.7%);
 coordination (excluding gait) abnormal 29/200 (14.5%) vs 30/195 (15.4%) vs 27/198 (13.6%);

Recruitment	No details given.
Setting	18 Veterans Affairs Medical Centres, USA.
Interventions/ Test/ Factor being investigated	GBP vs LTG vs CBZ.
Comparisons	Comparisons between Gabapentin vs Lamotrigine vs Carbamazepine.
Length of Study/ Follow-up	Option of continuing for additional 12 months.
Outcome measures studied	Primary: retention in the trail for 12 months; secondary: seizure freedom at 12 months, time to first seizure and drug toxicity.
Results	<p>LTG vs GBP vs CBZ: Reasons for withdrawal prior to 52 weeks: adverse reaction 24/199 (12.1%) vs 42/194 (21.65) vs 61/197 (31%), p=0.001 (differences between CBZ and LTG p<0.0001 and GBP and LTG p=0.015 were significant).</p> <p>Early terminations for adverse events (6 week titration phase): LTG 8/199 (4%) vs CBZ 41/199 (20.8%) vs GBP 29/194 (14.9%).</p> <p>Seizure freedom (titration and maintenance phase): at 3 months: 99/157 (63.1%) vs 84/135 (62.2%) vs 71/110 (64.5%); at 6 months: 74/132 (56%) vs 64/113 (56.6%) vs 57/88 (64.8%); at 12 months: 57/111 (51.4%) vs 45/95 (47.4%) vs 45/70 (64.3%). P=0.93 at 3 months; 0.39 at 6 months; 0.09 at 12 months.</p> <p>Seizure freedom in maintenance phase: at 3 months: 126/157 (80.3%) vs 108/135 (80%) vs 88/110 (80%); at 6 months: 90/132 (68.2%) vs 81/113 (71.7%) vs 64/88 (72.7%); at 12 months: 68/111 (61.3%) vs 57/95 (60%) vs 50/70 (71.4%). p=1 at 3 months; 0.73 at 6 months; 0.27 at 12 months;</p>
Safety and adverse effects	<p>Dosage reductions for side effects occurred in 31.3% (171/547) while dosage increases above target for inadequate seizure control occurred in 21.4% (117/547); Dosage increases above target occurred more often in patients receiving LTG as compared to CBZ (27.1% 51/188) vs 14% (25/179), p=0.002).</p> <p>No. of patients reporting systemic and neurologic toxicities at least once during first 12 months of treatment based on those patients having at least one follow-up visit (over 10%): GI problems 62/183 (33.9%) vs 43/177 (24.3%) vs 55/171 (32.2%), p=0.11; p=0.11; Weight gain (>4 lbs) 87/183 (47.5%) vs 120/177 (67.8%) vs 88/171 (51.5%); p=0.001; Large weight gain (>18 lbs) 7/183 (3.8%) vs 19/177 (10.7%) vs 5/171 (2.9%); p=0.003;</p>

Weight loss (> 4lbs) 66/183 (36.1%); 37/177 (20.9%); 44/171 (25.7%); p=0.004;
 Water retention 19/183 (10.4%) vs 35/177 (19.8%) vs 15/171 (8.8%); p=0.004;
 Hyponatremia 12/183 (6.6%) vs 7/177 (4%) vs 19/171 (11.1%); p = 0.03;
 Nystagmus 25/183 (13.7%) vs 25/177 (14.1%) vs 23/171 (13.5%); p=0.99;
 Dysarthria 17/183 (9.3%) vs 22/177 (12.4%); 15/171 (8.8%); p=0.48;
 Gait problems 51/183 (27.9%) vs 39/177 (22%); 29/171 (17.1%); p=0.93;
 Tremor 46/183 (25.1%) vs 39/177 (22%) vs 29/171 (17.1%); p=0.18;
 Sedation 73/183 (39.9%) vs 82/177 (46.3%) vs 86/171 (50.6%); p=0.13;
 Change in mood or affect: 55/183 (30.1%); 47/177 (26.6%) vs 56/171 (32.9%);
 p=0.43;
 Cognitive disturbances: 42/183 (23%) vs 53/177 (29.9%) vs 55/171 (32.4%); p=0.12;
 Dizziness: 50/183 (27.3%) vs 50/177 (28.2%) vs 55/171 (32.4%); p=0.55;
 Headaches: 35/183 (19.1%) vs 27/177 (15.3%) vs 30/171 (17.6%); p=0.62;

39 deaths occurred during the trial: 15 in CBZ group; 11 GBP; 8 LTG. There was no clustering of causes for death in any of the treatment arms to suggest a link between drugs and cause of deaths. None determined to be clearly due to study drug. 1 died 2 weeks after stopping study drug due to probable hypersensitivity reaction that led to multiple system organ failure. They were in the CBZ arm and had PHT for 1 week before enrollment thus obscuring the proximate cause.

Does the study answer the question?

The main limiting factor in patient retention was adverse drug reactions. Patients on LTG or GBP did better than those taking carbamazepine. Seizure control was similar in all groups. LTG and GBP should be considered as initial therapy for older patients with newly diagnosed seizures.

Effect due to factor in study?

Yes.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Grading: 1-

Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*

Craig I; Tallis R;

Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study

Ref ID 4635

1994

Study Type Randomised Controlled Trial **Funding** Sanofi UK; Parke Davis;

Number of participant Total randomised n=47; patients available for analysis at 6 weeks: PHT n=20; VPA n=18;

Inclusion/Exclusion Criteria Inclusion criteria: Aged >60 years; History of one or more unprovoked generalised tonic-clonic seizure or two or more partial seizures;
Exclusion criteria: uncertain diagnosis of epileptic seizures; clear provocation (alcohol, acute illness); evidence of a progressive cerebral condition (such as tumor); mental impairment sufficient to preclude cooperation with psychological tests; clinically significant abnormal liver function test; platelet counts <150x10⁹/L or other blood dyscrasia on entry; recent myocardial infarction or serious cardiac arrhythmias; history of excessive alcohol intake; treatment with medication known to affect psychomotor function (sedatives, hypnotics, antidepressants and major tranquilisers) or drugs known to affect plasma PHT or VPA levels when the regimen was likely to change during the trial period.

Patient Characteristics Phenytoin vs sodium valproate:
Mean age (range): 74.9 (67-84) vs 6.3 (62-88);
Mean dosage (range): 247 (175-275) vs 688 (400-1000);
Mean level mol/ml (range): 31 (18-80) vs 396 (201-545);
Seizure type: generalised 8 vs 8; partial with generalisation 6 vs 5; complex partial 6 vs 5.

Recruitment Referred by GPs or consultants in geriatric medicine.

Setting Salford or adjacent districts.

Interventions/ Test/ Factor being investigated Phenytoin versus sodium valproate.

Comparisons Comparison between Phenytoin and sodium valproate.

Length of Study/ Follow-up Participants are tested at 6 weeks, 3 months, 6 months and 1 year.

Outcome measures studied Attention, concentration, psychomotor speed, memory, adverse events.

Results Seizure control: Most had complete seizure control within 3 months: 2 VPA and 5 PHT continued to have infrequent minor seizures after 3 months.

Change in cognitive function between VPA and PHT:

Six week tests: showed no significant difference in impact of VPA or PHT on any of the psychological tests apart from Choice reaction Time. For the two -option tests and the intercept (Ao), PHT had a significantly less adverse impact.

3 month tests: PHT group showed greater improvement in depression scores and slightly less change in two and four option Choice Reaction times than VPA group.

6 month tests: no significant difference in any psychological tests apart from letter cancellation time, which appeared to be better in PHT group. Significant of this is doubtful as observed only once. Other tests unchanged.

1 year test: No significant difference in any of the psychological tests.

Adverse effects (no assessed VPA 17; PHT 25:
 VPA n(%) vs PHT n(%):
 Unsteadiness: 2(12) vs 9(36);
 Sleepiness 3(18) vs 7(28)
 Tremor 5(29) vs 0
 Oedema 3(18) vs 0
 Alopecia 2 (12) vs 0
 Depression 2 (12) vs 0
 Weight gain 2(12) vs 0

Safety and adverse effects

The following participants were unsuitable for analysis at 6 weeks due to: 3 had cerebral or extracerebral tumors; 1 had a stroke 4 weeks after entry; the consultant decided not to treat in 1 case; the relatives withdrew permission for the study in another; 3 were discontinued because of adverse effects; by the second assessment at 3 months 5 more dropped out (n=33) two were on VPA - a cerebrovascular accident; the other had started receiving antidepressants; 3 lost to PHT - one declined the tests, 1 was started on MST for ischemic foot pain; 1 complained of excessive sleepiness and discontinued PHT; by 6 months 4 more withdrew with events not directly related to the drugs - one of which was a sudden death not apparently related to seizure but in a patient with cardiac disease (VPA) and one by congestive cardiac failure (VPA); one PHT caused by cerebrovascular accident; between 6 months and 1 year - one VPA patient died in a nursing home of pneumonia.

Does the study answer the question?

Main conclusions: there was little difference between PHT and VPA regards to impact on cognitive function. Frequent no cognitive adverse events were reported. The choice of AED in the elderly may be more influenced by consideration of other adverse events.

Effect due to factor in study?

Unclear - no allocation concealment or power calculation, and only 38 participants assessed and no ITT.

Consistency of results with other studies?

Directly applicable to guideline population?

Direct.

Internal Validity

Nieto-Barrera M;Brozmanova M;Capovilla G;Christe W;Pedersen B;Kane K;O'Neill F;

A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy

Ref ID 4723

2001

Study Type Randomised Controlled Trial **Funding** Unknown

Number of participant LTG n=35; CBZ n=14.

Inclusion/Exclusion Criteria Inclusion: Newly diagnosed, untreated partial epilepsy ; 2 seizures in preceding 6 months
 Exclusion: Not discussed

Patient Characteristics Aged 65 years plus - subset of elderly patients from main study. No separate details given for elderly population.

Recruitment Unknown.

Setting Spain, Slovakia, Italy, Germany, Denmark, UK

Interventions/ Test/ Factor being investigated A comparison of monotherapy with lamotrigine or carbamazepine.

Comparisons Lamotrigine vs. carbamazepine.

Length of Study/ Follow-up	Not reported.
Outcome measures studied	Proportion of patients free of seizures during the last 16 weeks of treatment and proportion of patients who did not withdraw before the end of week 18 and were seizure free in the last 16 weeks of the study.
Results	All participants in the study: Efficacy was similar with both treatments (65% with lamotrigine, 73% with carbamazepine, p=0.085), i.e. patients who were seizure free during the last 16 weeks of treatment. More patients receiving lamotrigine completed the study (81%) compared with those receiving carbamazepine (77%). This was due to adverse events.
Safety and adverse effects	The proportion of patients who experienced adverse events in the lamotrigine group was lower (218 patients, 52%) compared with the carbamazepine group (120, 60%). Somnolence was the only adverse event reported at an incidence of greater than 5%. Paediatric patients and elderly patients showed better tolerability to lamotrigine than to carbamazepine (5%vs. 7% and 20% vs. 50% respectively). LTG vs CBZ: Incidence of adverse events over 10% in elderly population: asthenia 2/35 (6%) vs 2/14 (14%); rash 8/35 (23%) vs 2/14 (14%); dizziness 7/35 (20%) vs 1/14 (7%) Number of withdrawals from the study for all causes: 12/35 (34%) vs 9/14 (64%); Number of withdrawals from the study due to Aes: 7/35 (20%) vs 7/14 (50%);
Does the study answer the question?	Lamotrigine appears to be as effective as carbamazepine in patients with newly diagnosed partial epilepsy and also appears to be better tolerated.

**Effect due to factor in
study?** Yes

**Consistency of
results with other
studies?**

**Directly applicable to
guideline population?** See GRADE

Internal Validity

Saetre E;Abdelnoor M;Amlie JP;Tossebro M;Perucca E;Tauboll E;Anfinsen OG;Isojarvi J;Gjerstad L;

Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine

Ref ID 5089

2009 Aug

Study Type	Randomised Controlled Trial	Funding	GlaxoSmithKline, Eastern Norway Regional Health Authority AND Ullevaal University Hospital.
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Number of participant N= 108 (ITT population), N CBZ=54 and N LTG=54
N=75 (completers), N CBZ=36 and N LTG=39.

**Inclusion/Exclusion
Criteria** People aged >=65 years, a history of at least two partial seizures (with or without secondary generalization) or primarily generalized tonic-clonic seizures, at least one seizure in the preceding 6 months, and a life expectancy of at least 12 months. Subjects treated with any AED for >2 weeks in the previous 6 months and subjects with severe psychiatric disease or intellectual impairment, liver failure, alcohol or substance abuse, significant abnormalities in blood chemistry were excluded.

Patient Characteristics In both groups, there were almost similar proportions of females and males (M/F in LTG 15/16 and in CBZ 15/14). Both groups had similar age profiles (mean (sd) for LTG was 75.2 (6.8) and for CBZ was 73.6 (5.4). Stroke was the most common

	identified etiology of epilepsy in both groups.
Recruitment	Participants were recruited at Norwegian centers.
Setting	Norwegian centers.
Interventions/ Test/ Factor being investigated	Comparison of efficacy between lamotrigine and carbamazepine in the elderly.
Comparisons	Between lamotrigine and carbamazepine.
Length of Study/ Follow-up	There was a 4 week dose escalation and a 36 week maintenance phase.
Outcome measures studied	1)withdrawal due to adverse events
Results	1) withdrawal due to adverse events ITT analysis: LTG 15/54 and CBZ 9/54
Safety and adverse effects	No patient withdrew because of cardiovascular adverse events, except for one death due to a stroke occurred after the 4 week visit in a carbamazepine treated subject.
Does the study answer the question?	Yes. Although more participants in LTG withdrew due to adverse events compared to those in carbamazepine, this difference was not significant.
Effect due to factor in study?	This study was not designed to evaluate the proportion of participants withdrawn due to adverse events so uncertain what was the statistical power of the study and whether was enough to estimate this effect.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Saetre E;Abdelnoor M;Perucca E;Tauboll E;Isojarvi J;Gjerstad L;

Antiepileptic drugs and quality of life in the elderly: Results from a randomized double-blind trial of carbamazepine and lamotrigine in patients with onset of epilepsy in old age

Ref ID 611

2010

Study Type	Randomised Controlled Trial	Funding	Eastern Norway Regional Health Authority and Ullevaal University Hospital.
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Number of participant N=167 (CBZ 83 and LTG 84)

Inclusion/Exclusion Criteria Inclusion criteria:aged >=65 years, a history of at least two partial seizures with or without secondary generalization or primarily generalized tonic-clonic seizures, at least one seizure during the last 6 months, and a life expectancy of >=12 months. Exclusion: those who had received AEDs for >2 weeks in the previous 6 months and subjects with severe psychiatric disease or intellectual impairment, liver failure, alcohol or substance abuse, significant unpaced atrioventricular conduction defect, or clinically significant abnormalities of blood chemistry.

Patient Characteristics Apart from a slightly higher median age and quite higher proportion of females in the LTG group, the characteristics of the evaluable and nonevaluable groups were comparable.

Recruitment Enrollment took place at 29 centers in five countries- Croatia, Finland, France, Italy and Norway. Patients from Croatia were not included in these assessments.

Setting	Centers in these four countries.
Interventions/ Test/ Factor being investigated	Comparison on health related quality of life outcomes between lamotrigine and carbamazepine.
Comparisons	Comparison between lamotrigine and carbamazepine and within drug treatment between baseline and 40 weeks follow up.
Length of Study/ Follow-up	4 weeks escalation period and 36 week maintenance period.
Outcome measures studied	Health related quality of life (HRQOL).
Results	1)HRQOL within LTG treatment: Screening SEALS score median (range): 35 (7-75) and at week 40: 30 (5-80) 2)HRQOL within CBZ treatment:Screening SEALS score median (range): 27.5 (3-77) and at week 40: 27 (3-78) Difference in change of HRQOL for the period of 0-40 weeks between LTG and CBZ: Change in SEALS score for LTG: -2 (-32 TO 44) Change in SEALS score for CBZ: -1.5 (-26 to 44) (p of difference in change between LTG and CBZ 0.54)
Safety and adverse effects	None.
Does the study answer the question?	Yes, neither lamotrigine nor carbamazepine caused significant change in health related quality of life measures after 40 weeks of treatment
Effect due to factor in study?	Uncertain. A single blinded study with drop outs.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct.

Internal Validity

Saetre E;Perucca E;Isojarvi J;Gjerstad L;Study Group.;

An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly

Ref ID 231

2007 Jul

Study Type Randomised Controlled Trial **Funding** GlaxoSmithKline Inc.

Number of participant Total randomised n=186. Lamotrigine n=94; Carbamazepine n=92.

**Inclusion/Exclusion
Criteria** Inclusion criteria: aged 65 years or over; newly diagnosed epilepsy; history of two or more recurrent unprovoked seizures either partial (with or without secondary generalisation) or primarily generalised tonic-clonic), and at least one of the seizures occurring during the previous 6 months; clinical indication to initiate AED treatment; life expectancy >1 year; willingness to provided written free informed consent.
Exclusion criteria: a history of absence, tonic, atonic or myoclonic seizures; >2-week intake of any AED in the previous 6 months, or any previous intake of CBZ or LTG; treatment with any AED for five elimination half-lives in the period immediately preceding study entry; severe psychiatric disease or severe intellectual impairment; acute or chronic hepatic failure; significant unpaired AV defect; alcohol or substance abuse; clinically significant abnormalities in blood chemistry tests.

Patient Characteristics	LTG vs CBZ: Males/Females: 46/47 vs 56/35; Mean age +/- sd (range): 71.3+/-6.2 (65-91) vs 73.1 +/-5.5 (65-87) Classification: idiopathic/cryptogenic 33 (35%) vs 37 (41%); symptomatic: 60 (65%) vs 54 (59%);
Recruitment	Enrolment through the centres.
Setting	Croatia, Finland, France, Italy, Norway.
Interventions/ Test/ Factor being investigated	Lamotrigine (Lamictal 25 and 100mg chewable/dispersible tablets) vs sustained release carbamazepine (tegreol 100 and 200mg divisible tablets).
Comparisons	Lamotrigine vs carbamazepine.
Length of Study/ Follow-up	Those completing the study could continue on an open label basis. Those who withdrew from treatment had a 4-week taper down.
Outcome measures studied	Seizure freedom; Time to withdrawal; no. withdrawn; adverse events;
Results	<p>LTG vs CBZ: The ITT population: 25% fractile for the time to first seizure survival curve was 5.6 weeks compared to 4 weeks. No significant differences were identified in the ITT population. In the per protocol population the time to first seizure was significantly longer in the CBZ group (19.3 weeks) than the LTG group (8.4 weeks).</p> <p>Seizure freedom of completers after week 20 (% of ITT population): 48(52%) vs 52(57%), p value 0.45, OR (95% CI) 0.80 (0.45-1.43).</p> <p>See below for tolerability.</p>
Safety and adverse effects	<p>Tolerability: Withdrawal due to adverse events: 13/93 (14%) vs 23/91 (25%).</p> <p>No. of patients with treatment-emergent adverse events considered to be at least possibly related to study drug:</p> <p>Any drug-related adverse event: 51(55%) vs 51 (55%); Dizziness: 13 (14%) vs 9 (10%); Rash/skin reaction 5 (5%) vs 12 (13%); Headache 10 (11%) vs 10 (11%); Somnolence/sedation/hypersomnia 7 (7%) vs 9 (10%); Asthenia/fatigue 9 (10%) vs 9 (10%);</p>
Does the study answer the question?	Conclusions: There was a trend for higher seizure-free rates for CBZ and better tolerability with LTG. Differences in previous trials may related to different dosing rates and use of a sustained-release formulation for carbamazepine.
Effect due to factor in study?	190 patients required for 80% power.
Consistency of results with other studies?	
Directly applicable to guideline population?	Direct. Newly diagnosed epilepsy in the elderly.
Internal Validity	