Evidence Extractions

Question: How effective and cost-effective are anti-epileptic drugs for focal seizures with/without secondary generalisation
Gabapectin versus lamotrigine monotherapy: a double-blind comparison in newly diagnosed epilepsy

Brodie MJ; Chadwick DW; Anhut H; Otte A; Messmer SL; Maton S; Sauermann W; Murray G; Garofalo EA; Gabapentin Study Group;

Reference number 919  
Study Type Randomised Controlled Trial  
RID: 509

N=309 randomised, which were included in the ITT analysis. N=158 for GBP and n=151 for LTG.

Inclusion; patients were 16 years or older with a diagnosis of epilepsy. All had either partial seizures with or without secondary generalisation or primary generalised tonic-clonic seizures. No patient had absence or myclonic seizures as defined by the ILAE. Patients had either never been treated before or were untreated in the preceeding 6 months. Patients with newly diagnosed epilepsy were required to have a minimum of two seizures within the past 12 months or one in addtion to evidence of epilepsy. Untreated patients with a previous diagnosis of epilepsy were required to have had at least one seizure within the past 3 months.

Exclusion: patients with a history of status epilepticus, progressive central nervous system disease, had been previously treated with either GBP or LTG, or had received any investigational drug during the preceding 3 months. Also excluded were patients with seizures related to drugs, alcohol, acute medical illness or head trauma, or patients with situation-related seizures.

Patient Characteristics

GBP: 45.9% male and 54.1% female; mean age 35.8 ± 16.4 years; Generalised seizures: 20.9% and Partial seizures 79.1%. LTG: 58.7% male and 41.3% female; mean age 37.9 ± 16.7 years; Generalised seizures 18.9% and Partial seizures 81.1%.

Recruitment: From 41 centres in Europe and Australia.

Setting: Eight European countries and Australia.

Interventions/Test/Factor being investigated

Gabapentin versus lamotrigine.

GBP vs LTG: 600mg/day vs 25mg/day; increased to 1800mg/day vs 150mg/day. Adjustment in range of 1200mg/day vs 100-300mg/day.

Comparisons

Comparisons between treatments.

Length of Study/ Follow-up

Up to 30 weeks.

Outcome measures studies

Seizure freedom, exit events, percentage completers, time to first seizure, withdrawal due to adverse events.

Results

At the end of 30 weeks of the study, 80 (75.5%) [ITT 83 (76.1)%] patients taking GBP and 73 (76.0%) [ITT 76 (76.8)%] taking LTG were seizure-free during the last 12 weeks of double-blind treatment (95% CI -12.4% to 11.3% [ITT -12.2% to 10.9%]).

No difference was evident between GBP and LTG in terms of percentage of completers, time to first seizure, and withdrawal due to adverse events. The authors stated that such an analysis was not feasible for the percentage of patients remaining seizure free during the last 12 weeks as the parameter was not event related.

Funding

Sponsored by Parke-Davis GmbH Freiburg, a company of Pfizer Inc.

Does the study answer the question?

GBP and LTG are similarly effective and well tolerated.
Effect due to factor in study? Yes.

How directly applicable to population of the guideline? Relevant direct study population

Internal Validity

Overall well conducted trial. High drop-outs in the LTG group.

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**Tudur Smith C; Marson AG; Chadwick DW; Williamson PR;**

<table>
<thead>
<tr>
<th>Reference number</th>
<th>5292</th>
<th>Study Type</th>
<th>Meta-analysis</th>
<th>RID:</th>
<th>977</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple treatment comparisons in epilepsy monotherapy trials</td>
<td>2007</td>
<td>8</td>
<td>pgs 34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Number of subjects** RCT (double blinded, single blinded and unblinded)

**Inclusion/Exclusion Criteria:**

**Patient Characteristics**

**Recruitment:**

**Setting:**

**Interventions/Test Factor being investigated**

**Comparisons**

**Length of Study/ Follow-up Outcome measures studies**

**Results**

MRC funded work related to original systematic reviews.

In patients with partial onset seizure lamotrigine, carbamazepine, and oxcarbazepine had the best combination of seizure control and treatment failure. For results see Appendix O. This directly related to our question for focal seizures.

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23 December 2011
Individual patient data (IPD) came from the 8 Cochrane systematic reviews and the SANAD trial. The use of IPD data is regarded as the gold standard therefore it is a very well conducted meta-analysis. The quality was assessed in the individual Cochrane reviews. Internal consistency was explored.
Anhut H; Ashman P; Feuerstein TJ; Sauermann W; Saunders M; Schmidt B.

**Reference number** 4753  
**Study Type** Randomised Controlled Trial  
**Funding** Does the study answer the question?  
**Setting** 24 centres: Europe, Canada, South Africa and Australia  
**Recruitment** Unknown  
**Study Type** Randomised Controlled Trial  
**Number of subjects** 272 patients randomised; 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 child bearing 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 (88%) 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).

**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 baseline; 12 week treatment; 12 week open label extension phase.

**Outcome measures studies**
- Primary: Percentage of change in the frequency of partial seizures relative baseline; response and 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 ratio 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.

**Funding**
- Parke Davis

**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?**
- For a power of 80% a sample size of 180 patients was planned. The actual sample sizes were n=111, n=109 and n=52, total n=272.

**How directly applicable to population of the guideline?**
- Direct.

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**Grading:** 1+  
**Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias**
Internal Validity
Unclear risk of selection bias and performance bias - no details of randomisation and allocation concealment. Low risk of performance bias - study was double blinded. Self report diaries may be imprecise and result in detection bias. Unclear risk of attrition bias as different drop out rates in the three group ranging from 3.8% to 15%.

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

Reference number 4409  Study Type  Randomised Controlled Trial  RID: 53
Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures
2004 45  PGS 20 27

Number of subjects 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

<table>
<thead>
<tr>
<th>Pregabalin</th>
<th>Placebo</th>
<th>150 mg/day</th>
<th>600</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>96</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>38.1 (12.4)</td>
<td>36.5 (11.3)</td>
<td>36.4</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>54 (56.3)</td>
<td>44 (44.4)</td>
<td>47 (51.1)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89 (92.7)</td>
<td>93 (93.9)</td>
<td>84</td>
</tr>
<tr>
<td>(91.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1 (1.0)</td>
<td>2 (2.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (2.1)</td>
<td>2 (2.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>73.00 (14.49)</td>
<td>75.12 (18.39)</td>
<td>71.22</td>
</tr>
<tr>
<td>(16.21)</td>
<td></td>
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<td></td>
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<tr>
<td>Creatinine clearance at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (ml/min)</td>
<td>105.7</td>
<td>114.3</td>
<td>110.7</td>
</tr>
<tr>
<td>Years with epilepsy</td>
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<td></td>
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<tr>
<td>Mean (SD)</td>
<td>22.78 (13.58)</td>
<td>24.8 (12.65)</td>
<td>25.06</td>
</tr>
<tr>
<td>(11.63)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline 28-day seizure rate</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23.5 (41.1)</td>
<td>26.2 (40.8)</td>
<td>19.3</td>
</tr>
<tr>
<td>(24.4)</td>
<td></td>
<td></td>
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<tr>
<td>Seizure history at screening, N (%)</td>
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<td></td>
</tr>
<tr>
<td>Simple partial</td>
<td>47 (49.0)</td>
<td>40 (40.4)</td>
<td>37</td>
</tr>
<tr>
<td>(40.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex partial</td>
<td>88 (91.7)</td>
<td>89 (89.9)</td>
<td>88</td>
</tr>
<tr>
<td>(95.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Partial secondarily generalized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>72 (75.0)</td>
<td>65 (65.7)</td>
<td>69</td>
</tr>
<tr>
<td>(75.0)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Generalized</td>
<td></td>
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</tr>
<tr>
<td>Concurrent AED, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 AED</td>
<td>23 (24.0)</td>
<td>14 (14.1)</td>
<td>16</td>
</tr>
</tbody>
</table>
Recruitment: Unknown.

Setting: 45 centres worldwide.

Interventions/Test /Factor being investigated Comparisons Length of Study/ Follow-up Outcome measures studies

Pregabalin (PGB) 150 mg/day (50 mg three times a day) and PGB 600 mg/day (200 mg three times a day).

Comparisons are made between two doses of PGB and placebo as adjunctive therapy to currently used AEDs.

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

Results

Primary outcome

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 600 mg/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 \[-12.4 \ (\pm 20.5; -4.3) \] in the 150-mg/day PGB group and \[-32.3 \ (\pm 40.6; -24.0) \] 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).

Secondary outcomes

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).

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.

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).

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.

Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>150 mg/day</th>
<th>600 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>97</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>61 (63.5)</td>
<td>75 (75.8)</td>
<td>80 (87.0)</td>
</tr>
<tr>
<td>Discontinued with adverse event</td>
<td>6 (6.2)</td>
<td>10 (10.1)</td>
<td>17 (18.5)</td>
</tr>
<tr>
<td>Adverse events occurring in ≥10% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>7 (7.3)</td>
<td>6 (6.1)</td>
<td>27 (29.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (8.3)</td>
<td>19 (19.2)</td>
<td>24 (26.1)</td>
</tr>
</tbody>
</table>
Not reported.

Yes. PGB, 150mg/day and 600mg/day is effective as add-on therapy in patients with partial seizures.

Internal Validity

The risk of selection bias is unclear: randomisation is well described. Unclear allocation concealment. Risk of performance bias is low. Risk of attrition bias is high: The % of patients who withdrew in the pregabalin 600 mg group (25/92) was more 2 times more than in the placebo or 150mg treatment arms. 7/8 "other reasons" for withdrawal from the pregabalin 600mg group, higher than other groups (p=0.03). A similar number of patients withdrew before study end. Risk of detection bias was low: outcome was seizure rate and was measured in a valid and reliable way.

Funding

Not reported.

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.

How directly applicable to population of the guideline?

The study comprised subjects who suffered from partial seizures.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Group 1 (Pregabalin)</th>
<th>Group 2 (Lamotrigine)</th>
<th>Group 3 (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>3 (3.1)</td>
<td>2 (2.0)</td>
<td>16 (17.4)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (11.5)</td>
<td>13 (13.1)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>5 (5.2)</td>
<td>6 (6.1)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2 (2.1)</td>
<td>7 (7.1)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (15.6)</td>
<td>6 (6.1)</td>
<td>11 (12.0)</td>
</tr>
<tr>
<td>Tremor</td>
<td>3 (3.1)</td>
<td>3 (3.0)</td>
<td>10 (10.9)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>3 (3.1)</td>
<td>7 (7.1)</td>
<td>9 (9.8)</td>
</tr>
</tbody>
</table>

Baulac M; Leon T; O'Brien TJ; Whalen E; Barrett J;

Reference number: 5310

Study Type: Randomised Controlled Trial

A comparison of pregabalin, lamotrigine, and placebo as adjunctive therapy in patients with refractory partial-onset seizures

2010 Sep

Epilepsy Res

Number of subjects

N: 433

Group 1 (Pregabalin) N: 152

Group 2 (Lamotrigine) N: 141

Group 3 (Placebo) N: 141

Inclusion/Exclusion Criteria:

Inclusion criteria:

• ≥ 18 years of age
• ≥ 40kg
• Diagnosis of epilepsy consistent with results of an electroencephalogram performed within 2 years prior to randomisation.
• Partial seizures refractory to treatment (i.e. treatment with at least 3 AEDs from at least 2 different AED classes, each at or above the lowest recommended dose or the lowest adequate plasma concentration for a minimum of 3 months has failed.
• Minimum of 4 partial seizures during the 6 week baseline period and no 28 day period free of partial seizures.

Exclusion criteria:

• Pregnancy
• Lactation
• Previous treatment with pregabalin
• Previous treatment with lamotrigine within 6 months before entering baseline
• History of rash with lamotrigine

23 December 2011
Patients with a diagnosis of epilepsy with partial seizures (as defined by the International League Against Epilepsy Classification of Seizures)

% of women per group: placebo 61, pregabalin 49, lamotrigine 45

Recruitment: Not reported.

Setting: 97 centres in Europe, Canada and Australia

Interventions/Test Factor being investigated

Pregabalin vs lamotrigine vs placebo. Group 1 (Pregabalin) Dose: 300/600mg/day Group 2 (Lamotrigine) Dose: 300/400mg/day Group 3: placebo

Comparisons between pregabalin, lamotrigine and placebo

Length of Study/ Follow-up 28 days

Outcome measures studies

seizure frequency

% change from baseline in 28-day seizure rates

Results

Seizure frequency (phase I)

ITT population Group 1 (pregabalin): -36.5% Group 2 (lamotrigine): -24.9% Group 3 (placebo): -18.7%

Relative risk: 12.0 RR points

95% CI: -19.8, -4.2

p value (placebo v pregabalin): NS, 0.052 (adjusted)

Seizure frequency (all double blind phases I and II)

ITT population Group 1 (pregabalin): -39.4% Group 2 (lamotrigine): -28.0% Group 3 (placebo): -16.7%

p value (placebo v pregabalin): 0.0008

p value (pregabalin v lamotrigine): NS (0.0825=primary efficacy comparison)

Seizure frequency (fixed dose phases I and II)

ITT population Group 1 (pregabalin): -45.1% Group 2 (lamotrigine): -33.9% Group 3 (placebo): -19.0%

p value (placebo v pregabalin): <0.001

p value (pregabalin v lamotrigine): NS (0.0912)

p value (placebo v lamotrigine): 0.0228

Adverse events

Placebo: somnolence, asthenia, headache, accidental injury

Pregabalin: dizziness, somnolence, asthenia, headache

Lamotrigine: dizziness, somnolence, headache, infection, diplopia, vertigo

Funding

Pfizer Inc

Does the study answer the question? Yes

Effect due to factor in study? The power calculation was based on previous pregabalin add-on studies and for a power of 90% or over a sample size of 142 was required in each group at randomisation. The sample sizes were n=141, n=152, n=141.
How directly applicable to population of the guideline?

Direct.

Internal Validity

adverse events: 24 (pregabalin, 25 (lamotrigine), 10 (placebo).
Selection bias: unclear risk - unclear randomisation method and allocation concealment.
Performance bias: low risk.
Attrition bias: high risk - relatively high drop out rates in all groups.
Detection bias: low risk.

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

2007 48

Number of subjects
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

<table>
<thead>
<tr>
<th>mg/day Characteristic</th>
<th>Placebo (n = 97)</th>
<th>LCM 200 mg/day (n = 107)</th>
<th>LCM 400 mg/day (n = 108)</th>
<th>LCM 600 (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>38.9 ± 11.11</td>
<td>39.9 ± 11.71</td>
<td>41.2 ± 11.61</td>
<td>39.4 ± 10.53</td>
</tr>
<tr>
<td>Range</td>
<td>19 – 66</td>
<td>18 – 65</td>
<td>18 – 68</td>
<td>18 – 64</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (48%)</td>
<td>46 (43%)</td>
<td>53 (49%)</td>
<td>45 (42%)</td>
</tr>
<tr>
<td>Female</td>
<td>50 (52%)</td>
<td>61 (57%)</td>
<td>55 (51%)</td>
<td>61 (58%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>88 (91%)</td>
<td>98 (92%)</td>
<td>100 (93%)</td>
<td>101 (95%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (6%)</td>
<td>4 (4%)</td>
<td>5 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0 (0%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Weight, Kg (mean ± SD)</td>
<td>79.5 ± 20.90</td>
<td>74.5 ± 17.16</td>
<td>77.5 ± 18.63</td>
<td>75.7 ± 19.40</td>
</tr>
<tr>
<td>Mean time since diagnosis (year)</td>
<td>24.6 ± 11.77</td>
<td>25.1 ± 12.89</td>
<td>24.7 ± 13.08</td>
<td>23.6 ± 12.74</td>
</tr>
<tr>
<td>Seizure type at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple partial-onset seizures (47)</td>
<td>33 (34%)</td>
<td>48 (45%)</td>
<td>41 (38%)</td>
<td>50 (47%)</td>
</tr>
<tr>
<td>Complex partial-onset seizures (91)</td>
<td>83 (86%)</td>
<td>101 (94%)</td>
<td>94 (87%)</td>
<td>96 (88%)</td>
</tr>
<tr>
<td>Partial-onset seizures with secondary generalization (66)</td>
<td>73 (75%)</td>
<td>79 (74%)</td>
<td>77 (71%)</td>
<td>70 (68%)</td>
</tr>
</tbody>
</table>

23 December 2011  Page 10 of 364
Four different doses of lacosamide (200, 400 or 600mg per day) as adjunctive therapy with currently used AEDs.

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

Interventions/Test /Factor being investigated

Comparisons

Recruitment: Not reported

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

Interventions/Test /Factor being investigated

Comparisons

Length of Study/ Follow-up

Outcome measures studies

Primary outcomes

Results

Primary outcomes

Results

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

<table>
<thead>
<tr>
<th>600mg/d Lacosamide Total</th>
<th>Placebo (n = 97)</th>
<th>LCM 200mg/d (n = 107)</th>
<th>LCM 400mg/d (n = 108)</th>
<th>LCM (n = 106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>68 (70)</td>
<td>85 (79)</td>
<td>87 (81)</td>
<td>98 (92)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (10)</td>
<td>26 (24)</td>
<td>28 (26)</td>
<td>58 (55)</td>
</tr>
</tbody>
</table>
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.

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).

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.

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).

Funding

Not reported.

Effect due to factor in study?

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.

How directly applicable to population of the guideline?

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

Internal Validity

Risk of selection and performance bias is unknown since there is little description of randomisation or concealment of allocation methods. A substantial number of patients withdrew from the study especially in the lacosamide groups at larger doses. However, the final analysis is based on an ITT population. The method of measuring the outcome is valid and reliable. Attrition and detection bias risk is low.

Ben-Menachem E; Falter U;

Reference number 4741

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 2000 41

Number of subjects

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, digitals, glucosides or coumarins

Patient Characteristics

286 enrolled patients (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n=105</th>
<th>LEV n=181</th>
<th>Total n=286</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>36(12)</td>
<td>37(12)</td>
<td>36(12)</td>
</tr>
</tbody>
</table>

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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

To evaluate the efficacy and tolerability of levetiracetam (LEV) monotherapy in selected patients with refractory partial seizures

Comparison is made between treatment and placebo

Funding
Grant from UCB S.A. Pharma Sector, Braine l'Alleud, Belgium

Effect due to factor in study? The ultimate patient population is small and this drug needs to be studied further.

How directly applicable to population of the guideline? See GRADE

Internal Validity
Complex study design with ethical implications which affected ITT analysis in final phase. In this multicenter, double-blind, placebo-controlled, parallel-group, responder-selected study, patients were randomized (2:1 ratio) to receive oral LEV 1500 mg twice daily or placebo during a 12-week add-on phase. Treatment responders (patients with a reduction in partial seizure frequency of 50% or more compared with baseline) entered a monotherapy phase that included a maximum 12-week down-titration period and 12 weeks of monotherapy at 1500 mg twice daily. In both phases, responder rate, seizure frequency, and adverse events were analyzed.

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

Reference number 4748 Study Type Randomised Controlled Trial
RID: 218

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Inclusion/Exclusion 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 lateralisated 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.

TPM titrated to 800mg/day or maximum tolerated dose vs placebo. The mean dose reached was 568mg/day. Only 11/25 reached 800mg/day

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 studies

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

Proportion of seizure free (GENERALISED seizure) participants (100% reduction vs baseline)

TPM: 6/11 (46%)
Placebo: 2/13 (18%)
P value not reported

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

Proportion of participants experiencing at least a 50% reduction in GENERALISED seizure frequency (i.e. responders)
The proportion of participants having treatment withdrawn due to adverse event:

TPM: 6/28 (21%)
Placebo: 0/28 (0%)

P value not reported

Incidence of adverse events >10%

<table>
<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>

(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, diarrhea, dyspepsia, insomnia and nystagmus in the (placebo group); respiratory infection (both groups)

Funding

Not reported, 1 co author from Johnson Pharmaceutical

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.

Baseline characteristics not reported for each group

Median monthly baseline seizure rate higher in treatment group.

How directly applicable to population of the guideline?

See GRADE.

Internal Validity

Unclear risk of selection bias as no allocation concealment method is reported and no details of randomization. Baseline data not reported by group. Median seizure rate at baseline higher for treatment group. Low risk of performance and detection bias. Unlikely risk of attrition bias as 10.7% in the TPM group dropped out compared to none in placebo group

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

Reference number 4726

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

1997 27 Epilepsy Res 195 204

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

**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 studies**  
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**

<table>
<thead>
<tr>
<th></th>
<th>OXC (n=118)</th>
<th>PHT (n=119)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure frequency per week: Mean/median</td>
<td>0.08/0</td>
<td>0.06/0</td>
<td>p=0.72</td>
</tr>
<tr>
<td>Total number of seizures mean/median</td>
<td>3.57/0</td>
<td>2.13/0</td>
<td></td>
</tr>
</tbody>
</table>

Number of patients with:  
- No seizures: 70 vs. 69  
- 1 seizure: 17 vs. 20  
- 2-15 seizures: 26 vs. 26  
- 16-50 seizures: 3 vs. 4  
- More than 50 seizures: 2 vs. 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).

**Funding**  
International Adult Oxcarbazepine/Phenytoin Trial Group and Novartis Pharma

**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

**How directly applicable to population of the guideline?**  
See GRADE

**Internal Validity**  
Unlikely risk of selection bias, as study had good randomization process. High risk of attrition bias as high drop outs. Low risk of performance bias as study was double blinded. Low risk of detection bias.
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

Number of subjects
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.

Study Type
Randomised Controlled Trial

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 studies
Primary outcome was seizure frequency defined as the total count of all seizures.
No secondary outcomes defined although adverse events were reported.

Results
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.

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
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 maculopapular 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.

Funding

Not reported. However, one of the authors was from the Wellcome Research Laboratories, Beckenham, UK.

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.

How directly applicable to population of the guideline?

The patient population is directly comparable with 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

This is an RCT with a within-patients, crossover design. That is, each patient is randomised to lamotrigine or placebo for 12 weeks and then he/she crosses over to the other treatment for 12 weeks. For safety reasons one unblinded investigator issued trial medication based on concomitant medication to blinded investigators. However, it is not clear why that same investigator was also responsible for randomising patients. The risk of selection bias therefore is unknown. The remaining investigators and patients were kept 'blind' throughout the study and so the risk of performance bias appears to be low. Patients were seen every 2 weeks and seizure counts (primary study outcome) were checked. The risk of detection bias appears to be low. The average dose used (242 +/- 81) was towards the lower limit of usual dose that would impact the results.

Brodie MJ;

Reference number 2599  Study Type Randomised Controlled Trial RID: 634
Zonisamide clinical trials: European experience

2004  13  pgS  S66  S70

Number of subjects
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 8 generalised tonic-clonic seizures while awake during the 4 months prior to the study, significant mental retardation, a history of drug or alcohol abuse, or abnormal laboratory values unrelated to AED therapy.
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.
4 weeks titrated 100mg/day for 1 week increased to 200mg/day for second week and to 400mg/day for third and fourth week. After titration dosages adjusted by a nonblinded observer. Random adjustments made in no. of placebo capsules to maintain study blind.

Comparisons
Treatment versus placebo.

Length of Study/ Follow-up
Titration: 4 weeks. Treatment: 8 weeks: 12 weeks total. Open label extension study to look at long-term safety and efficacy of zonisamide after the double-blind study.

Outcome measures studies
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

Funding
Not reported.

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?
No power calculation given. Numbers randomised n=73 and n=71.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Modified ITT: n =137 as seizure data not obtainable for 7 patients.
Selection bias: unclear risk of bias - no details of allocation concealment.
Performance bias: low risk of bias - double blinded. No details of responders in placebo arm.
Attrition bias: low risk of bias.
Detection bias: low risk of bias - double blinded.
Patient demographics and baseline characteristics (safety population)

<table>
<thead>
<tr>
<th>Interventions/Test Factor being investigated</th>
<th>Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dependent safety and efficacy of zonisamide: a randomized, double-blind, placebo-controlled study in patients with refractory partial seizures</td>
<td>100mg, 300mg and 500mg per day</td>
</tr>
</tbody>
</table>

**Reference number**: 4286  
**Study Type**: Randomised Controlled Trial  
**RID**: 51

**Number of subjects**: 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**

<table>
<thead>
<tr>
<th>Patient demographics and baseline characteristics (safety population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/day</td>
</tr>
<tr>
<td>Gender: no (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age at screening (yr)</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Time since epilepsy onset (mo)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Seizure start date: median (range) (yr)</td>
</tr>
<tr>
<td>CP seizure (1–64)</td>
</tr>
<tr>
<td>SP+CP seizures (1–64)</td>
</tr>
<tr>
<td>All seizures (1–64)</td>
</tr>
<tr>
<td>Historic SP frequency/28 days</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Historic CP frequency/28 days</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Historic SG frequency/28 days</td>
</tr>
<tr>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Concomitant AEDs: N (%)</td>
</tr>
</tbody>
</table>

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

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.

**Primary outcome**

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)

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

The incidence of withdrawals due to AEs was higher for the 300-mg/day and 500-mg/day...
Elan Pharmaceuticals.

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.

Internal Validity

This is a generally well conducted study with a low risk of bias. Randomisation was by blocks of 6 but randomisation concealment methods not described. Blinding was well described. Drop out rates are high for treatment arm but clearly detailed and an ITT analysis performed. However drop out rates were quite different between treatment arms. Outcomes are also measured in a valid and reliable manner.

Funding

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.

How directly applicable to population of the guideline?

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

Brodie MJ; Perucca E; Ryvlin P; Ben-Menachem E; Meencke HJ; Levetiracetam Monotherapy Study Group;

Reference number 287

Study Type Randomised Controlled Trial

RID: 394

Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy.[20]

2007 Feb 6 68 Pgs

Reference number 287

Number of subjects

n=285 in the LEV arm and n=291 in the CBZ-CR group.

Inclusion/Exclusion Criteria:

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.

Exclusion criteria: pseudo seizures, seizures in clusters, and clinical or electroencephalographic findings suggestive of idiopathic generalized epilepsy.

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>LEV</th>
<th>CBZ-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>285</td>
<td>291</td>
</tr>
<tr>
<td>Age, years Mean (SD)</td>
<td>39.8 (16.6)</td>
<td>39.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male n (%)</td>
<td>146 (51.2)</td>
<td>171</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>139 (48.8)</td>
<td>120</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White n (%)</td>
<td>262 (91.9)</td>
<td>268</td>
</tr>
<tr>
<td>Black n (%)</td>
<td>5 (1.8)</td>
<td>10</td>
</tr>
<tr>
<td>Asian n (%)</td>
<td>1 (0.4)</td>
<td>4</td>
</tr>
<tr>
<td>Other n (%)</td>
<td>17 (6.0)</td>
<td>9</td>
</tr>
<tr>
<td>Height, cm Mean (SD)</td>
<td>170.0 (9.7)</td>
<td>171.1</td>
</tr>
</tbody>
</table>

23 December 2011
Levetiracetam (LEV) 1000mg to 3000mg/day vs. Carbamazepine (CBZ-CR) 400mg to 1200mg/day

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.

Recruitment: Unknown.
Setting: 85 centres in Europe and in South Africa.
Interventions/Test Factor being investigated: Levetiracetam and controlled-release carbamazepine produced equivalent seizure freedom rates in newly diagnosed epilepsy.
Comparisons: For the purposes of the primary outcome follow-up was 29 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 studies: Primary outcome was proportion of study subjects in each arm who were seizure-free at 6 months, 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.

UCB SA
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.
How directly applicable to population of the guideline? This study includes a population of newly diagnosed epilepsy patients.
Internal Validity
Low risk of selection and performance bias: randomisation and allocation concealment well described. Risk of attrition bias low: similar drop out rates between groups. Risk of detection bias low: 6 month follow-up, pts used diaries and visits to record seizures by number and type.

Callaghan N; Kenny RA; O’Neill B; Crowley M; Goggin T;
Patients with generalised tonic clonic seizures (without focal features):

Carbamazepine vs phenytoin vs sodium 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 sodium 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.

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 dosage of 300mg daily for adults and 5-10mg/kg body weight for children; sodium valporate in a dosage of 600mg daily for adults and 5-10mg/kg body weight for children.

Comparisons Carbamazepine versus phenytoin versus 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 studies 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.

Funding
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.

How directly applicable to population of the guideline? Yes.

The statistician set up a randomisation plan where each patient was allocated three drugs depending on first, second and third preference for each patient (drug A carbamazepine, drug B sodium valproate and drug C phenytoin). When a patient was selected for study the drug of first preference was selected on a sequential basis from the randomisation list by a secretary in the department of neurology. Low risk of selection bias as the randomization procedure and the allocation concealment were adequately addressed. High risk of performance bias as the study was not blinded. Low risk of attrition bias as an ITT analysis was performed and compensated for the unequal proportions of drop out rates. Low risk of detection bias (outcome measures were valid and reliable).

Patients who dropped out were analysed as patients with poor control for ITT.

Selection bias: low risk of bias.
Performance bias: high risk of bias - no mention of blinding of allocation of participants or those administering care.
Attrition bias: unclear risk of bias - drop-out PHT 14%; CBZ 11%; VPA 5%.
Detection bias: high risk of bias - no mention of blinding of participants exposure to
Cereghino JJ; Biton V; Bou-Khalil B; Dreifuss F; Gauer LJ; Leppik I;

Reference number: 4740  Study Type: Randomised Controlled Trial  RID: 210

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

2000 55  pgs 236 242

Number of subjects: 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

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

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
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)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lev 1000mg/d</th>
<th>3000mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least squares mean (LSM) number of seizures per wk (SE).</td>
<td>1.366(-0.053)</td>
<td>1.131 (0.050)</td>
<td>1.041(0.049)</td>
</tr>
</tbody>
</table>

23 December 2011  Page 26 of 364
Secondary outcomes
Median % reduction vs. placebo 20.9* 27.7*
Median % reduction vs baseline 6.8 32.5* 37.1*
50% responder rate 10.0 33.0* 39.8*

*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)
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 AEs (>=10%) with incidences higher than placebo were infection, headache, somnolence, dizziness, asthenia, rhinitis, and flu syndrome.

Funding
UCB Pharma.

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.

How directly applicable to population of the guideline?
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
The risk of selection bias is low: clear methods of randomisation and allocation concealment. Similarly the risk of performance bias is low. The risk of attrition bias was low: more patients dropped out of the 100mg/day group than the placebo or 300mg/day group but the study used an ITT analysis. Detection bias risk was also low: investigators were blinded and the measures used were as precise and reliable as they could have been.

Chadwick D;

Reference number 4718 Study Type Randomised Controlled Trial RID: 189

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

1999 354 pg 13 19

Number of subjects 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 was an exclusion criterion.
Male: 122 (54%) in carbamazepine and 117 (53%) in Vigabatrin.
Mean age (sd): 36(16) in carbamazepine and 35(15) in Vigabatrin

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

44 multinational centres - recruitment: 1993-1996

Vigabatrin vs Carbamazepine (mono-therapies). All were divided into twice daily dosing. Initial dose (up to Week 6): vigabatrin - 1g/day, carbamazepine - 200mg/day. Maintenance(Wk 6-52): vigabatrin-2g/day,max 4g, min 1.5g/day; carbamazepine-600mg/day, max 1600mg/day, min 400mg/day.

Patients were on twice daily dosing.

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

Patient Characteristics

Interventions/Test  /Factor being investigated Comparisons Length of Study/ Follow-up Outcome measures studies

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

Setting:
44 multinational centres - recruitment: 1993-1996

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%)
Industry: Hoechst Marion Roussel (HMR)

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?
Sample size was calculated as 168 patients for each group for 80% power. The numbers randomised were n=230 and n=228. There were high drop-out rates, therefore there were n=132 and n=130 completing the study. During the study they changed emphasis to time to treatment failure, the authors state that had this been designed with this outcome the sample size would have been smaller.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Criteria for withdrawing patients due to "lack of efficacy" or "adverse events", i.e. what type or how severe, were not specified.

The study was designed was an equivalence study (to exclude Vigabatrin being 15% more or less effective than carbamazepine) with an assumption of treatment failure rate of 40%. However, prior to unmasking, the analysis was changed to emphasis on time to treatment failure - this increased the statistical power to detect a difference. Low risk of selection bias. Unclear risk of performance bias as blinding and outcome measures are poorly described. High risk of attrition bias.

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

Reference number 4767
Study Type Randomised Controlled Trial
RID: 237

A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. International Gabapentin Monotherapy Study Group 945-77
1998 51

Number of subjects 292 patients were randomised: 74 to carbamazepine (CBZ) 600 mg; 72 to Gabapentin (GBP) 300mg; 72 to GBP 900 mg and 74 to GBP 1800mg.

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
<table>
<thead>
<tr>
<th>Gender</th>
<th>300 (n=72)</th>
<th>900 (n=72)</th>
<th>1800 (n=74)</th>
<th>CBZ 600 (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>56%</td>
<td>49%</td>
<td>55%</td>
<td>55%</td>
</tr>
<tr>
<td>Women</td>
<td>44%</td>
<td>51%</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>Age, y</td>
<td>37(17.3)</td>
<td>34(16.0)</td>
<td>37(16.9)</td>
<td>34(16.4)</td>
</tr>
<tr>
<td>Mean (SD) Duration of epilepsy, m</td>
<td>1.0(2.2)</td>
<td>0.0(1.0)</td>
<td>1.5(4.5)</td>
<td>1.3(2.3)</td>
</tr>
</tbody>
</table>

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

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for gabapentin groups: titration period (7 days) and 24 week evaluation phase. For carbamazepine, titration period (21 days) and 24 week evaluation phase. Primary efficacy variable was time to exit event.

**Results**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GBP 300 mg/d</th>
<th>GBP 900 mg/d</th>
<th>GBP 1800 mg/d</th>
<th>CBZ 600 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n=72</td>
<td>n=72</td>
<td>n=74</td>
<td>n=74</td>
</tr>
<tr>
<td>Completion rate</td>
<td>18(25.5%)</td>
<td>28(38.9%)</td>
<td>28(37.8%)</td>
<td>27(36.5%)</td>
</tr>
<tr>
<td>Exit event rate</td>
<td>45(62.5%)</td>
<td>29(40.3%)</td>
<td>32(43.2%)</td>
<td>22(29.7%)</td>
</tr>
<tr>
<td>AE withdrawal</td>
<td>0(0.0%)</td>
<td>3(4.2%)</td>
<td>10(13.5%)</td>
<td>18(24.3%)</td>
</tr>
<tr>
<td>Exit +AE withdrawal rate</td>
<td>45(62.5%)</td>
<td>32(44.4%)</td>
<td>42(56.8%)</td>
<td>40(54.1%)</td>
</tr>
</tbody>
</table>

Parke Davis

**Funding**

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?**

A power calculation was done and 60 evaluable patients per dosage group was required to provide 95% power. The sample sizes at randomisation were N=72, n=72, n=74, n=74. Number completing were n=18, n=28, n=28, n=17. The primary outcome was time to exit.

**Internal Validity**

Low risk of selection bias. Unclear/high risk of performance bias - no blinding of carbamazepine arm. Low risk of detection bias as all relevant outcomes are measured in a standard, valid and reliable way.

**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

1997 26 Epilepsy Res pgs 451 460

**Reference number** 4770  **Study Type** Randomised Controlled Trial  **RID:** 284

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

23 December 2011
oxcarbazepine versus sodium valproate.

Between treatments.

No follow up reported

Number of patients who were seizure free, side effects, withdrawal

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

None reported

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.
Internal Validity
Unclear risk of selection bias due to absence of reporting of allocation concealment, and randomisation method. Low risk of performance bias as study was double blinded. High risk of attrition bias. Low risk of detection bias.

Effect due to factor in study?
The final sample size had the statistical power to detect an effect of the study intervention.

How directly applicable to population of the guideline?
See GRADE.

Chung S; Sperling MR; Biton V; Krauss G; Hebert D; Rudd GD; Doty P; Study Group;

Reference number 5301

Study Type Randomised Controlled Trial

RID: 880

Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial

Number of subjects
405. placebo-104, lacosamide 400mg/day-204, lacosamide 600mg/day-97

Inclusion/Exclusion Criteria:
Inclusion criteria:
Age 16-70 years
At least a 2 year history of partial onset seizures despite treatment with at least 2 AEDs (concurrently or sequentially).
Currently experiencing at least 4 partial onset seizures per 28 days, with no seizure free period longer than 21 days during the 8 weeks prior to baseline and during the 8 week baseline period.
Have been on a stable dosage regimen of one to three AEDs with or without VNS (stable settings), in the 4 weeks before enrolment and during baseline.

Exclusion criteria:
• Previously received lacosamide or had participated in any other investigational trial within the last 2 months.
• Females who were pregnant, breast-feeding or of childbearing potential and not using approved contraception methods.
• History of chronic alcohol or drug abuse
• Any medical condition that might jeopardise their health or compromise their ability to participate
• LFT results of at least 2 times the upper limit of normal
• Creatinine clearance <50ml/min
• Diastolic BP <50 mmHg or > 105 mmHg
• Pulse <50 or >110 beats per min after 3 min in a sitting position
• Heart rate on ECG <50 or >110 beats per min
• Confirmed clinically significant ECG abnormality
• History of severe anaphylactic reaction or serious blood dyscrasias
• Nonepileptic events incl. psychogenic seizures
• Seizure clustering during the 8 week period before trial entry or during baseline
• History of primary generalised seizures
• History of status epilepticus in the last 12 months
• Concomitant or previous felbamate or vigabatrin therapy within the last 6 months
• Any other clinically significant condition or recent chronic consumption of non-AEDs that might interfere with drug absorption, distribution, metabolism or excretion
• Regular use of the following medications influencing the CNS- neuroleptics, MAOIs, barbiturates (except when taken as concomitant anticonvulsant treatment) or narcotic analgesics within 4 weeks prior to enrolment.

Patient Characteristics
Men and women 16-70 years old with partial-onset seizures, with or without secondary generalisation. Diagnosis was based on the Classification of Epileptic Seizures (Commission on Classification and terminology of the International League Against Epilepsy, 1981) and supported by EEG and either MRI or CT consistent with a diagnosis

23 December 2011
of epilepsy.

Recruitment: Not reported.
Setting: USA

Interventions/Test Factor being investigated
Group 1 (Lacosamide 400mg/day), Group 2 (lacosamide 600mg/day), Placebo

Comparisons Lacosamide 400mg/day vs lacosamide 600mg/day vs placebo.

Length of Study/ Follow-up Outcome measures studies
- 8 week baseline period, 18 week treatment period (6 week forced titration period) 12 weeks maintenance period. Efficacy- 28 days
- change in seizure frequency, responder rate, efficacy by seizure type, seizure freedom

Results

Seizure frequency (median % reduction)
Group 1 (Lacosamide 400mg/day): 37.3
Group 3 (placebo): 20.8
Difference: 21.6%
95% CI: 6.3-34.5
p value: 0.008

Seizure frequency (median % reduction) Group 2 (lacosamide 600mg/day) : 37.8
Group 3 (placebo): 20.8
Difference: 24.6%
95% CI: 7.8-38.3
P value: 0.006

50 % response to treatment (% of 50% responders)
Group 1 (Lacosamide 400mg/day): 38.3
Group 3 (placebo): 18.3
p value: 0.001

50 % response to treatment (% of 50% responders)
Group 2 (lacosamide 600mg/day): 41.2
Group 3 (placebo): 18.3
p value: 0.001

median % reduction by partial onset seizure type (50% responder rate)
all seizure types
placebo: 20.8 (18.3)
lacosamide 400: 37.3 (38.3)
lacosamide 600: 37.8 (41.2)

secondarily generalised tonic-clonic
placebo: 14.3 (33.3)
lacosamide 400: 59.4 (56.0)
lacosamide 600: 93.0 (70.2)

complex partial seizures
placebo: 22.2 (24.4)
lacosamide 400: 38.7 (40.0)
lacosamide 600: 44.4 (44.0)

simple partial seizures
placebo: 47.6 (43.9)
lacosamide 400: 34.9 (38.4)
lacosamide 600: 22.6 (37.1)

Funding
Schwarz biosciences inc., UCB Group sponsored and funded the trial.
Yes the study does help answer the question. The main conclusions of the authors were that adjunctive treatment with lacosamide 400mg/day and 600mg/day reduced seizure frequency for patients with uncontrolled partial-onset seizures. Lacosamide 400mg/day provided a good balance of efficacy and tolerability and 600mg/day may provide additional benefit for some patients.

Effect due to factor in study? Yes

How directly applicable to population of the guideline? Direct.

Internal Validity
Selection bias: low risk of bias - Randomisation by interactive voice response system (IVRS) used to randomly assign treatment to patients based on a predetermined computer-generated (pseudorandom number generator) schedule.
Attrition bias: unknown risk of bias - high drop-out rate in the lacosamide arms. This occurred mainly in the forced titration stage.
Detection bias: low risk of bias.
We removed the 600mg arm from our analysis as this was outside the normal dosing range.

Cramer JA; Arrigo C; Van HG; Gauer LJ; Cereghino JJ;
Reference number 4763 Study Type Randomised Controlled Trial RID: 233
Effect of levetiracetam on epilepsy-related quality of life. N132 Study Group
2000 41 pgs 868 874

Number of subjects
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.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n=81)</th>
<th>LEV 1000mg (n=80)</th>
<th>LEV 3000mg (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>38.5(11.3)</td>
<td>39.1(11.3)</td>
<td>38.5(10.2)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>54.3%</td>
<td>61.3%</td>
<td>64.7%</td>
</tr>
<tr>
<td>Age at epilepsy onset (mean years)</td>
<td>13.9(11.9)</td>
<td>15.3(12.7)</td>
<td>13.6(10.8)</td>
</tr>
<tr>
<td>Duration of epilepsy (mean years)</td>
<td>24.6(12.0)</td>
<td>23.8(12.7)</td>
<td>24.9(12.1)</td>
</tr>
<tr>
<td>No. of AEDs (%)</td>
<td>29.6</td>
<td>36.3</td>
<td>38.8</td>
</tr>
<tr>
<td>One</td>
<td>1.2</td>
<td>3.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Two</td>
<td>39.2</td>
<td>60.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Three or more</td>
<td>64.2</td>
<td>65.0</td>
<td>69.4</td>
</tr>
<tr>
<td>Mean no. of partial-onset seizures per week at baseline</td>
<td>5.6(18.79)</td>
<td>7.55(13.99)</td>
<td>5.15(15.58)</td>
</tr>
<tr>
<td>Seizure type (%)</td>
<td>35.8</td>
<td>31.3</td>
<td>29.4</td>
</tr>
<tr>
<td>SPS or CPS</td>
<td>0.0</td>
<td>3.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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

Setting:

23 December 2011 Page 34 of 364
Internal Validity

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.

Results

Mean values of QOLIE-31 at follow-up assessment

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

*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)

Funding

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.

How directly applicable to population of the guideline?

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

References

de la Loge C; Hunter SJ; Schiemann J; Yang H;

Reference number 5304  Study Type Randomised Controlled Trial  RID: 882

Assessment of behavioral and emotional functioning using standardized instruments in children and adolescents with partial-onset seizures treated with adjunctive levetiracetam in a randomized, placebo-controlled trial

2010  18  Jul

Number of subjects  All patients
N:  98
Group 1 (adjunctive LEV)
N:  64

23 December 2011
Inclusion/Exclusion Criteria:

Inclusion criteria:
- Age 4-16 years old
- Diagnosis of epilepsy with partial-onset seizures for ≥6 months
- One or more seizures during the 4 weeks before baseline
- Stable regimen of one or two AEDs for 2 weeks prior to randomisation
- IQ ≥65 at baseline

Exclusion criteria: none reported

Patient Characteristics

Children and adolescents aged 4-16 years with uncontrolled partial-onset seizures

Group 1 (adjunctive LEV)
N: 64
Gender, male n (%): 39 (60.9)
Age, mean (S.D.): 10.6 (3.5)
Min-max: 4.8-16.7
Race, n (%)
Caucasian: 40 (62.5)
Other/mixed: 6 (9.4)
Black: 15 (23.4)
Asian: 3 (4.7)
Leiter-R IQ score mean (SD): 89.8 (18.2)
Min-max: 42-135
Drop outs: 18

Group 2 (placebo)
N: 34
Gender, male n (%): 17 (50.0)
Age, mean (S.D.): 10.3 (3.7)
Min-max: 4.1-16.4
Race, n (%)
Caucasian: 18 (52.9)
Other/mixed: 5 (14.7)
Black: 8 (23.5)
Asian: 3 (8.8)
Leiter-R IQ score mean (SD): 89.1 (14.9)
Min-max: 67-124
Drop outs: 7

Recruitment:
Not reported.

Setting:
USA, South Africa, Canada

Interventions/Test /Factor being investigated
adjunctive levetiracetam 20-60mg/kg/day

Comparisons
levetiracetam v placebo

Length of Study/ Follow-up
end points followed up at end of study (12 weeks)

Outcome measures studies
assessments of cognitive functioning, Child Behaviour Checklist (CBCL), Child Health Questionnaire- Parent Form 50 (CHQ-PF50)

Results

CBCL competence scores (per protocol population)
Activities (range 0-15)change from baseline:
Group 1 (LEV): -0.01
Standard error: 0.39
Group 2 (placebo): -1.37
Standard error: 0.54
p value: 0.049

CBCL competence scores (per protocol population)
Social (range 0-14)change from baseline:
Group 1: -0.27
SE: 0.26
Group 2: -0.34
CBCL competence scores (per protocol population)
School (range 0-6) Change from baseline:
Group 1: 0.27
SE: 0.14
Group 2: 0.19
SE: 0.18
p value: 0.740

CBCL competence scores (per protocol population)
Total competence (range 0-35) Change from baseline:
Group 1: -0.17
SE: 0.58
Group 2: -1.41
SE: 0.79
p value: 0.217

CBCL problem scores (PP population)
Anxious/depressed (range 0-26) Change from baseline
Group 1: -0.57
SE: 0.40
Group 2: -0.71
SE: 0.56
p value: 0.832

CBCL problem scores (PP population)
Withdrawn/depressed (range 0-16) Change from baseline
Group 1: 0.24
SE: 0.34
Group 2: -0.84
SE: 0.47
p value: 0.068

CBCL problem scores (PP population)
Somatic complaints (range 0-22) Change from baseline
Group 1: 0.46
SE: 0.37
Group 2: -1.05
SE: 0.52
p value: 0.36

CBCL problem scores (PP population)
social problems (range 0-22) change from baseline
Group 1: 0.22
SE: 0.37
Group 2: -0.56
SE: 0.52
p value: 0.226

CBCL problem scores (PP population)
thought problems (range 0-30) change from baseline
Group 1: 0.00
SE: 0.35
Group 2: -1.13
SE: 0.48
p value: 0.064

CBCL problem scores (PP population)
attention problems (range 0-20) change from baseline
Group 1: -0.81
SE: 0.42
Group 2: -0.09
SE: 0.59
p value: 0.325
CBCL problem scores (PP population)
rule-breaking behaviour (range 0-34)
change from baseline
Group 1: 0.37
SE: 0.28
Group 2: -0.51
SE: 0.39
p value: 0.074

CBCL problem scores (PP population)
aggressive behaviour (range 0-36)
change from baseline
Group 1: 1.39
SE: 0.69
Group 2: -1.68
SE: 0.97
p value: 0.013

CBCL problem scores (PP population)
internalising syndromes (range 0-64)
change from baseline
Group 1: -0.72
SE: 0.90
Group 2: -2.73
SE: 1.26
p value: 0.199

CBCL problem scores (PP population)
externalising syndromes (range 0-70)
change from baseline
Group 1: 1.76
SE: 0.88
Group 2: -2.17
SE: 1.23
p value: 0.011

CBCL problem scores (PP population)
total problems (range 0-240)
change from baseline
Group 1: 2.32
SE: 2.82
Group 2: -9.22
SE: 3.94
p value: 0.020

CHQ-PF50 components scores related to behavioural and emotional functioning at baseline and change from baseline to evaluation (PP population)
role/social-emotional/behavioural (0-100)
change from baseline
Group 1: 1.96
SE: 3.43
Group 2: -3.69
SE: 4.42
p value: 0.316

behaviour (0-100)
Group 1: -1.43
SE: 1.94
Group 2: -0.91
SE: 2.50
p value: 0.871

mental health (0-100)
Group 1: 0.46
SE: 1.96
Group 2: 3.30
SE: 2.53
p value: 0.379
psychosocial summary (0-100)
Group 1: 1.36
SE: 1.07
Group 2: 1.65
SE: 1.39
p value: 0.870

Adverse events:
Levetiracetam:
headache, URTI, upper abdominal pain, nasopharyngitis, fatigue, vomiting, somnolence, aggression

Placebo:
headache, URTI, nasopharyngitis, fatigue, dizziness, psychomotor hyperactivity

Funding

Does the study answer the question? Yes

Effect due to factor in study? See GRADE.

How directly applicable to population of the guideline? Direct

CBCL and CHQ-PF50 analysed in the per-protocol population.
Selection bias: unclear risk of selection bias as no details on allocation concealment.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.

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

Reference number 4611

Study Type Randomised Controlled Trial

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

1999 53

Number of subjects 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

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Lamotrigine (n=98)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>6-12</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>&gt;12</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>47/51</td>
<td>56/45</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>14</td>
</tr>
</tbody>
</table>

23 December 2011
Other              6                                           9
Weight,           36.1 +/- 19.4                          32.5 +/- 19.1
kg mean +/- SD
Height,           1.31 +/- 0.22                          1.26 +/- 0.23
m, mean +/- SD

Recruitment:      Not described
Setting:          40 study sites in US and France

Interventions/Test /Factor being investigated
Glaxo Wellcome Research and Development Lamotrigine was effective for adjunctive treatment of partial seizures in children and adolescents with partial seizures.
For patients taking concurrent enzyme inducing Aes and no valproate, the mean dose for lamotrigine was 11.6 +/- 3.6 (median 12.9) mg/kg/day and for patients taking valproate alone or with a non enzyme inducing AEs the mean dose for lamotrigine was 2.7 +/- 0.4 (median 2.7) and for patients taking concurrent valproate and enzyme inducing Aes was 3.9 +/- 0.9 (median 4.2).

Comparisons Treatment (lamotrigine) and placebo

Length of Study/ Follow-up
8 week baseline and 18 week trial periods

Outcome measures studies
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 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 28% placebo (p<0.015) and during weeks 7-18 was 45% with lamotrigine compared with 30% with placebo (p=0.0023).

Funding
Glaxo Wellcome Research and Development

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

How directly applicable to population of the guideline?
See GRADE

Internal Validity
Low risk of selection, performance and detection bias.
Attrition bias: unclear risk of bias - 14% dropped out in the lamotrigine arm and 18% in the placebo arm.

Elger CE; Brodie MJ; Anhut H; Lee CM; Barrett JA;
Pregabalin add-on treatment in patients with partial seizures: a novel evaluation of flexible-dose and fixed-dose treatment in a double-blind, placebo-controlled study

2005 46

P5 1926 1936

Number of subjects

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 Characteristics

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Placebo (n = 73)</th>
<th>Pregabalin flexible dose (n = 131)</th>
<th>Pregabalin fixed dose (n = 137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in yr</td>
<td>40.3 (12.5)</td>
<td>40.0 (13.5)</td>
<td>41.1 (12.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>71 (97.3)</td>
<td>128 (97.7)</td>
<td>133 (97.1)</td>
</tr>
<tr>
<td>Black</td>
<td>0</td>
<td>0</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.7)</td>
<td>3 (2.3)</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (50.7)</td>
<td>64 (48.9)</td>
<td>69 (50.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.6 (15.6)</td>
<td>74.0 (17.4)</td>
<td>75.1 (16.3)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>107.2 (28.9)</td>
<td>109.4 (33.8)</td>
<td>108.0 (31.7)</td>
</tr>
</tbody>
</table>

Recruitment:

Unknown.

Setting:

53 centres worldwide

Interventions/Test /Factor being investigated

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 studies

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

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 R Ratio treatment difference of −11.2 (−20.8, −1.6).
Secondary outcomes

Responder rate
The responder rate (≥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

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

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%).

Not reported.

Effect due to factor in study?
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.

How directly applicable to population of the guideline?
The study population comprised patients who all had suffered from partial seizures.

Internal Validity
Risk of selection bias is low: methods of randomisation and concealment of allocation are well described. Risk of performance bias is low: the comparison groups received the same care apart from the intervention studied. The proportion of patients dropping out were about twice as many as patients in the fixed dose group and placebo group, so risk of attrition bias is high. Risk of detection bias is unclear. It is not known whether the investigator was independent and blind to treatment allocation.
A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group

1999 52 pgs

Reference number 4608
Study Type Randomised Controlled Trial
 RID: 74

Number of subjects
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. 6mg/kg/day

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 studies
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%.

Funding
R.W. Johnson Pharmaceutical Research Institute

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

How directly applicable to population of the guideline?
See GRADE

Unclear risk of selection bias due to absence of reporting on allocation concealment. Low risk of performance bias as both groups were treated equally and were blinded to treatment/placebo. Low risk of attrition bias as none dropped out from the study.
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]

2001 57 Nov 27

PGS 1774 1779

Number of subjects
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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A (n=85)</th>
<th>Group B1 (n=80)</th>
<th>Group B2 (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>35 (41)</td>
<td>37 (62)</td>
<td>32 (55)</td>
</tr>
<tr>
<td>Women</td>
<td>50 (59)</td>
<td>23 (38)</td>
<td>26 (45)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72 (85)</td>
<td>50 (83)</td>
<td>51 (88)</td>
</tr>
<tr>
<td>African-American</td>
<td>9 (11)</td>
<td>7 (12)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (4)</td>
<td>2 (3)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Age, y Mean (SD)</td>
<td>34.2(11.4)</td>
<td>35.8(11.4)</td>
<td>33.6(11.2)</td>
</tr>
<tr>
<td>Range</td>
<td>14–67</td>
<td>13–66</td>
<td>15–68</td>
</tr>
<tr>
<td>Age at seizure onset, y Mean(SD)</td>
<td>12.2(12.2)</td>
<td>12.0(10.7)</td>
<td>12.9(11.7)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean(SD)</td>
<td>75.0(18.4)</td>
<td>81.2(20.3)</td>
<td>75.6(18.7)</td>
</tr>
<tr>
<td>Range</td>
<td>45–140</td>
<td>44–133</td>
<td>44–128</td>
</tr>
<tr>
<td>Median baseline seizure frequency</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All partial-onset</td>
<td>13.0</td>
<td>11.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Complex partial</td>
<td>7.0</td>
<td>6.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Seizure characteristics, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex partial</td>
<td>81 (95)</td>
<td>57 (95)</td>
<td>57 (98)</td>
</tr>
<tr>
<td>Simple partial</td>
<td>4 (5)</td>
<td>3 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Secondarily generalized tonic-clonic</td>
<td>20 (24)</td>
<td>14 (23)</td>
<td>12 (21)</td>
</tr>
</tbody>
</table>

Recruitment:
Not reported.

Setting:
20 epilepsy centres in the United States.

Interventions/Test Factor being investigated
Zonisamide in three different doses.
Target dose of 400mg/day at treatment end in all three groups. Group A patients received placebo, along with their concomitant antiepilepsy drugs, for 12 weeks. At week 13, they were crossed over to zonisamide treatment, starting at 100 mg/d and increasing in 100-mg/d weekly increments to a maximum of 400 mg/d for the final 5 weeks (weeks 16 through 20) of the study. Group B1 patients received 100 mg/d of zonisamide for weeks 1 through 5, 200 mg during week 6, 300 mg during week 7, and 400 mg for the final 13 weeks (weeks 8 through 20). Group B2 patients received 100 mg/d of zonisamide for the first week, 200 mg/d over weeks 2 through 6, 300 mg/d for week 7, and 400 mg/d for weeks 8 through 20.

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

23 December 2011
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.

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).

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 (Bl, 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

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Weeks 1-5</th>
<th>Weeks 1-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>400mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A (placebo)</td>
<td>n=85</td>
<td>n=118</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (15.3)</td>
<td>18 (15.3)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (9.4)</td>
<td>17 (14.4)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>13 (15.3)</td>
<td>17 (14.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12 (14.1)</td>
<td>16 (13.6)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>15 (17.6)</td>
<td>14 (11.9)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6 (7.1)</td>
<td>12 (10.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (14.1)</td>
<td>11 (9.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (12.9)</td>
<td>11 (9.3)</td>
</tr>
</tbody>
</table>

Funding
Dainippon Pharmaceutical USA Corp. Teaneck NJ.

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.

How directly applicable to population of the guideline?
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
Randomisation allocation and concealment methods were not described. Blinding methods not described - no indication that patients had the same dosing schedule or blood levels of drugs taken during visits were masked from investigators. 28% of patients in the zonisamide groups, vs 15% from the placebo group dropped out before study completion, although an ITT analysis was conducted. The dose used (maximum 400 mg/daily) was within the limits of usual therapeutic dose (300-500 mg/daily) for adjunctive thereapy of zonisamide in partial seizures.

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

Reference number 4699 Study Type Randomised Controlled Trial RID: 171
Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group
1996 46

Number of subjects
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
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);

<table>
<thead>
<tr>
<th>Placebo</th>
<th>200 mg</th>
<th>400mg</th>
<th>600mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>13.1</td>
<td>29.6</td>
<td>47.8</td>
</tr>
<tr>
<td>p-value</td>
<td>0.051</td>
<td>0.007</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Treatment responders

<table>
<thead>
<tr>
<th>Number</th>
<th>8/45</th>
<th>12/45</th>
<th>21/45</th>
<th>21/46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>18</td>
<td>27</td>
<td>47</td>
<td>46</td>
</tr>
<tr>
<td>p-value</td>
<td>0.620</td>
<td>0.013</td>
<td>0.027</td>
<td></td>
</tr>
</tbody>
</table>

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.

The measure of global improvement and patients’ overall assessment of study medication was a subjective evaluation. Seizure rate calculations depended on patient diary evaluated by investigator. Unclear risk of selection bias as unclear randomisation method and allocation concealment. Low risk of attrition bias. No information on measures of outcome so unclear risk of detection bias.

Robert Wood Johnson

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?
See GRADE.

How directly applicable to population of the guideline?
See GRADE

Outcome measures studies

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

2003 60

Reference number 4589 Study Type Randomised Controlled Trial RID: 55

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 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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Pregabalin dose (mg/d)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>300</td>
</tr>
</tbody>
</table>

n = 100 n=88 n=86 n=90 n=89

French JA; Kugler AR; Robbins JL; Knapp LE; Garofalo EA;
Age, mean (SD)          39.5 (12.6)  38.9 (11.0)  37.4 (13.3)  37.8 (11.4)  38.0 (11.1)
Women, n (%)            48 (48.0)   49 (55.7)   50 (58.1)   42 (46.7)   46 (51.7)
Race, white, n (%)      84 (84.0)   76 (86.4)   73 (84.9)   78 (86.7)   74
Weight, mean (SD), kg   80 (19.7)   79 (19.4)   73 (17.8)   80 (23.8)   80 (21.6)
28-Day seizure rate     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:  
Setting:  
76 centres in the United States and Canada.

Interventions/Test Factor being investigated  
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  
Outcome measures studies  
20 weeks: 8 week baseline period and 12 week treatment period.

The primary outcome was reduction in seizure frequency as measured by response ratio (RRatio). Efficacy was also assessed on basis of responder rate (>=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 <= 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<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 (>=50% reduction)  
The responder rate was greater than placebo in the pregabalin 150 (p=0.006), 300 (p=0.001), and 600 (p<=0.001) mg/d groups and was also dose related. The analyses of RRatio (p=0.0001) and responder rate (p<=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
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.

### Adverse events

<table>
<thead>
<tr>
<th>Pregabalin dose (mg/d)*</th>
<th>Placebo</th>
<th>50</th>
<th>150</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>n=100</td>
<td>n=88</td>
<td>n=86</td>
<td>n=90</td>
</tr>
<tr>
<td><strong>Any AE Incidence</strong></td>
<td>74 (74.0)</td>
<td>59 (67.0)</td>
<td>61 (70.9)</td>
<td>76 (84.4)</td>
</tr>
<tr>
<td><strong>AEs of severe intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>6 (6.0)</td>
<td>6 (6.8)</td>
<td>4 (4.7)</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>Dizziness Incidence</td>
<td>9 (9.0)</td>
<td>8 (9.1)</td>
<td>14 (16.3)</td>
<td>28 (31.1)</td>
</tr>
<tr>
<td>Somnolence Incidence</td>
<td>11 (11.0)</td>
<td>9 (10.2)</td>
<td>15 (17.4)</td>
<td>16 (17.8)</td>
</tr>
<tr>
<td>Accidental injury Incidence</td>
<td>5 (5.0)</td>
<td>13 (14.8)</td>
<td>5 (5.8)</td>
<td>10 (11.1)</td>
</tr>
<tr>
<td>Ataxia Incidence</td>
<td>3 (3.0)</td>
<td>3 (3.4)</td>
<td>9 (10.5)</td>
<td>9 (10.0)</td>
</tr>
<tr>
<td>Asthenia Incidence</td>
<td>8 (8.0)</td>
<td>5 (5.7)</td>
<td>7 (8.1)</td>
<td>11 (12.2)</td>
</tr>
<tr>
<td>Headache Incidence</td>
<td>13 (13.0)</td>
<td>6 (6.8)</td>
<td>8 (9.3)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Infection Incidence</td>
<td>10 (10.0)</td>
<td>8 (9.1)</td>
<td>8 (9.3)</td>
<td>5 (5.6)</td>
</tr>
<tr>
<td>Blurred vision Incidence</td>
<td>5 (5.0)</td>
<td>3 (3.4)</td>
<td>3 (3.5)</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>Tremor Incidence</td>
<td>3 (3.0)</td>
<td>3 (3.4)</td>
<td>3 (3.5)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Weight gain Incidence</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Incoordination Incidence</td>
<td>1 (1.0)</td>
<td>2 (2.3)</td>
<td>2 (2.3)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Dry mouth Incidence</td>
<td>1 (1.0)</td>
<td>2 (2.3)</td>
<td>1 (1.2)</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

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.

### Funding

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.

### How directly applicable to population of the guideline?

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

### Internal Validity

Unclear risk of selection bias as allocation concealment not described. Method of randomisation well described. Not clear how investigators were blinded. Performance bias is low. Risk of attrition bias high - more than 2x more patients randomised to 150mg, 300 mg and 600 mg dropped out compared to the placebo arm. Analysis done on ITT basis. Risk of detection bias is low. Reliable and valid measurement of seizures and other outcomes.

---

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

**Reference number** 4752  **Study Type** Randomised Controlled Trial  **RID:** 222

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

1996  46  **Pgs:** 54  61

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

23 December 2011  Page 49 of 364
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.

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 studies
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

<table>
<thead>
<tr>
<th>Percent change in seizures</th>
<th>Placebo</th>
<th>Vigabatrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50% increase</td>
<td>14 (15.6)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>1-50% increase</td>
<td>21 (23.3)</td>
<td>14 (15.2)</td>
</tr>
<tr>
<td>0-49% reduction</td>
<td>38 (42.2)</td>
<td>34 (36.9)</td>
</tr>
<tr>
<td>50-99% reduction</td>
<td>16 (17.8)</td>
<td>34 (36.9)</td>
</tr>
<tr>
<td>100% reduction</td>
<td>1 (1.1)</td>
<td>6 (6.5)</td>
</tr>
</tbody>
</table>

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 (>=50% reduction) was attained in 40 of the vigabatrin patients (49%) 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)

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

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.

Marion Merrell Dow Inc.

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.

How directly applicable to population of the guideline?
All patients in this study had complex partial seizures which were difficult to control with established AED therapy.

Risk of performance bias is low. No details of sequence generation and allocation concealment. Risk of attrition bias is low. A small number of patients dropped out and an ITT analysis was done. Risk of detection bias also low. Outcomes measured by diary and clinic visits for standard tests.

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

Reference number 4719
Study Type Randomised Controlled Trial
An active-control trial of lamotrigine monotherapy for partial seizures

1998 51

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

23 December 2011 Page 51 of 364
Patient Characteristics

**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.

**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, 8 week transition phase (4 week intro of LTG or VPA and 4 week withdrawal of usual AED) and 12 weeks maintenance monotherapy phase.

**Outcome measures studies**

- 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**

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

**Recruitment:**
- Not reported.

**Setting:**
- 36 centres in United States.

<table>
<thead>
<tr>
<th>N(%) of completed patients</th>
<th>Total</th>
<th>Completed monotherapy</th>
<th>Escaped</th>
<th>Withdrawn</th>
<th>Median time to escaped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per protocol analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>50</td>
<td>28(56)*</td>
<td>22(44)</td>
<td>NA</td>
<td>168*</td>
</tr>
<tr>
<td>VPA</td>
<td>64</td>
<td>13(20)</td>
<td>51(80)</td>
<td>NA</td>
<td>57</td>
</tr>
<tr>
<td>Intent to treat analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>76</td>
<td>28(37)*</td>
<td>32(42)</td>
<td>16(21)</td>
<td>NA</td>
</tr>
<tr>
<td>VPA</td>
<td>80</td>
<td>13(16)</td>
<td>55(69)</td>
<td>12(15)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Adverse events**

**Intent to treat population: adverse experiences (AE)**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Monotherapy period LTG</th>
<th>Monotherapy period VPA</th>
</tr>
</thead>
</table>

23 December 2011 Page 52 of 364
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 a half times greater than the proportion of patients completing monotherapy treatment with a low dose of VPA.

**Internal Validity**

There is a low risk of selection bias as the study gave a clear description of methods of randomisation and blinding. There is a risk of performance bias. Patients in the VPA group received a low dose while those in the Lamotrigine group received a high target dose.

**Funding**

Not reported.

**Does the study answer the question?**

Yes. Results show that Lamotrigine therapy is effective in adults with partial seizures.

**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.

**How directly applicable to population of the guideline?**

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

There is a low risk of selection bias as the study gave a clear description of methods of randomisation and blinding. There is a risk of performance bias. Patients in the VPA group received a low dose while those in the Lamotrigine group received a high target dose.

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

**Reference number** 5082

**Study Type** Randomised Controlled Trial

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

**2009 Nov** Acta Neurol Scand

**Number of subjects** 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);

---

n=43, n(%)  n=44, n(%)  

<table>
<thead>
<tr>
<th>AE</th>
<th>n=43, n(%)</th>
<th>n=44, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with &gt;=1 AE</td>
<td>26(60)</td>
<td>19(43)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3(7)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3(7)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Headache</td>
<td>3(7)</td>
<td>6(14)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3(7)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0(0)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1(2)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Coordination abnormalities</td>
<td>3(7)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4(9)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Rash</td>
<td>1(2)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Tremor</td>
<td>2(5)</td>
<td>3(7)</td>
</tr>
</tbody>
</table>

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Patient Characteristics

Mean age placebo 37.7 +/-12.07 vs ESL 800mg 36.8 +/-10.65 and ESL 1200mg 36 +/-11.43.
Males: 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, topiramate, lamotrigine, phenobarbital, clobazam, primidone, clonazepam.

Recruitment:
Not reported.

Setting:
39 sites in Mexico, Portugal and Spain.

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
2 weeks titration, 12 weeks maintenance, 4 weeks tapering off period.

Outcome measures studies
Proportion with at least 50% reduction in seizure frequency, seizure freedom, seizure exacerbation; incidence of adverse events, withdrawal due to adverse events.

Results
Placebo vs eslicarbazepine 800mg vs eslicarbazepine 1200mg:
At least 50% reduction in seizure frequency (titration and maintenance): placebo 22.6%, 800mg 34.5%; 1200mg 37.7%.
Proportion of seizure free (titration and maintenance): placebo 1.2%, 800mg 4.8%; 1200mg 3.9%.
Exacerbation in seizure frequency >/=25% placebo 22.5; 800mg 16.7% , 1200mg 13%.
Adverse events (over 10%) n (%):
dizziness 9 (10.3) vs 16 (18.8) vs 24 (30)
somnia 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)
Withdrawal due to treatment emergent adverse events:
6 (6.9) vs 7 (8.2) vs 9 (11.3) from abnormal coordination, dizziness and nausea.

Funding
BIAL (Portela & Ca SA).

Does the study answer the question?
Yes.

Effect due to factor in study?
A power calculation was done for 80% power and the sample size reached this adequately, however there were high drop-outs.

How directly applicable to population of the guideline?
Direct.
ITT was a modified ITT analysis those who had been administered at least one dose and had one postbaseline seizure frequency assessment.
Selection bias: unclear risk of bias - unclear allocation concealment. Although states double-blinded but no details of blinding given.
Performance bias: low risk of bias.
Attrition bias: high risk of bias - there was a high rate of drop-out in the placebo and the eslicarbazepine 1200mg arm (over 20%).
Detection bias: low/unclear risk of bias.

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]

2006 Jun 13 66 pgs 1654 1660

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
<th>RID:</th>
</tr>
</thead>
<tbody>
<tr>
<td>382</td>
<td></td>
<td></td>
<td>408</td>
</tr>
</tbody>
</table>

Number of subjects: 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)

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

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.
Target dose of 60mg/kg/day. An initial dose of 20 mg/kg/day, increasing every 2 weeks to a final target dose of 60 mg/kg/day. Could be reduced to 40mg if not tolerated.

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

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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)

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*

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

* 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.

UCB Inc.

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.

Internal Validity

Risk of selection and performance bias is low. Methods of randomisation and concealment of allocation well described. Attrition bias risk low due to low drop out rates and intent to treat analysis. Investigators and patients blinded to treatment and outcomes measured in a valid and reliable manner. Therefore, risk of detection bias is low.

Note: A modified ITT was used - 18 patients were excluded before breaking the blind because of violation of the protocol, including 2 patients who did not take any study medications.

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
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</thead>
<tbody>
<tr>
<td>4603</td>
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</tr>
</tbody>
</table>

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

2000 54

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

<table>
<thead>
<tr>
<th>Sex</th>
<th>OXC (n=138)</th>
<th>Placebo (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>51%(70)</td>
<td>55%(71)</td>
</tr>
<tr>
<td>Female</td>
<td>49%(68)</td>
<td>45%(58)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>OXC (n=138)</th>
<th>Placebo (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>87%(120)</td>
<td>87%(112)</td>
</tr>
<tr>
<td>Other</td>
<td>13%(18)</td>
<td>13%(17)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, y mean (range)</th>
<th>OXC (n=138)</th>
<th>Placebo (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11%(3-17)</td>
<td>11%(3-17)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight, kg mean (range)</th>
<th>OXC (n=138)</th>
<th>Placebo (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>44%(16-130)</td>
<td>44%(16-89)</td>
<td></td>
</tr>
</tbody>
</table>

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. OXC 30-46 mg/kg/day.
Comparisons
OXC vs. placebo

Length of Study/ Follow-up
112 days

Outcome measures studies
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).

Funding
Novartis Pharmaceuticals Corporation

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

How directly applicable to population of the guideline?
See GRADE

Internal Validity
Low risk of selection and performance bias. Unclear the risk from attrition bias as a higher proportion of patients in OXC group dropped out of the study compared to patients in PCB group.

Guberman A;Neto W;Gassmann-Mayer C;

Reference number
4747

Study Type
Randomised Controlled Trial

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

2002 106 Acta Neurol Scand pgs 183 189

Number of subjects
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

Interventions/Test Factor being investigated
Comparisons
200mg/day, dose administered twice daily. In one group Topiramate was titrated to 200mg/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)
Active treatment vs. placebo addition to stabilised AED regimen

Recruitment:
Not stated

Setting:
Multicentre trial, mainly European centres

Length of Study/ Follow-up
12 weeks plus 4 weeks baseline.

Outcome measures studies
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
Proportion of seizure free participants:
  Week 1-12 (double blind period):
  Placebo: 2/91 (2%)  All topiramate: 10/168 (6%)**
  Week 9-12 (Maintenance period):
  Placebo: 8/88 (9%)  All topiramate: 30/150 (20%)**

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%)*  Topiramate 50/50: 42/83**
  (51%)  All topiramate: 75/168 (45%)**
  Week 9-12 (Maintenance period):
  Placebo: 29/88 (33%)  Topiramate 25/25: 49/76 (64%)*  Topiramate 50/50: 38/74 (51%)
  * All topiramate: 87/150 (58%)**

  Week 1-2 (early titration period):
  Placebo: 27/91 (30%)  Topiramate 25/25: 30/85 (35%)*  Topiramate 50/50: 40/84
  (48%)
  All topiramate: 70/169 (41%)
  * p<0.05, **p=0.001

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

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%)

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%)

23 December 2011  Page 59 of 364
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.

The study did not report sample size calculation and power.

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

The method of blinding for patients - using double dummy placebo and randomisation generation methods were well covered. Low risk of performance bias as the study was blinded and there was ITT analysis. Low risk of attrition bias.

The ITT population was defined as randomised patients with at least one efficacy evaluation.

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

**Reference number**: 4615  **Study Type**: Randomised Controlled Trial  **RID**: 280

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

1997 27

**Number of subjects**: 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
oxcarbazepine versus phenytoin. 100mg phenytoin and 300mg oxcarbazepine.

Between treatments.

8 weeks titration, 48 weeks maintenance.

Number of patients who were seizure free, side effects, withdrawal

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.

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.

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.
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.
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.

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 loss 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 loss 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.

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.

Funding
None reported

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.

For 80% power the sample size required in maintenance period was n=182. The number randomised was n=97 and n=96 (total n=193) however only n=161 (total) reached the maintenance period.

How directly applicable to population of the guideline?
Had to impute the figures for partial seizures as partial and generalised.

Low risk of selection bias. Performance bias low risk as study was double blinded. High risk of attrition bias as study had high number of drop outs. Low risk of detection bias.

Internal Validity
Low risk of selection bias. Performance bias low risk as study was double blinded. High risk of attrition bias as study had high number of drop outs. Low risk of detection bias.

23 December 2011
Reference number 1034 Study Type Randomised Controlled Trial RID 540

Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial

2009 50 pgs 443 453

Number of subjects
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)

<table>
<thead>
<tr>
<th>Total</th>
<th>Placebo</th>
<th>200 mg/day</th>
<th>Lacosamide 400mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=485</td>
<td>n=163</td>
<td>n=163</td>
<td>n=159</td>
</tr>
</tbody>
</table>

**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, 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), 0 (0), 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/m² (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. Patients started on 100mg/day each week until target dose reached. Dose reduced only once if maximum dose not tolerated.

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.

23 December 2011
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**

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)

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

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).

**Funding**

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

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

Reference number 4689  
Study Type Randomised Controlled Trial  
RID: 162  

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

1996 25  
Epilepsy Res  

Number of subjects  
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  
<table>
<thead>
<tr>
<th>Gender</th>
<th>Placebo</th>
<th>TGB</th>
<th>Placebo</th>
<th>TGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40(14)</td>
<td>37(9)</td>
<td>37(10)</td>
<td></td>
</tr>
<tr>
<td>Full Scale IQ Mean (SD)</td>
<td>88(20)</td>
<td>82(18)</td>
<td>84(22)</td>
<td></td>
</tr>
</tbody>
</table>

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. Tiagabine; 30 mg/day in three equally divided doses.

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 studies  
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 see in the 18-24 month phase but there was improvement in the List learning test and in auditory reaction times. The 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).

Funding  
Unknown
In this study the neuropsychological and neurophysiological evaluation did not indicate any adverse effects of TGB.

This is a small study and should be repeated.

See GRADE

Cognitive functioning tested via battery of 10 tests and were scored by a blinded neuropsychologist. No inter-rater reliability for scoring. Details of study design in a multicentre evaluation of tiagabine are presented in a separate report. Unclear risk from the absence on reporting of allocation concealment. Low risk of attrition bias.

Unclear the risk from the absence on reporting of allocation concealment.

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

Reference number 4761  Study Type Randomised Controlled Trial  RID: 231

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

<table>
<thead>
<tr>
<th></th>
<th>TGB, n=77</th>
<th>Placebo, n=77</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.4 (18.7-59.7)</td>
<td>36.0 (17.9-71.3)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>34 (44%)</td>
<td>30 (39%)</td>
</tr>
<tr>
<td>Male</td>
<td>43 (56%)</td>
<td>47 (61%)</td>
</tr>
<tr>
<td>Years with epilepsy</td>
<td>24.9 (2-52)</td>
<td>23.0 (1-49)</td>
</tr>
</tbody>
</table>

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. 12 mg/day - 30 mg/day (max) taken in three divided doses. The maximum dose was reduced to 24mg/day if the patient experienced problems of tolerance.

Comparisons
Treatment with fixed dose vs. placebo

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

Outcome measures studies
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.
The present study shows that tiagabine, at a dose of 10 mg administered three-times daily, is generally well tolerated and demonstrates efficacy for the treatment of refractory partial seizures. 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).

Unclear risk of selection bias due to absence of allocation concealment in the study. Low risk of performance bias as the study was double blinded and low risk of attrition bias as the different drop out rates were compensated by an ITT analysis.

**Koeppen D;Baruzzi A;Capozza M;Chauvel P;Courjon J;Favel P;Harmant J;Lorenz H;Oller FV;Procaccianti G;;**

<table>
<thead>
<tr>
<th>Reference number</th>
<th>4645</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
<th>RID:</th>
<th>115</th>
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<tbody>
<tr>
<td>Clobazam in therapy-resistant patients with partial epilepsy: a double-blind placebo-controlled crossover study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>129 patients began this cross over study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion Criteria:</td>
<td></td>
</tr>
<tr>
<td>Inclusion: Patients with refractory epilepsy who were on basic antiepileptic medication</td>
<td></td>
</tr>
<tr>
<td>Exclusion: Not addressed</td>
<td></td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td></td>
</tr>
<tr>
<td>Age: 33 +/- 12</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male 56</td>
<td></td>
</tr>
<tr>
<td>Female 73</td>
<td></td>
</tr>
<tr>
<td>Recruitment:</td>
<td></td>
</tr>
<tr>
<td>Not discussed</td>
<td></td>
</tr>
<tr>
<td>Setting:</td>
<td></td>
</tr>
<tr>
<td>Five European centres</td>
<td></td>
</tr>
<tr>
<td>Interventions/Test/Factor being investigated</td>
<td></td>
</tr>
<tr>
<td>Clobazam in therapy resistant patients with partial epilepsy</td>
<td></td>
</tr>
<tr>
<td>Comparisons</td>
<td></td>
</tr>
<tr>
<td>Clobazam vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Length of Study/ Follow-up</td>
<td></td>
</tr>
<tr>
<td>7 months</td>
<td></td>
</tr>
</tbody>
</table>

23 December 2011
Primary: Difference in seizure reduction
Secondary: EEG signs, mood ratings and global impressions

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

There is evidence of the therapeutic value of Clobazam as adjunct medication in therapy resistant partial seizures.

No power calculation, although 129 participants were randomised in this cross-over study.

Unclear risk of selection bias due to unclear allocation concealment and randomisation. Low risk of performance bias. Unclear risk of detection bias as the ITT analysis was poorly addressed.

The maximum dose used (40mg/daily) was towards the upper limit of usual dose for this drug (20-30mg/daily, max 60 mg/daily).

Korean Topiramate Study Group

Reference number 4746 Study Type Randomised Controlled Trial RID: 216

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

1999 40

n=91 in topiramate arm and n=86 in placebo arm.

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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Topiramate n=91</th>
<th>Placebo n=86</th>
<th>Total n=177</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>47</td>
<td>48</td>
<td>95</td>
</tr>
<tr>
<td>Women</td>
<td>44</td>
<td>38</td>
<td>81</td>
</tr>
</tbody>
</table>

Age Mean (+/-) 29.58(7.80) 29.77(8.71)

23 December 2011
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
onic-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. Up to a target maximum dose of 600mg. If dose increases in the titration phase not tolerated then reduced to the previous week’s dose.

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

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

Outcome measures studies
Results

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Topiramate (n=89)</th>
<th>Placebo (n=85)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median seizure freq (episodes per 4wks)</td>
<td>5.6</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Baseline phase</td>
<td>0.9</td>
<td>2.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Experimental phase</td>
<td>51.3%</td>
<td>9.1%</td>
<td>0.0001</td>
</tr>
<tr>
<td>MSFRR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary outcomes
Responder rate  45(50.6%)  11(12.9%)  0.04
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
Anorexia  19(20.9%)  5(5.8%)  0.003
Abdominal. Discomfort  19(20.9%)  2(2.3%)  0.001
Dizziness  18(19.8%)  18(21%)  0.85
Somnolence  18(19.8%)  8(9.3%)  0.85
Nausea/vomiting  15(16.5%)  7(8.1%)  0.09
Headache  10(11%)  6(7.0%)  0.52
Amblyopia  10(11%)  4(4.7%)  0.12

Subgroup analysis
<table>
<thead>
<tr>
<th>Type of seizure</th>
<th>Median seizure frequency reduction rate (MSFRR)</th>
<th>Topiramate (n=9)</th>
<th>Placebo (n=4)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPMS</td>
<td>87.5</td>
<td>72.9</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>CPS</td>
<td>49.4</td>
<td>-14.3</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>GTCS</td>
<td>100</td>
<td>40.26</td>
<td>0.25</td>
<td></td>
</tr>
</tbody>
</table>

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

23 December 2011  Page 68 of 364
Janssen Korea Ltd.

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.

How directly applicable to population of the guideline?
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
The risk of selection bias appears to be low: methods of randomisation and concealment of allocation were not well described, but the groups did appear to be comparable at baseline. The risk of performance bias is unclear: no description of patient or investigator blinding was given. Risk of attrition bias was low: although 16% of pts in the topiramate group and 10% in the placebo group dropped out before study end only 3 patients were not included in the final ITT analysis because they had no outcome data (2 in topiramate group and 1 in placebo group). The risk of detection bias is unclear: the study does not report how well investigators were blinded although a precise definition of outcome was reported and methods to determine the outcome appear reliable.

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

Reference number 40  Study Type Randomised Controlled Trial  RID: 329

Effects of lamotrigine compared with levetiracetam on anger, hostility, and total mood in patients with partial epilepsy 2009 Mar 50  pgs 434 442

Number of subjects
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

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine</th>
<th>Levetiracetam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>38.3(12.3)</td>
<td>39.1(11.6)</td>
</tr>
<tr>
<td>Female n(%)</td>
<td>63(48)</td>
<td>56(41)</td>
</tr>
<tr>
<td>Race n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0(0)</td>
<td>2(1)</td>
</tr>
<tr>
<td>Black</td>
<td>22(17)</td>
<td>23(17)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>11(8)</td>
<td>11(8)</td>
</tr>
<tr>
<td>White</td>
<td>94(71)</td>
<td>99(73)</td>
</tr>
<tr>
<td>Other</td>
<td>5(4)</td>
<td>1(&lt;1)</td>
</tr>
</tbody>
</table>

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. For lamotrigine starting dose was 50mg/day to the target dose of 400mg/day over weeks 1 to 8. For levetiracetam the starting dose was 500mg/day to the target dose of 2000mg/day over weeks 1 to 8.

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/studies
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).

<table>
<thead>
<tr>
<th>Lamotrigine (n=125)</th>
<th>Levetiracetam (n=126)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score Anger-Hostility</td>
<td>Mean (SD)</td>
<td>10.6(9.0)</td>
</tr>
<tr>
<td>Mean change (SD)</td>
<td>-2.0(8.2)</td>
<td>-0.3(8.4)</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td>Median % decrease</td>
<td>60</td>
</tr>
<tr>
<td>Pts showing any improvement in CGI-%</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>Adverse events</td>
<td>% patients &gt;=1 event</td>
<td>82</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>% patients</td>
<td>11</td>
</tr>
<tr>
<td>Most common AEs as % of AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

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

Funding
GlaxoSmithKline Research and Development.

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.

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.
How directly applicable to population of the guideline?

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

There appears to be an unknown risk of bias: there was no details of randomisation method or allocation concealment. The groups were comparable at baseline. Similarly, the risk of performance bias appears to be low. The risk of attrition bias appears to be low: a similar proportion dropped out of each group but the analysis was done on an ITT basis and outcome data was available for similar number of participants. Risk of detection bias was also low: a pre-specified precise, reliable measure was chosen as primary study endpoint and verified in a similar manner between groups.

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

Reference number 1032

Study Type Randomised Controlled Trial

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

2009 50

Number of subjects 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:

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

Recruitment: Not reported.

Setting: 9 centres in Korea.
Pregabalin in a flexible dose (up to 600mg/day). PGB treatment was initiated at 150 mg/day (75 mg/day twice daily, in the morning and evening). Dose adjustment was at 2-week intervals from week 0 (visit 3) through week 8 (visit 7), at 150 mg/day increments up to a maximum dose of 600 mg/day based on clinical response and tolerability at the discretion of investigators.

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 studies**
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**

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All seizures</td>
<td>55 (46.2)</td>
<td>19 (32.2)</td>
<td>0.068b</td>
</tr>
<tr>
<td>SGTCs</td>
<td>28 (62.2)</td>
<td>20 (80.0)</td>
<td>0.143b</td>
</tr>
<tr>
<td>PCH in 28 days seizure rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>-38.3 (-48.2)</td>
<td>-20.3 (-32.4)</td>
<td>0.012d</td>
</tr>
<tr>
<td>95% CI for median</td>
<td>53.1 to -36.5</td>
<td>-44.1 to -11.9</td>
<td></td>
</tr>
<tr>
<td>Seizure free rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-blind phase (%)</td>
<td>5 (4.2)</td>
<td>2 (3.4)</td>
<td>1.00e</td>
</tr>
<tr>
<td>Any 28-day period (%)</td>
<td>51 (43)</td>
<td>22 (37)</td>
<td>0.52e</td>
</tr>
<tr>
<td>Change in number of SFD per 28 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDB-BL (95% CI) *</td>
<td>1.09 (1.07 to 1.10)</td>
<td>1.05 (1.03 to 1.08)</td>
<td></td>
</tr>
<tr>
<td>RDB-BL of PGB/Placebo (95% CI)*</td>
<td>1.03 (1.01 to 1.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGTC, secondarily generalized tonic-clonic seizures; PCH, percent change; CI, confidence interval; SFD, seizure free days.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*Ratio of ratios of change in number of SFD per 28 days from baseline to double-blind phase (pregabalin-RDB-BL/placebo-RDB-BL).

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD-A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score (SD)</td>
<td>8.23 (3.87)</td>
<td>8.41 (3.67)</td>
<td></td>
</tr>
<tr>
<td>Week-12 score (SD)</td>
<td>7.87 (3.96)</td>
<td>7.69 (3.97)</td>
<td></td>
</tr>
<tr>
<td>ANCOVA of week-12 score:</td>
<td>7.91 (0.32)</td>
<td>7.56 (0.44)</td>
<td></td>
</tr>
<tr>
<td>LS mean (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in LS means (95% CI)</td>
<td>0.35 (-0.70 to 1.41)</td>
<td>0.507</td>
<td></td>
</tr>
<tr>
<td>HAD-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score (SD)</td>
<td>9.29 (3.65)</td>
<td>9.02 (3.85)</td>
<td></td>
</tr>
<tr>
<td>Week-12 score (SD)</td>
<td>8.82 (4.16)</td>
<td>7.69 (3.89)</td>
<td></td>
</tr>
<tr>
<td>ANCOVA of week-12 score:</td>
<td>8.71 (0.33)</td>
<td>7.79 (0.46)</td>
<td></td>
</tr>
<tr>
<td>LS mean (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in LS means (95% CI)</td>
<td>0.92 (-0.16 to 2.00)</td>
<td>0.095</td>
<td></td>
</tr>
</tbody>
</table>
Pfizer Inc.
Yes. PGB was effective as add-on treatment in an Asian population with refractory partial-onset seizures.

Internal Validity
This appears to be a well conducted RCT but methods of randomisation and allocation concealment are not well described so selection and performance bias risk is unclear. More patients discontinued treatment in the PGB arm but an ITT analysis was conducted so risk of attrition bias is low. Risk of detection bias is low: outcomes were measured in a reliable and valid way.

Funding
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.

How directly applicable to population of the guideline?
All patients in this study had a diagnosis of partial seizures.

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

Pfizer Inc.

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=119</td>
<td>Treatment related</td>
<td>n=59</td>
<td>Treatment related</td>
</tr>
<tr>
<td></td>
<td>All causality</td>
<td>2.06 (2.09)</td>
<td>2.21 (2.36)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint SIS (SD)</td>
<td>1.67 (2.00)</td>
<td>2.22 (2.51)</td>
<td></td>
</tr>
<tr>
<td>ANCOVA of endpoint SIS:</td>
<td>LS mean (SE)</td>
<td>1.62 (0.13)</td>
<td>2.07 (0.18)</td>
<td></td>
</tr>
<tr>
<td>Difference in endpoints</td>
<td>(95% CI)a</td>
<td>-0.45 (-0.87 to -0.02)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QOLIE-31</td>
<td>Baseline score</td>
<td>48.0 (7.96)</td>
<td>49.0 (9.08)</td>
</tr>
<tr>
<td></td>
<td>Week-12 score</td>
<td>50.4 (8.45)</td>
<td>49.3 (8.31)</td>
<td></td>
</tr>
<tr>
<td>ANCOVA of week-12 score:</td>
<td>LS mean (SE)</td>
<td>50.7 (0.73)</td>
<td>49.2 (1.01)</td>
<td></td>
</tr>
<tr>
<td>Difference in endpoints</td>
<td>(95% CI)a</td>
<td>1.4 (-1.0 to 3.8)</td>
<td>0.245</td>
<td></td>
</tr>
</tbody>
</table>

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.

Adverse events
Cognitive and behavioral effects of lamotrigine and carbamazepine monotherapy in patients with newly diagnosed or untreated partial epilepsy

Number of subjects
All patients
N: 110
Group 1(carbamazepine)
N: 53
Group 2 (lamotrigine)
N: 57

Inclusion/Exclusion Criteria:
Inclusion criteria:
Age 16-60 years
Newly diagnosed partial epilepsy
Partial epilepsy recently untreated for at least 1 year
At least 1 partial seizure with or without secondary generalisation in the 12 months before study commencement

Exclusion criteria:
Use of any AED treatment within the past 1 year (except as an emergency treatment for ≤2 weeks).
Full-scale intelligence quotient (FSIQ) less than 70
Idiopathic generalised epilepsy
Active CNS infection
Any progressive CNS disease
Any medical or neurological disorder that required frequent changes in medication or dosage.

Patient Characteristics
Group 1(carbamazepine)
N: 53
Age (mean): 36.8
Drop outs: 19
M/F: 23/11
Duration of epilepsy, mean (SD) (years): 7.2 (10.4)
Number of seizures in previous 6 months: 3.6 (5.6)

Group 2 (lamotrigine)
N: 57
Age (mean): 34.8
Drop outs: 18
M/F: 19/20
Duration of epilepsy, mean (SD) (years): 5.5 (7.9)
Number of seizures in previous 6 months: 3.6 (6.4)

Recruitment:
Not reported.

Setting:
Republic of Korea

Interventions/Test
Factor being investigated
Group 1(Carbamazepine)
Dose
8 weeks titration period:
100mg/day for weeks 1-2
200mg/day for weeks 3-4
400mg/day for weeks 5-6
600mg/day for weeks 7-8
Maintenance period: dose increased to a max. of 1200mg/day if the patient continued to experience seizures.

Method
Controlled release preparations
Frequency
2 divided doses per day
Group 2 (lamotrigine)
Dose
8 week titration period: 25mg/day for weeks 1-2
50mg/day for weeks 3-4
100 mg/day for weeks 5-6
200 mg/day for weeks 7-8
Maintenance period: dose increased to a max. of 500mg/day if the patient continued to experience seizures.
Frequency
2 divided doses per day

Comparisons
carbamazepine v lamotrigine

Length of Study/ Follow-up
48 weeks

Outcome measures
phonemic fluency, stroop word/colour interference, obsessive-compulsive, paranoid ideation, global severity index, positive symptom total

Results
Cognitive Data
Significant group-by-time interaction was identified only in the phonemic fluency of COWAT (p=0.0032) and Stroop Color-Word Interference (p=0.0283), with the LTG group performing significantly better. The CBZ and LTG groups did not differ significantly at baseline. However, the LTG group was significantly better than the CBZ group in phonemic fluency at both 16 (p=0.0062) and 48 (p=0.0032) weeks and in Stroop Color-Word Interference (p=0.0229) at 48 weeks. Time effects were significant only in the LTG, not the CBZ, group. In the LTG group, phonemic fluency was significantly better, relative to baseline, at 16 (p=0.0003) and 48 (p<0.0001) weeks, and Stroop-Color-Word Interference was significantly better at 48 weeks (p=0.0002). All other cognitive tests, including those of language and memory, did not show significant group-by-time interactions.
Psychological and quality of life data
Significant group by time interactions were identified in Obsessive-Compulsive (p=0.0005), Paranoid Ideation (p=0.0454), Global Severity Index (p=0.0194), and Positive Symptom Total (p=0.0197) scores of the SCL-90, with significant improvements in the CBZ group. Obsessive-Compulsive subscale did not differ between the CBZ and LTG groups at baseline, but was significantly better in the CBZ than in the LTG group at 48 weeks (p=0.0427). In addition, the Obsessive-Compulsive subscale was significantly improved at 48 weeks, compared with baseline, in the CBZ (p=0.0012), but not in the LTG group. Paranoid Ideation, Global Severity Index and Positive Symptom Total at 16 (p=0.0129) but not at 48 weeks. The other dimensions of the SCL-90 and the total and subscale scores of the QOLIE-31 did not show any significant group by time interactions.

Funding
GlaxoSmithKline Korea

Does the study answer the question?
Yes.

Effect due to factor in study?
No power calculation given and 57 and 53 sample size.

How directly applicable to population of the guideline?
See GRADE.

Internal Validity
Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: a randomized, double-blind, placebo-controlled, noninferiority trial

Inclusion/Exclusion Criteria:
- Inclusion criteria: • Age 4-16 years old • Diagnosis of epilepsy with partial-onset seizures for ≥6 months • One or more seizures during the 4 weeks before baseline • Stable regimen of one or two AEDs for 2 weeks prior to randomisation • IQ ≥65 at baseline
- Exclusion criteria: none reported

Patient Characteristics
- Children and adolescents aged 4-16 years with uncontrolled partial-onset seizures
- Group 1 (adjunctive LEV)
  - N: 64
  - Gender, male n (%): 39 (60.9)
  - Age, mean (S.D): 10.6 (3.5)
  - Min-max: 4.8-16.7
  - Race, n (%)
    - Caucasian: 40 (62.5)
    - Other/mixed: 6 (9.4)
    - Black: 15 (23.4)
    - Asian: 3 (4.7)
  - Leiter-R IQ score mean (SD): 89.8 (18.2)
  - Min-max: 42-135
  - Drop outs: 18
- Group 2 (placebo)
  - N: 34
  - Gender, male n (%): 17 (50.0)
  - Age, mean (S.D): 10.3 (3.7)
  - Min-max: 4.1-16.4
  - Race, n (%)
    - Caucasian: 18 (52.9)
    - Other/mixed: 5 (14.7)
    - Black: 8 (23.5)
    - Asian: 3 (8.8)
  - Leiter-R IQ score mean (SD): 89.1 (14.9)
  - Min-max: 67-124
  - Drop outs: 7

Recruitment: Not reported.
Setting: USA, South Africa, Canada
Interventions/Test Factor being investigated
adjunctive levetiracetam 20-60mg/kg/day
Comparisons levetiracetam v placebo

Length of Study/ Follow-up: end points followed up at end of study (12 weeks)
assessments of cognitive functioning, Child Behaviour Checklist (CBCL), Child Health Questionnaire- Parent Form 50 (CHQ-PF50)

Results

CBCL competence scores (per protocol population)
Activities (range 0-15) change from baseline:
Group 1 (LEV): -0.01
Standard error: 0.39
Group 2 (placebo): -1.37
Standard error: 0.54
p value: 0.049
Levetiracetam versus placebo:

50% reduction in seizure frequency over evaluation period: 62.5% (40/64) vs 41.2% (14/34).

Seizure freedom over evaluation period: 46.9% (30/64) vs 8.8% (3/34).

Adverse events over 10%:
headache: 17/64 (26.6%) vs 9/34 (14.7%)
upper respiratory tract infection: 12/64 (18.8%) vs 9/34 (26.5%)
upper abdominal pain: 11/64 (17.2%) vs 3/34 (8.8%);
nasopharyngitis: 10/64 (15.6%) vs 4/34 (11.8%);
fatigue: 9/64 (14.1%) vs 4/34 (11.8%);
vomiting: 9/64 (14.1%) vs 3/34 (8.8%);
somnolence: 9/64 (14.1%) vs 3/34 (8.8%);
agression: 8/64 (12.5%) vs 3/34 (8.8%);
dizziness: 6/64 (9.4%) vs 4/34 (11.8%);
psychomotor activity: 4/64 (6.3%) vs 5/34 (14.7%).

Withdrawal due to adverse events: 7/64 vs 2/34;
Withdrawal due to lack of efficacy: 1/64 vs 1/34.

Change from baseline in WRAML-2 index scores: lev (n=46) plcbl n=27
General memory: +3.4 (1.5) vs +6.9 (2.1); lev -pcb: -3.4 (2.7); 95% CI: -8.8, 1.9; p value: 0.202.
Visual memory: +7.3 (2.0) vs +10.8 (2.7); lev -pcb: -3.5 (3.4); 95% CI: -10.2, 3.3; p value 0.311.
Verbal memory: +2.6 (1.7) vs +1.3 (2.4); lev -pcb: +1.3 (3.0); 95% CI -4.7, 7.3; p value 0.657.
Attention/concentration: -0.2 (1.3) vs +2.0 (1.9); lev -pcb: -2.1 (2.3); 95% CI -6.7, 2.4; p value 0.354.

Change from baseline in Leiter-R examiner’s rating scale:
Cognitive/social: +1.4 (2.1) vs +0.6 (2.7); lev -pcb: +0.9 (3.4); 95% CI -5.9, 7.7; p value 0.794.
Emotions/regulations: +2.0 (2.2) vs +1.4 (2.9); lev -pcb: +0.6 (3.7); 95% CI -6.8, 8.0; p value 0.880.

Funding
UCB

Does the study answer the question?
Yes.

Effect due to factor in study?
Powered for 60 and 20 participants per protocol, the actual sample size was 46 and 27, therefore this study was slightly underpowered.

How directly applicable to population of the guideline?
Direct

Internal Validity
Risk of selection bias: unclear risk of bias as no details of allocation concealment.
Risk of performance bias: low risk.
Risk of attrition bias: unclear bias as 22% dropped out of levetiracetam arm and 15% out of the placebo arm.
Risk of detection bias: low risk.
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.

**Summary:**

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.

**Patient Characteristics**

- **Gender**: Men 28(56%), Women 23(44%)
- **Age, y**: Median (range) 34.5(13-68) for GBP and 33(14-56) for VGB
- **Weight (kg)**: Median (range) 77.5(53-155) for GBP and 69.0(46-104) for VGB
- **Duration of epilepsy, m**: Median (range) 3.5(0-36) for GBP and 9.5(0-43) for VGB

**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. GBP 900mg/day initial dose, titrated up during 5 days to first maintenance dosage level of 1800mg/day, if seizures persisted 2400mg/day and 3600mg/day; VGB 1000mg/day, if seizures persisted 2000mg/day and 4000mg/day;

**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 studies**

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**

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

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

**Funding**

Unknown

**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?**

Study powered for 80% if both groups had 125 participants. Discontinued prematurely so sample size not met.
The study was discontinued prematurely after screening of 115 patients instead of the originally intended 280 patients. The recruitment was stopped when it became apparent that vigabatrin could induce visual field defects.

Patient diaries of seizure frequency may contain inaccuracies. Unclear risk of selection bias as no details on randomization procedure and allocation concealment. Unknown risk of attrition bias as more participants in GBP group dropped out before the study was completed compared to participants in VGB. Low risk of performance and detection bias.

Loiseau P; Yuen AW; Duchê 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

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 12.91);

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. Full dose was 300 mg/day for patients taking enzyme inducing
drugs and 150 mg/day for “inhibited” patients.
Randomised double blind placebo-controlled crossover trial of LTG added on to existing
AEDs
Comparing LTG to placebo
Comparisons
Length of Study/ Follow-up
8 weeks in one drug and cross over for 8 weeks in the other drug. Trial lasted 28 weeks.

Outcome measures studies
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
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
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)
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)
2/ SEIZURE DAYS; Reported as the total number of seizure days
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)
Comparator
Data not reported
3/ PHYSICIAN/PATIENT GLOBAL EVALUATION OF
IMPROVEMENT/EFFICACY/TOLERABILITY; Physician reported global evaluation of
improvement
Intervention
Number of patients considered better on LTG than placebo (10/23)
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. The study aimed to recruit 20 completed (in line with ILAE recommendations) and 23 participants were randomised.

There were small differences between the 2 groups at baseline in terms of seizure types and aetiology. Appropriate paired analysis does not appear to have been performed. Data skewed by the inclusion of one participant with very large number of seizures. One patient receiving concurrent chronic medication for another condition (thyroxine for hypothyroidism). For both groups, doses used were within the limits of usual therapeutic dose for LTG with valproate (100-200 mg/daily) and LTG with enzyme inducers (200-400 mg/daily). Unclear risk of selection and performance bias. Low drop out rate so the risk of attrition bias is low.

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

Lu Y; Xiao Z; Yu W; Xiao F; Xiao Z; Hu Y; Chen Y; Wang X;

Efficacy and safety of adjunctive zonisamide in adult patients with refractory partial-onset epilepsy: a randomized, double-blind, placebo-controlled trial

2011 31 Clinical Drug Investigation 975 221 229

Number of subjects: No. randomised: ZNS n=53; PCB n=51.

Inclusion/Exclusion Criteria:
- patients seizures classified as partial seizures (including simple partial seizure, complex partial seizure and secondary generalised seizure, according to the seizure classification proposed by the ILAE);
- aged between 18 and 70 years;
- at least one seizure every 4 weeks during the 12-week baseline;
- already received one or two AED treatments, and there had been no change to those treatments in the past 3 months;
- brain CT or MRI showed no brain tumour and no progressive neurological disease;
- patient exhibited good compliance.

Exclusion criteria:
- progressive neurologival disease;
- history of nonepileptic seizures, such as pseudoseizures;
serious mental retardation or an unstable mental status;
serious internal diseases, such as heart disease, liver disease, kidney disease, haematological diseases and uncontrolled hypertension (systolic b.p>150mmHg and or diastolic b.p>100mmHg);
- history of carcinoma;
- history of renal stones;
- history of alcohol abuse or drug abuse within the past 2 years;
- allergy to sulphas drugs;
- pregnancy or breast-feeding;
- abnormal laboratory test results considered to be of clinical importance;

Patient Characteristics  
ZNS vs PCB:  
age: 36.83 +/-10.77 vs 29.81 +/-8.24;  
males: 29 vs 32  
females: 24 vs 19  
Body weight (kg mean +/- SD): 58.16 +/-7.81 vs 58.73 +/-9.40;  
Simple partial seizures: 2 vs 1  
complex partial seizures: 15 vs 18;  
secondary generalised seizures (including partial and sec. Gen. Seizures): 36 vs 32;  
seizure frequency (median, range): 19.07 (3-83) vs 19.46 (3-95)

Setting:  
Recruited in the Epilepsy centre of the first affiliated hospital, Chongqing Medical University, Chongqing, Southwest China between 2006 and 2007.

Interventions/Test /Factor being investigated:  
Zonisamide adjunctive therapy versus placebo. Target dosage: 300mg/day or 400mg/day.

Comparisons:  
Between treatment and placebo: ZNS versus placebo.

Length of Study/ Follow-up:  
Baseline period 12 weeks; 4 weeks titration; stabilisation phase 12 weeks.

Outcome measures studies:  
% responders (50% reduction in seizure frequency), seizure freedom, adverse events.

Results:  
ZNS vs PCB (number completed given in study):  
50% reduction in seizure frequency: 29/52 vs 18/50  
300mg/day arm 16/29 vs 400mg/day arm 13/23.
Seizure freedom: 3/52 vs 1/50.  
WAE: 0/52 vs 0/50.  
WLE: 0/52 vs 0/50.
Adverse events (over 10%):  
dizziness 2/52 vs 6/50;  
somnolence 2/52 vs 6/50;  
increase in liver enzymes: 35/52 vs 37/50;  
decreased leukocyte count: 8/52 vs 10/50;  
decreased platelet count: 11/52 vs 13/50;  
increase in serum creatinine 7/52 vs 5/50;  
weight gain: 29/52 vs 32/50;  
weight loss: 9/52 vs 8/50.

Funding:  
No sources of funding used to assist in study.

Does the study answer the question?  
Yes this study helps answer the question

Effect due to factor in study?  
Yes. For power of 90% n=50 per group was required, assuming a 5% drop-out. The sample size was n=53 and n=51 and the number completed was n=52 and n=51.

23 December 2011  
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Randomisation: tablets randomly numbered by study sponsors and concealed by numbered containers.
Blinding: identical tablets. Investigators blind until end of trial.
Allocation concealment by the use of numbered containers.
There were two different titration strategies used for tablets (ZNS and PCB) obtained from Eisai co, Ltd they received ZNS 100mg/day for 1st 2 weeks then 200mg/day at week 3 and then 300mg/day at week 4. Tablets (ZNS and PCB) from Shenzhen Zifu co. Ltd started at 100mg/day and increasaed weekly by 100mg to target dose of 400mg/day at week 4.
The zonisamide group were older than the placebo group.

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

Reference number 1496
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial

2007 11 Health Technol Assess

Number of subjects
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(%):
idioapathic 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);
idioapathic 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.
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 0:1:1.

Drug was randomised but drug, dosage and preparation were those usually by the clinician.

Guidelines for initial maintenance doses and rates of titration: children aged <16 years: LTG 3-6mg/kg/day; TPM 3-6mg/kg/day; VPA 20-30mg/kg/day. Adults aged over or 16 years: LTG 150mg/dg; TPM 150mg/dg; VPA 1000mg/dg.

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 studies
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 1.29)

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).

Yes.

Randomisation by telephone using minimisation (stratified by centre, sex and drug history (newly diagnosed and untreated, treated with ineffective monotherapy, relapse after remission of epilepsy)) and a list of random allocations was prepared to break ties.

Ratio of male to female subjects indicates reluctance of clinicians to randomise younger women to Arm B, where they might have been randomised to VPA.

Selection bias: low risk of bias.
Performance bias: unknown risk of bias - no blinding of treatment allocation.
Attrition bias: low risk of bias.
Detection bias: unknown risk of bias - no blinding of investigators.

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

Reference number 4739 Study Type Randomised Controlled Trial RID: 209

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

1993 43 PGS 2284 2291

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

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=73</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300mg/day n=71</td>
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<tr>
<td></td>
<td>500 mg/day n=72</td>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
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<th>30(42%)</th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td>51 (70%)</td>
<td>41(58%)</td>
<td>57(79%)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>34</td>
<td>33</td>
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<tr>
<td>Range</td>
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<td>20-57</td>
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<tr>
<td>Race</td>
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<td></td>
<td>Black</td>
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<tr>
<td>Mean duration (yr)</td>
<td>21.5</td>
<td>22.4</td>
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</tbody>
</table>

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 studies 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.

Funding Unknown

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? For 80% power 165 participants (55 per group) were required. This was met and those completing were still above the required sample size.

How directly applicable to population of the guideline? See GRADE

Internal Validity

Patient self report diaries could be inaccurate so detection bias may be unclear. Unclear risk of selection bias as no details given of randomisation method or allocation concealment. Low risk of performance bias and attrition bias.
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 50-1 26 kg). Patients must have experienced \( \leq 40 \) 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 50-1 26 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 studies

Not specified. Aim of study was to assess dose tolerability and safety of lamotrigine. Also, to determine the pharmacokinetic profile at doses \( \geq 500 \) mg/day.

Results

Adverse events

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

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>LTG (n=8) incidence (%)</th>
<th>Placebo (n=4) incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5(63)</td>
<td>3(75)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5(63)</td>
<td>2(50)</td>
</tr>
<tr>
<td>Faintness</td>
<td>4(50)</td>
<td>2(50)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4(50)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1(13)</td>
<td>2(50)</td>
</tr>
</tbody>
</table>

23 December 2011 Page 87 of 364
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.

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.

Most of the patients enrolled suffered from partial seizures.

This is a very small study (n=12, n=8 in treatment group and n=4 in placebo group). However, it appears to be conducted in a proper randomized, double-blind fashion and so selection bias and performance bias appear to be low. No patients dropped out and outcomes were measured in a standard way, so there is a low risk of attrition or detection bias.

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

Lamotrigine extended-release as adjunctive therapy for partial seizures

2007 Oct 16

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

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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
  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 >=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 >=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 doubleblind 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 doubleblind 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 doubleblind 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

Amantadine reported in \( \geq 5\% \) of patients in either treatment group
(safety population)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Lamotrigine extended-release ( n=118 )</th>
<th>Placebo ( n=121 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>20 (17)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (18)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (3)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (7)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8 (7)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (3)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (7)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Tremor</td>
<td>6 (5)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Funding
GlaxoSmithKline Research and Development (GSK R&D).

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.

How directly applicable to population of the guideline?
The study was comprised of patients with a diagnosis of epilepsy with partial seizures with or without secondarily generalized seizures.

Internal Validity
Very few details are given about randomisation and concealment of allocation so risk of selection and performance bias is unknown. 20\% of patients dropped out of lamotrigine group but analysis was conducted on an ITT basis. Therefore, risk of attrition bias low. Outcomes were measured in a standard way and so risk of detection bias is low.
A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy

2001 46 Epilepsy Res 145 155

Number of subjects

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 studies

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.

Funding

Unknown

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?

No power calculation but large sample size.

How directly applicable to population of the guideline?

See GRADE

Internal Validity

High risk of performance bias as study was unblinded and unclear risk of selection bias as no details allocation concealment. High risk of attrition bias due to high number of participants dropping out.

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

Reference number 5087  Study Type Randomised Controlled Trial  RID: 43

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

2010 74  Pgs 714 720

Mar 2

23 December 2011 Page 91 of 364
### Patient Characteristics

**Interventions/Test Factor being investigated**

- 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 (6.4).
- 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 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.

### 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%.

### Funding

Johnson and Johnson Pharmaceuticals.

**Does the study answer the question?**

Yes
The study was powered for 30 infants per group (120 total) for a power of 80%. The numbers randomised were above this and all but one group had a sample size above this at completion.

Internal Validity

ITT and MITT analysis.
Selection bias: low risk of bias
Performance bias: unclear risk of bias - less boys (38%) in placebo group than the topiramate groups (58%, 51% and 62%).
Attrition bias: unclear risk of bias - higher drop out in the placebo arm.
Detection bias: low risk of bias.

Effect due to factor in study?

How directly applicable to population of the guideline?

Direct.

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/m2)
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 studies
Primary outcome is frequency of partial-onset seizures per week over the treatment period.
Secondary outcomes: responders (>=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)

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

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 >=5% patients in either treatment group (safety population)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Placebo (N = 79)</th>
<th>LEV XR (N = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one adverse event, n (%)</td>
<td>43 (54.4)</td>
<td>41 (53.2)</td>
</tr>
<tr>
<td>Somnolence, n (%)</td>
<td>2 (2.5)</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Irritability, n (%)</td>
<td>0</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Headache, n (%)</td>
<td>11 (13.9)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>2 (2.5)</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Influenza, n (%)</td>
<td>3 (3.8)</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Nasopharyngitis, n (%)</td>
<td>4 (5.1)</td>
<td>5 (6.5)</td>
</tr>
<tr>
<td>Nausea, n (%)</td>
<td>2 (2.5)</td>
<td>4 (5.2)</td>
</tr>
</tbody>
</table>

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 was 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.

UCB, Inc and UCB Pharma, SA.

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.

How directly applicable to population of the guideline?
All patients in the study had a diagnosis of partial-onset seizures.

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

Reference number 4817 Study Type Randomised Controlled Trial RID: 714
Effect of valproate on cognitive functioning. Comparison with carbamazepine. The Department of Veterans Affairs Epilepsy Cooperative Study 264 Group
1996 53 Arch Neurol 1008 1016
Oct
Number of subjects 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

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

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 studies
Not stated

Results
Cognitive tests:
There were no significant differences 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 either CBZ or valproate did not show practice effects experienced by normal controls

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

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.

How directly applicable to population of the guideline?
Uncertain. Selective group of patient. The main study was not included in the review.

Internal Validity
Unclear randomisation allocation and concealment and, blinding methods, therefore unclear risk of selection, performance and detection bias. Low risk of attrition bias. Small sample size.
Privitera M; Fincham R; Penry J; Reife R; Kramer L; Pledger G; Karim R;

Reference number 4700

Study Type Randomised Controlled Trial

Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. Topiramate YE Study Group
1996 46

Funding

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?

No power calculation given.

Number of subjects

190 total: 48 to 600 mg/day; 48 to 800 mg/day; 47 to 1000 mg/day; 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 studies

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

<table>
<thead>
<tr>
<th>% seizure reduction</th>
<th>Placebo</th>
<th>600 mg</th>
<th>800 mg</th>
<th>1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>1.2</td>
<td>40.7</td>
<td>41.0</td>
<td>37.5</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Treatment responders (>50% reduction in seizure frequency)

<table>
<thead>
<tr>
<th>Number</th>
<th>Placebo</th>
<th>600 mg</th>
<th>800 mg</th>
<th>1000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>8.5</td>
<td>43.8</td>
<td>39.6</td>
<td>38.3</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Robert Wood Johnson

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The measure of global improvement and patients' overall assessment of study medication was a subjective evaluation. Seizure rate calculations depended on patient diary evaluated by investigator.

Unclear risk of selection bias as unclear randomisation method and allocation concealment. Low risk of performance bias. Unclear risk of attrition bias as no information are provided on drop out rates. Unclear the risk of detection bias as no information on outcome measures is given.

### Patient Characteristics

- **Number of subjects**: 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**: Inclusion: newly diagnosed patients who were previously untreated; over the age of 17 years. 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.
- **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 studies**: 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. Secondary: major and minor side effects
- **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.
- **Funding**: Southern Foundation for Brain Research

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.
Internal Validity

This appears to be a multi-centre study with patient self report via calendars of seizure events. This is a head-to-head drug trial with no placebo arm for ethical reasons. Low risk of selection bias and performance bias. Unclear the risk of attrition bias due to high drop out rate.

Rastogi P; Mehrotra TN; Agarwala RK; Singh VS;

Reference number: 4662
Study Type: Randomised Controlled Trial
RID: 281

Comparison of sodium valproate and phenytoin as single drug treatment in generalised and partial epilepsy

1991 J Assoc Physicians India

Number of subjects: 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 studies: 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(1005) --
Sec. gen. of Partial seizures 4 -- 1(25%) 3(75%)  
Unknown

It appears that while sodium valproate and phenytoin were equally effective in controlling generalised epilepsy, valproate was a better drug for controlling partial seizures.

Selection bias: high risk of bias - no allocation concealment and groups not comparable at baseline.
Performance bias: high risk of bias - no blinding reported.
Attrition bias: low risk of bias.
Detection bias: High risk of bias - The actually measurement technique for seizure frequency was not described. There was no blinding reported.

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

Reference number 4737 Study Type Randomised Controlled Trial RID: 207

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

1997 54 Arch Neurol pgs 595 601

Number of subjects 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 addiction or severe psychiatric illness.

Patient Characteristics Demographic and clinical characteristics of 318 randomized patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Tiagabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=107</td>
<td>n=106</td>
</tr>
<tr>
<td>Sex, F:M, %</td>
<td>50:50</td>
<td>39:61</td>
</tr>
<tr>
<td>Race, white: black; other %</td>
<td>86:7</td>
<td>84:9:7</td>
</tr>
<tr>
<td>Mean age (range), y</td>
<td>35.3(13-71)</td>
<td>33.4(12-67)</td>
</tr>
<tr>
<td>Mean weight (range) kg</td>
<td>71(41-118)</td>
<td>76(37-162)</td>
</tr>
<tr>
<td>Median period with epilepsy (range) y</td>
<td>24(2-62)</td>
<td>18(3-54)</td>
</tr>
<tr>
<td>Mean No. of antiepilepsy drugs ever taken (range)</td>
<td>6.5(2-20)</td>
<td>6.0(1-14)</td>
</tr>
</tbody>
</table>

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.

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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

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 placebo) 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<=.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 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=.69 vs 16mg x 2; p=.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<.001 and p<.002, respectively).

Adverse events

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=107</th>
<th>16mg x 2 n=106</th>
<th>8mg x 4 n=105</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>0.9</td>
<td>9.4*</td>
<td>10.5*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.8</td>
<td>9.4*</td>
<td>3.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.9</td>
<td>7.5*</td>
<td>9.5*</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>0.9</td>
<td>0.9</td>
<td>7.6*</td>
</tr>
<tr>
<td>Amnesia</td>
<td>0.9</td>
<td>6.6*</td>
<td>4.8</td>
</tr>
<tr>
<td>Other pain</td>
<td>2.8</td>
<td>9.4*</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* P<=.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).
Abbott Laboratories, North Chicago Ill.

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.

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.

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

Patients appear to be randomised and blinded to study treatment, as were investigators. Similar proportions of patients dropped out of each of the study groups and an intent-to-treat analysis was conducted.

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

Reference number 996  Study Type Randomised Controlled Trial  RID: 531

Randomized, controlled clinical trial of zonisamide as adjunctive treatment for refractory partial seizures

Number of subjects 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

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

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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. Starting dose 7mg/kg/d titrated up to a maximum of 400 to 600mg/d.

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

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>All partial</th>
<th>Complex partial</th>
<th>All seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in seizure frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>n = 74</td>
<td>n = 72</td>
<td>n = 74</td>
</tr>
<tr>
<td></td>
<td>−4.7%</td>
<td>0.5%</td>
<td>−6.6%</td>
</tr>
<tr>
<td>ZNS</td>
<td>n = 78</td>
<td>n = 78</td>
<td>n = 78</td>
</tr>
<tr>
<td></td>
<td>28.9%</td>
<td>27.4%</td>
<td>25.5%</td>
</tr>
<tr>
<td>p Value</td>
<td>0.0009</td>
<td>0.0007</td>
<td>0.0005</td>
</tr>
<tr>
<td>Responder rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>n = 74</td>
<td>n = 72</td>
<td>n = 74</td>
</tr>
<tr>
<td></td>
<td>16.2%</td>
<td>13.9%</td>
<td>16.2%</td>
</tr>
<tr>
<td>ZNS</td>
<td>n = 78</td>
<td>n = 78</td>
<td>n = 78</td>
</tr>
<tr>
<td></td>
<td>26.9%</td>
<td>30.8%</td>
<td>28.2%</td>
</tr>
<tr>
<td>p Value</td>
<td>0.1141</td>
<td>0.0159</td>
<td>0.0796</td>
</tr>
</tbody>
</table>

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.

Funding
Dainippon Pharmaceutical Company and Elan Pharmaceuticals, Inc.

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?
The study 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.

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All patients had an unequivocal history of partial seizures.

Randomisation and concealment of allocation methods are well described and clear. The risk of selection and performance bias are low. There is a risk of attrition bias for some outcomes: more patients dropped out of the zonisamide group, but an intent to treat analysis was conducted. And outcomes were measured in a valid and reliable manner. Therefore, the risk of detection bias is low.

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

Reference number: 4733

Study Type: Randomised Controlled Trial

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

1990 6

Epilepsy Res

PGS 221 226

Number of subjects: 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), phenobarbital (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.2 Starting doses were chosen depending on co-medication; the LTG dosages for the 2 patient types were: (a) 50 mg twice daily rising to 100 mg twice daily by week 2 for those not taking sodium valproate; (b) 25 mg twice daily rising to 50 mg twice daily by week 2 for those taking sodium valproate. For patients without adverse effects, and who had had less than 50% reduction in seizures during the first 4 weeks of treatment, the protocol enabled an increase in lamotrigine or placebo dose by 50%.

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 studies: 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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 0-4</th>
<th>Week 5-8</th>
<th>Week 9-12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gener. Total</td>
<td>Gener. Total</td>
<td>Gener. Total</td>
<td>Gener. Total</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>76</td>
<td>371</td>
<td>72</td>
<td>450</td>
</tr>
<tr>
<td>Placebo</td>
<td>66</td>
<td>344</td>
<td>53</td>
<td>298</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Placebo</th>
<th>Lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Diplopia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Funding

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.

Does the question answer the question?

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.

Effect due to factor in study?

The study comprised patients with severe epilepsy who all had partial complex seizures with or without generalized seizures.

How directly applicable to population of the guideline?

Very little detail is given on randomisation and concealment of allocation in this crossover study. The risk of selection and performance bias is unclear. Nurses in the residential home reported on seizures rather than patients but the method of reporting is not described. Therefore, the risk of detection bias is unclear. However, the doses used in the two groups were within the limits of the usual therapeutic doses for that drugs.

Schachter SC; Leppik IE; Matsuo F; Messenheimer JA; Faught E; Moore EL;

Reference number 4775

Lamotrigine: a six-month, placebo-controlled, safety and tolerance study.

1995 8

Number of subjects

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

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine (N=334)</th>
<th>Placebo (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:</td>
<td>173(52%)</td>
<td>63(56%)</td>
</tr>
<tr>
<td>Mean age:</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Range:</td>
<td>18-64</td>
<td>18-64</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>290(87%)</td>
<td>96(86%)</td>
</tr>
<tr>
<td>Black</td>
<td>33(10%)</td>
<td>10(9%)</td>
</tr>
<tr>
<td>Other</td>
<td>11(3%)</td>
<td>6(5%)</td>
</tr>
<tr>
<td>Duration of epilepsy (year)</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Mean age of epilepsy onset (year)</td>
<td>12</td>
<td>11.5</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 concomitant AED</td>
<td>43%</td>
<td>46%</td>
</tr>
<tr>
<td>2 concomitant AEDs</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>3 concomitant AEDs</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>38%</td>
<td>45%</td>
</tr>
<tr>
<td>Primidone</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>13%</td>
<td>14%</td>
</tr>
</tbody>
</table>

### Recruitment:
Patients were recruited from 34 centres

### Setting:
Multicentre – 34 centres.

### Interventions/Test Factor being investigated
Lamotrigine twice daily (to 500 mg/day)
Placebo

### Comparisons
All patients received 1-3 marketed AEDs (except VPA)

### 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 studies
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%

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>LTG</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>167/334(50%)</td>
<td>20/112(18%), p≤0.05</td>
</tr>
<tr>
<td>Diplopia</td>
<td>110/334(33%)</td>
<td>12/112(11%), p≤0.05</td>
</tr>
<tr>
<td>Ataxia</td>
<td>80/334(24%)</td>
<td>6/112(5%), p≤0.05</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>77/334(23%)</td>
<td>10/112(9%), p≤0.05</td>
</tr>
<tr>
<td>Nausea</td>
<td>73/334(22%)</td>
<td>17/112(15%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>47/334(14%)</td>
<td>8/112(7%), p≤0.05</td>
</tr>
<tr>
<td>Coordination abnormality</td>
<td>40/334(12%)</td>
<td>7/112(6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>33/334(10%)</td>
<td>6/112(5%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>33/334(10%)</td>
<td>6/112(5%)</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>23/334(7%)</td>
<td>15/112(13%)</td>
</tr>
</tbody>
</table>

23 December 2011
Boroughs Wellcome (one of the companies merged to form GSK)

LTG doses \( \leq 500\text{mg/day} \) are well tolerated as an add on therapy for a 6-month treatment period in outpatients with refractory partial seizures.

No power calculation given but there was a good sample size.

The placebo group received identical looking medications and a matching titration schedule. Unclear risk of selection bias due to unclear randomisation method. Low attrition bias, as almost similar drop out rates were reported in the two groups.

**Schapel GJ;Beran RG;Vajda FJ;Berkovic SF;Mashford ML;Dunagan FM;Yuen WC;Davies G;**

**Reference number** 4758  **Study Type** Randomised Controlled Trial  **RID:** 228

Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures

1993  56  J Neurol Neurosurg Psychiatry  pgs 448 453

**Number of subjects**

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**

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) |

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

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

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

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)

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)

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 or 300mg daily) compared to placebo

Length of Study/ Follow-up 12 weeks
Outcome measures studies 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
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.

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).

Concomitant AED plasma concentrations were virtually unchanged.

There was a significant reduction in the number of seizure days on LTG (p<0.001)

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.

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 Mnesic functions)
Parametric statistical methods were impossible to use because of differing format of scores across tests ( scaled scores, percentiles, IQ scores...)

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.
GlaxoSmithKline

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?
First aim of study was to recruit 30 patients with 20 completing but subsequent information said that it would be too low so it was changed to 40-50 randomised (40 completing). Number randomised was n=41.

Internal Validity
Unclear risk of selection bias as randomisation method and allocation concealment not stated. Performance bias unclear; the study was double-blind throughout, except for the last 3 weeks of each washout period, when the study was single-blind. Both groups, patients on enzyme inducers and patients on enzyme inducers and valproate had received daily dosages within the limits of the usual therapeutic range. Unlikely risk of attrition bias as no drop outs were reported.

Sharief M; Viteri C; Ben-Menachem E; Weber M; Reife R; Pledger G; Karim R;

Reference number 4745 Study Type Randomised Controlled Trial RID: 215
Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy

Number of subjects 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Topiramate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>n=24</td>
<td>n=23</td>
<td>n=47</td>
</tr>
<tr>
<td>Men</td>
<td>19</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Age, y Mean (SD)</td>
<td>32.6(11.1)</td>
<td>35.4(14.0)</td>
<td>34(12.6)</td>
</tr>
<tr>
<td>Race</td>
<td>24</td>
<td>23</td>
<td>47</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Weight (kg)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73.1+/-12.3</td>
<td>74.9+/-12.4</td>
<td>74+/-12.2</td>
</tr>
</tbody>
</table>

Recruitment: Unknown
Setting: Sweden, Spain, UK and France

Interventions/Test Factor being investigated Safety and efficacy of topiramate as adjunctive therapy 400 mg/day.

Comparisons Topiramate vs. placebo
3 week titration and 8 week stabilization

Seizure type and frequency data and global evaluations of investigators and patients.

Internal Validity

Unclear risk of selection bias due to absence of randomisation method and allocation concealment. Unclear risk of detection bias because of the use of patient diaries that could result in inaccuracies. Global assessments are subjective. Unclear also is the risk of attrition bias on the validity of the study due the difference in the proportions of drop out rates between topiramate group (26%) and placebo (4%).

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.

Funding

Unknown

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.

How directly applicable to population of the guideline?

See GRADE

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

Reference number: 4742

Study Type: Randomised Controlled Trial

Number of subjects: 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.
- 18-65 years old
- Seizures persisted at least the previous 2 years despite treatment with 1-2 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**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LEV1000mg/d</th>
<th>LEV2000mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=112</td>
<td>N=106</td>
<td>N=106</td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD (yrs):</td>
<td>37±12</td>
<td>36±10</td>
<td>37±12</td>
</tr>
<tr>
<td>Males:</td>
<td>55(49%)</td>
<td>51(48%)</td>
<td>51(48%)</td>
</tr>
<tr>
<td>Weight±SD:</td>
<td>7±1.5</td>
<td>7±1.7</td>
<td>7±1.7</td>
</tr>
<tr>
<td>Duration of epilepsy (yrs):</td>
<td>23.2±11.0</td>
<td>23.8±12.3</td>
<td>23.6±13.3</td>
</tr>
<tr>
<td>Idiopathic/cryptogenic:</td>
<td>64(57.1%)</td>
<td>59(55.7%)</td>
<td>60(56.6%)</td>
</tr>
</tbody>
</table>

Seizure type:
- Simple partial: 40(36%) vs 31(29%) vs 30(28%)
- Complex partial: 93(83%) vs 84(79%) vs 93(88%)
- Secondary generalised: 26(23%) vs 28(26%) vs 29(27%)
- Others: 8(7%) vs 4(4%) vs 10(9%)

Median baseline seizures: 2.50 vs 2.82 vs 2.58

Number of concomitant AEDS:
- 1: 18(16%) vs 23(22%) vs 19(18%)
- 2: 88(79%) vs 76(72%) vs 83(78%)
- ≥3: 6(5%) vs 7(7%) vs 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 studies**
- 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**

Proportion of patients experiencing ≥50% reduction in partial seizure frequency (responder rate):
- 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

Proportion of seizure free patients:
- LEV 1000mg/day: 5/101 (5.0%)
- LEV 2000mg/day: 2/95 (2.0%)
- Placebo: 1/106 (0.9%)

Withdrawal due to adverse events:
- LEV 1000mg/day: 8/106 (7.5%)
- LEV 2000mg/day: 15/106 (14.2%)
- Placebo: 6/112 (5.4%)

Incidence of adverse events ≥10%:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LEV1000mg/day</th>
<th>LEV2000mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=112</td>
<td>N=106</td>
<td>N=106</td>
<td></td>
</tr>
<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>Aesthesia*:</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>

* "more commonly reported" in LEV groups

**Funding**
- UCB Pharma funded. Statistical analysis support from UCB.

**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

23 December 2011
Internal Validity

Unknown risk of selection bias as randomisation and concealment methods not clearly reported. Low risk of performance bias as study was double blinded. Unlikely risk of attrition bias as drop outs ranged from 11-18%. Low risk of detection bias.

Sivenius J;Kalviainen R;Ylinen A;Riekkinen P;

Reference number 4754  Study Type Randomised Controlled Trial  RID: 224

Double-blind study of Gabapentin in the treatment of partial seizures

1991  32  pgs 539  542

Number of subjects 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 studies Percentage of change of seizure frequency in the treatment group as compared with baseline

Results

<table>
<thead>
<tr>
<th>Seizure reduction %</th>
<th>GBP 900 n(%)</th>
<th>GBP 1200 n(%)</th>
<th>Placebo n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worse</td>
<td>6(38)</td>
<td>0</td>
<td>5(27)</td>
</tr>
<tr>
<td>0-24</td>
<td>4(25)</td>
<td>2(22)</td>
<td>7(39)</td>
</tr>
<tr>
<td>25-49</td>
<td>4(25)</td>
<td>4(45)</td>
<td>3(17)</td>
</tr>
<tr>
<td>50-74</td>
<td>2(12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;75</td>
<td>0</td>
<td>3(33)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

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).

23 December 2011 Page 112 of 364
Parke Davis/Warner Lambert GBP appears to be effective in the treatment of partial epileptic seizures in a dosage-related manner.

Internal Validity
Unclear risk of selection bias: sequence generation method was not detailed and no details of allocation concealment. Low risk of performance bias as study was double blinded and unlikely risk of attrition bias as no drop out. Patient self reported seizure frequency could lack accuracy and affect on detection bias.

Funding
No power calculation given. This is a small study and should be repeated.

How directly applicable to population of the guideline?
See GRADE

Smith D; Baker G; Davies G; Dewey M; Chadwick DW;

Reference number 4694 Study Type Randomised Controlled Trial

Outcomes of add-on treatment with lamotrigine in partial epilepsy

1993 34 pgs 312 322


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.
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.

<table>
<thead>
<tr>
<th>Interventions/Test Factor being investigated</th>
<th>Comparisons</th>
<th>Length of Study/ Follow-up</th>
<th>Outcome measures studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of responders; reported as number of patients in the given response categories with LTG compared with placebo</td>
<td>Total: 46 weeks, Baseline 4 weeks, Treatment period 1: 18 weeks, Washout: 6 weeks, Treatment period 2: 18 weeks, Washout: 4 weeks</td>
<td>Seizure frequency; seizure severity; health-related quality of life; neuropsychological tests; number of patients responding.</td>
<td>Proportion of responders; reported as number of patients in the given response categories with LTG compared with placebo:</td>
<td></td>
</tr>
<tr>
<td>Intervention 1: First-phase data LTG (n = 41): 4/41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-phase data: Total seizures (n = 62): Worse (&gt;26% increase): n = 7 No change (±25%): n = 26 Mild improvement (26–49% decrease): n = 18 Marked improvement (≥ 50% decrease): n = 11 Partial seizures (n = 62): Worse (&gt;26% increase): n = 10 No change (±25%): n = 23 Mild improvement (26–49% decrease): n = 17 Marked improvement (≥ 50% decrease): n = 12 Secondarily generalised seizures (n = 36): Worse (&gt;26% increase): n = 4 No change (±25%): n = 17 Mild improvement (26–49% decrease): n = 5 Marked improvement (≥ 50% decrease): n = 10 Comparator First-phase data placebo (n = 40): 1/40 End-phase data: not reported</td>
<td>Change in seizure frequency; percentage seizure reduction comparing LTG with placebo:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td>Intervention 1: LTG (n = 53) PERCEPT: mean = 25.19 ICTAL: mean = 19.47</td>
<td>23 December 2011 Page 114 of 364</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 liability (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 liability (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)

Funding
Industry: GlaxoSmithKline.

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.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Crossover study.
ILAE 1981 classification used for seizures; diary used for classification of seizures
frequency.
Linked studies: Industry trial report (Adults HTA 378); abstracts (Adults HTA 376, 377).
Randomisation mentioned but does not say how this was done. Unclear the risk of
selection bias.

Steiner TJ;Dellaportas CI;Findley LJ;Gross M;Gibberd FB;Perkin GD;Park
DM;Abbott R;

Reference number 4705 Study Type Randomised Controlled Trial RID: 286
Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin
1999 40 PG5 601 607

Number of subjects
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.

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**Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>LTG, n=86</th>
<th>PHT, n=95</th>
<th>All, n=181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>55/45</td>
<td>57/43</td>
<td>56/44</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>28 (13-70)</td>
<td>27 (13-74)</td>
<td>28(13-74)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Age at first seizure (yr)</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

**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.

Capsules of high and low strengths of both drugs: LTG 50 and 25mg; PHT 100 and 50mg, once daily at night; the doses for the first 2 weeks were LTG 100mg, and PHT 200mg and these were increased to 150 and 300mg, respectively for the second 2 weeks, then the dose of either drug could be increased by one capsule if seizure control was inadequate and no clinically significant adverse events.

**Comparisons**

Comparison between lamotrigine and phenytoin.

**Results**

6 week titration and a treatment phase for less than or equal to 48 weeks.

**Outcome measures studies**

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.

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.

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%.

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%.

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).

Adverse events led to discontinuation of 13 (15%) patients from LTG and 18 (19%) from PHT.

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

**PHT**
- Asthenia: 28/95*
- Rash: 12/95
- Headache: 9/95
- Dizziness: 8/95
- Somnolence: 6/95*
- Ataxia: 0/95

* P<0.05
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.

Wellcome Foundation Ltd.

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

90% power calculation required n=86 in each group. The number randomised was n=86 and n=95. However there was a 15% and 19% drop-out.

See GRADE

Selection bias: high/unclear risk of bias - no details of randomisation method or allocation concealment.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: unknown risk of bias - diaries used to assess seizure frequency.

Stolarek I; Blacklaw J; Forrest G; Brodie MJ;

Vigabatrin and lamotrigine in refractory epilepsy

1994 57 J Neurol Neurosurg Psychiatry pgs 921 924

Number of subjects 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 Total length of treatment for placebo for lamotrigine was 12 weeks, in increasing dose (from 25 mg twice daily to 50 mg twice daily and then 100 mg twice daily). The patients were followed up during treatments (week 0, 4, 8 and 12).

Outcome measures studies This was not stated
Funding was not stated. The lamotrigine and placebo tablets were supplied by Wellcome Trust. There was no statistically difference in number of adverse events between the two treatment arms for this very small cross over RCT.

Internal Validity
This was a cross-over, dose ranging study. After an initial 4-weeks run in, two 12 week treatment periods were followed by 4 week washout period. Baseline data not reported. One patient had dropped out from the study because of side effects while on the placebo arm and this was not included in the analysis. The doses used in all three phases (Phase I: 25mg twice daily, Phase II: 50 mg daily, Phase III: 100 mg daily) were within the limits of usual daily dose (100-200mg/daily).

The analysis was carried out using Wilcoxon ranked test for matched pairs. Selection bias: Unclear risk of bias - as no details of randomisation method or allocation concealment. Low risk of performance, attrition and detection bias.

Result
Proportion of patients with at least 50% reduction in seizure:
Phase I: 25 mg twice daily : 3/20(15%)
Phase II: 50 mg twice daily : 7/20(35%)
Phase III: 100mg twice daily : 9/20 (45%)
Overall - 12 weeks: 4/20 (20%)
(p values not reported in paper)

Number of seizure free patients: 3, while on 100 mg twice daily lamotrigine. This was not reported for placebo or other treatment doses.

Withdrawal from study : 1/22 on placebo arm (due to adverse events)

Outcomes related to cognitive effects:
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)

16/20 patients preferred the LTG treatment

There were no significant difference in the total number of requested or spontaneously reported side effects 6 for lamotrigine and 7 for placebo.

Funding was not stated. The lamotrigine and placebo tablets were supplied by Wellcome Trust.

There was no statistically difference in number of adverse events between the two treatment arms for this very small cross over RCT

Funding

Does the study answer the question?

No power calculation given.

Effect due to factor in study?

See GRADE.

How directly applicable to population of the guideline?

Tanganelli P;Regesta G;

Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study

Reference number 4692 Study Type Randomised Controlled Trial

Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study

Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study

Number of subjects
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.

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Internal Validity
Unclear the risk of selection bias as no allocation concealment is reported. Unclear the risk of performance bias due to lack of blindness. The maximum doses given for both drugs were slightly higher than the maximum doses recommended (vigabatin max given 3.5g/daily, max recommended 3g/daily, carbamazepine max given 1.4g/daily, max recommended 1.2g/daily).

Tassinari CA; Michelucci R; Chauvel P; Chodkiewicz J; Shorvon S; Henriksen O; Dam M; Reife R; Pledger G; Karim R;

Reference number 4688  
Study Type Randomised Controlled Trial  
RID. 161

Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy

1996 37  
Number of subjects 60-30 in each arm

Inclusion/Exclusion 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 or 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
Condition being investigated: TPM 600mg, titrated over 4 weeks from 100mg/day to 100mg bd, 200mg bd to 300 mg bd, vs placebo
Mean dose in the TPM group: 519.3 (57% used 600mg TPM)

Comparisons
Adjunctive: TPM vs placebo

Length of Study/ Follow-up
8 weeks baseline, plus 12 weeks treatment (including 4 week of titration)

Outcome measures
Not stated

Results
Proportion of seizure free participants
TPM: 0/30
Placebo: 0/30
P value: NS

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

The proportion of participants having treatment withdrawn due to adverse events:
TPM: 4/30
Placebo: 1/30

Incidence of adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>TPM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=30, [%]</td>
<td>n=30, [%]</td>
</tr>
<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>
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<tr>
<td>Weight decrease</td>
<td>2[7]</td>
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</tr>
<tr>
<td>Confusion</td>
<td>0[0]</td>
<td>4[13]</td>
</tr>
</tbody>
</table>
Johnson Pharmaceutical

Internal Validity

No details of randomisation, allocation concealment and blinding methods. Unclear risk of selection and performance bias. Unclear risk of attrition bias due to difference in the drop out rates between the two groups.

Funding

Johnson Pharmaceutical

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

How directly applicable to population of the guideline?

No indirectness ascertained.

Summary of baseline demographic characteristics for the intention-to-treat population of 94 randomized patients

<table>
<thead>
<tr>
<th>Demographic characteristic</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>0.146 d</td>
</tr>
<tr>
<td>Number of females (%)</td>
<td>30 (63.8%)</td>
<td>22 (46.8%)</td>
<td></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>
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<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>
</tbody>
</table>

Tsai JJ; Yen DJ; Hsih MS; Chen SS; Hiersemenzel R; Edrich P; Lai CW;

Reference number 437

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

2006 Jan

Number of subjects

n=94 (n=47 in LEV group and n=47 in placebo group)

Inclusion/Exclusion Criteria:

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.

Patient Characteristics

Summary of baseline demographic characteristics for the intention-to-treat population of 94 randomized patients

RID: 416

Reference number 437

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

2006 Jan

Number of subjects

n=94 (n=47 in LEV group and n=47 in placebo group)

Inclusion/Exclusion Criteria:

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.

Patient Characteristics

Summary of baseline demographic characteristics for the intention-to-treat population of 94 randomized patients

<table>
<thead>
<tr>
<th>Demographic characteristic</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>0.146 d</td>
</tr>
<tr>
<td>Number of females (%)</td>
<td>30 (63.8%)</td>
<td>22 (46.8%)</td>
<td></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>
</tbody>
</table>
Age at onset (yr)                                      14.3 (±8.5)            13.1 (±8.7)          0.499
Cause unknown
[number (% of patients] 13 (27.7%)            20 (42.6%)          0.194
Withdrawal seizures
[number (% of patients] 4 (8.5%)            7 (14.9%)           0.523
Status epilepticus
[number (% of patients] 6 (12.8%)            10 (21.3%)          0.411
Documentation of spikes or
Spike–waves on EEG
[number (% of patients] 41 (87.2%)            45 (95.7%)          0.267
Baseline seizure frequency per week
Partial seizures Mean (SD) 4.0 (±14.1)            4.0 (±5.6)
Median (interquartile range) 1.6 (1.2–2.5)        2.0 (1.1–3.9)        0.378
Total seizures Mean (SD) 4.0 (±14.1)            4.3 (±7.0)
Median (interquartile range) 1.6 (1.2–2.5)        2.0 (1.1–3.9)        0.378
Number of concomitant AEDs taken by patients
(overall study) [number (% of patients]
One 7 (14.9%)            11 (23.4%)        0.314
Two 19 (40.4%)            18 (38.3%)
Three 21 (44.7%)        16 (34.0%)
Four or more 0 (0.0%)        2 (4.3%)
Recruitment: Not reported.
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 studies
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 0.6 (−0.1 to 1.4) 0.3 (−0.2 to 0.7) 0.129
(absolute decrease from baseline)b
Weekly seizure frequency 45.4 (−13.1 to 76.9) 15.6 (−5.7 to 41.4) 0.010
(percentage decrease from baseline)c
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 week 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
Adjunctive LEV therapy, <=1000mg twice daily, was significantly more effective than placebo in Taiwanese adults with treatment-resistant partial-onset seizures.

### Least square mean

<table>
<thead>
<tr>
<th></th>
<th>LEV (n = 47)</th>
<th>PLA (n = 47)</th>
<th>LEV (n = 47)</th>
<th>PLA (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% reduction over placebo</td>
<td>24.1% (95% CI, 10.6%–35.6%)</td>
<td>0.001% reduction over placebo</td>
<td>24.1% (95% CI, 10.6%–35.6%)</td>
<td>0.001% reduction over placebo</td>
</tr>
<tr>
<td>Weekly seizure frequency (absolute decrease from baseline)</td>
<td>0.6 (−0.1–1.4)</td>
<td>0.3 (−0.2–0.7)</td>
<td>0.129</td>
<td></td>
</tr>
<tr>
<td>Weekly seizure frequency (percent decrease from baseline)</td>
<td>45.4 (−13.1–76.9)</td>
<td>15.6 (−5.7–39.1)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients free of seizures</td>
<td>4 (8.5%); [47]</td>
<td>0 (0.0); [47]</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>Number of seizure-free days per 4 wks</td>
<td>24.2 (±3.3); [46]</td>
<td>21.3 (±6.4); [46]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LEV, levetiracetam; NA, not applicable; PLA, placebo.

*Values in square brackets indicate numbers of evaluable patients.

### Adverse events

Number (%) of patients with adverse events observed with an incidence of ≥5% during the evaluation period (data for the intention-to-treat population)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>LEV (n = 47)</th>
<th>PLA (n = 47)</th>
<th>LEV (n = 47)</th>
<th>PLA (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>19a (40.4%)</td>
<td>7 (14.9%)</td>
<td>19a (40.4%)</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (14.9%)</td>
<td>4 (8.5%)</td>
<td>5 (10.6%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (10.6%)</td>
<td>4 (8.5%)</td>
<td>3 (6.4%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>4 (8.5%)</td>
<td>2 (4.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>3 (6.4%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (6.4%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (4.3%)</td>
<td>6 (12.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociation (psychiatric)</td>
<td>0</td>
<td>3 (6.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0</td>
<td>3 (6.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG, electrocardiogram; LEV, levetiracetam; PLA, placebo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse events considered at least possibly related to study medication by the investigator.

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).

Not reported.

### Funding

Yes. Adjunctive LEV therapy, <=1000mg 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.

### How directly applicable to population of the guideline?

All patients had a diagnosis of partial-onset seizures with or without secondary generalization.

Risk of selection and performance bias is low. The study clearly describes methods used to ensure randomisation and blinding. Risk of attrition bias is low: very few dropped out and an ITT analysis was performed. Outcomes were measured in a valid way and investigators were blind to treatment. Risk of detection bias is low.
Which drug for the adult epileptic patient: phenytoin or valproate?

1985 290  Br Med J (Clin Res Ed) pg$ 815 819

Number of subjects 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

<table>
<thead>
<tr>
<th></th>
<th>Valproate (70 patients)</th>
<th>Phenytoin (70 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16-69 (30 median)</td>
<td>16-70 (30 median)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Male</td>
<td>34</td>
<td>39</td>
</tr>
</tbody>
</table>

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 studies

Achievement of a two year remission and 'time to first seizure'.

Results

<table>
<thead>
<tr>
<th>Results</th>
<th>Valproate</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>No achieving 2 year remission</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>No controlled for &lt;2 years</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>No continuing to have seizures</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Idiosyncratic adverse effect requiring drug withdrawal</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-compliant or lost to follow-up</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

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.

Funding Sanofi
This study showed no major difference in efficacy between sodium valproate and phenytoin in adults with recent onset of epilepsy.

No power calculation given but sample size was 70 in each arm.

Selection bias: high risk of bias - allocation concealment and method of randomisation not reported.
Performance bias: high risk of bias - does not report blinding of allocation.
Attrition bias: unclear/unknown risk of bias - no ITT analysis.
Detection bias: high risk of bias - no blinding reported, unusual outcomes - no achieving 2 year remission and no. controlled for under 2 years.

UK Gabapentin Study Group.

Gabapentin in partial epilepsy.

1990 335

Number of subjects 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. 1200mg gabapentin.
Comparisons Gabapentin vs. placebo
Length of Study/ Follow-up 12 weeks
Outcome measures studies 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 ration for gabapentin (-0.192)was significantly better than the ration of -0.060 for placebo (p=0.0056) by analysis of variance.

Funding Unknown
Gabapentin is an effective additional treatment for patients with partial epilepsy refractory to standard therapy.

Sample size required was n=120, and the number randomised was n=127.

Selection bias: no details of randomisation and unclear allocation concealment.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.

Uthman BM; Rowan AJ; Ahmann PA; Leppik IE; Schachter SC; Sommerville KW; Shu V;

Reference number 4760 Study Type Randomised Controlled Trial RID: 230

Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial

1998 55 Arch Neurol pgs 56 62

Number of subjects 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)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M ratio, %</td>
<td>42:58</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>34.0 (12.0-77.0)†</td>
</tr>
<tr>
<td>Medical history, median (range)</td>
<td></td>
</tr>
<tr>
<td>History of epilepsy, y</td>
<td>22.9 (1.4-65.8)</td>
</tr>
<tr>
<td>No. of different AEDs ever taken</td>
<td>7.0 (2.0-20.0)</td>
</tr>
<tr>
<td>Concomitant AEDs, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>As monotherapy</td>
<td>77 (26)</td>
</tr>
<tr>
<td>Combined with other AED</td>
<td>128 (43)</td>
</tr>
<tr>
<td>Phenytoin sodium</td>
<td></td>
</tr>
<tr>
<td>As monotherapy</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Combined with other AED</td>
<td>69 (23)</td>
</tr>
<tr>
<td>Divalproex sodium§</td>
<td>79 (27)</td>
</tr>
<tr>
<td>Primidone</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>76 (26)</td>
</tr>
</tbody>
</table>

*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.

Unknown.

21 treatment sites in the United States.

Tiagabine in four daily doses: 16mg, 32mg or 56mg as adjunctive therapy to currently used AEDs.

The comparison is between the 3 doses of tiagabine and placebo as adjunctive therapy.

**Interventions/Test / Factor being investigated**

- 32 weeks: a 12 week baseline phase, a four week titration phase and a 16 week maintenance period.

- 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.

- 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 >=50% Seizure**

<table>
<thead>
<tr>
<th>Reduction</th>
<th>Median Change</th>
<th>P vs Placebo</th>
<th>Median % Change</th>
<th>No. (%)</th>
<th>P vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.7</td>
<td>. .</td>
<td>-11</td>
<td>4 (4)</td>
<td>. .</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>-0.8</td>
<td>.44</td>
<td>-13</td>
<td>5 (8)</td>
<td>.42</td>
</tr>
<tr>
<td>16 mg/d</td>
<td>-2.2</td>
<td>.03</td>
<td>-25†</td>
<td>17 (20)</td>
<td>.002</td>
</tr>
<tr>
<td>32 mg/d</td>
<td>-2.8</td>
<td>.03</td>
<td>-33‡</td>
<td>16 (29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>56 mg/d</td>
<td>-2.3</td>
<td>.04</td>
<td>-23.7</td>
<td>11 (28.2)</td>
<td>.03</td>
</tr>
<tr>
<td>32 and 56 mg/d, combined</td>
<td>-2.6</td>
<td>.004</td>
<td>-25.0</td>
<td>29 (35.4)</td>
<td>.001</td>
</tr>
</tbody>
</table>

*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 >=50% Seizure**

<table>
<thead>
<tr>
<th>Reduction</th>
<th>Median Change</th>
<th>P vs Placebo</th>
<th>Median % Change</th>
<th>No. (%)</th>
<th>P vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.9</td>
<td>. .</td>
<td>10.5</td>
<td>5 (9.8)</td>
<td>. .</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>-2.3</td>
<td>.001</td>
<td>-23.7</td>
<td>11 (28.2)</td>
<td>.03</td>
</tr>
<tr>
<td>16 mg/d</td>
<td>-1.7</td>
<td>.04</td>
<td>-12.4</td>
<td>17 (34.7)</td>
<td>.003</td>
</tr>
<tr>
<td>32 mg/d</td>
<td>-3.3</td>
<td>.003</td>
<td>-36.3</td>
<td>12 (36.4)</td>
<td>.005</td>
</tr>
<tr>
<td>56 mg/d</td>
<td>-3.3</td>
<td>.003</td>
<td>-36.3</td>
<td>12 (36.4)</td>
<td>.005</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23 December 2011  Page 129 of 364
Adverse Events for Which Significant Differences Between Tiagabine and Placebo Groups Were Observed*

<table>
<thead>
<tr>
<th>Adverse Event†</th>
<th>Placebo Group (n=91)</th>
<th>16 mg/d (n=61)</th>
<th>32 mg/d (n=88)</th>
<th>56 mg/d (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>15 (16)</td>
<td>18 (30) [.71]</td>
<td>29 (33) [.02]</td>
<td>17 (30) [.07]</td>
</tr>
<tr>
<td>Tremor</td>
<td>3 (3)</td>
<td>6 (10) [.16]</td>
<td>13 (15) [.008]</td>
<td>12 (21) [.001]</td>
</tr>
<tr>
<td>Abnormal thinking‡</td>
<td>3 (3)</td>
<td>2 (3) [.99]</td>
<td>7 (8) [.21]</td>
<td>8 (14) [.02]</td>
</tr>
<tr>
<td>Depression</td>
<td>0</td>
<td>4 (7) [.02]</td>
<td>2 (2) [.24]</td>
<td>4 (7) [.02]</td>
</tr>
</tbody>
</table>

*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.

Funding
Abbott Laboratories; the study drugs were also provided by Abbott Laboratories.

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.

How directly applicable to population of the guideline?
All patients had had at least 6 complex partial seizures in the 8 weeks preceding study enrolment.

Internal Validity
Unclear risk of selection bias as unclear randomisation details and no details of allocation concealment. Low risk of performance bias. The risk of attrition bias is high due to high drop-out. The study documents the numbers of patients withdrawing from treatment and an intent to treat analysis is performed. Outcomes are measured in a valid and reliable manner and treatment is concealed: risk of detection bias appears to be low.

Wu XY; Hong Z; Wu X; Wu LW; Wang XF; Zhou D; Zhao ZX; Lv CZ;

Reference number 4841 Study Type Randomised Controlled Trial
Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in Chinese patients with refractory partial-onset seizures
2009 50
Mar

Number of subjects 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>
<thead>
<tr>
<th></th>
<th>Placebo (n=100)</th>
<th>LEV (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), mean (SD)</strong></td>
<td>32.8 (11.9)</td>
<td>32.7 (13.4)</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>16–64</td>
<td>15–70</td>
</tr>
<tr>
<td><strong>Gender, male, n (%)</strong></td>
<td>54 (54.0)</td>
<td>51 (50.0)</td>
</tr>
<tr>
<td><strong>Weight (kg), mean (SD)</strong></td>
<td>63.2 (13.6)</td>
<td>60.7 (11.6)</td>
</tr>
<tr>
<td><strong>Age at onset of epilepsy (years), mean (SD)</strong></td>
<td>15.2 (10.9)</td>
<td>16.0 (11.0)</td>
</tr>
<tr>
<td><strong>Duration of epilepsy (years), mean (SD)</strong></td>
<td>17.3 (12.1)</td>
<td>16.5 (12.7)</td>
</tr>
<tr>
<td><strong>Seizure type at baseline, n (%)</strong></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>

*a n=99, bUsed by >=5% of patients in either treatment group.

AED, antiepileptic drug; LEV, levetiracetam; SD, standard deviation.

### 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 studies

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)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=100)</th>
<th>LEV (n=102)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Historical baseline weekly seizure frequency</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1–Q3)</td>
<td>1.75 (1.13–4.00)</td>
<td>1.81 (1.13–3.38)</td>
<td></td>
</tr>
<tr>
<td>Treatment period weekly seizure frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Q1–Q3)</td>
<td>1.74 (0.90–3.67)</td>
<td>0.85 (0.25–2.54)</td>
<td></td>
</tr>
<tr>
<td>Transformed LSmean 1.23 0.92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage reduction over placebo (95% CI)</td>
<td>&lt;0.001</td>
<td>26.8% (14.0–37.7)</td>
<td></td>
</tr>
<tr>
<td>Absolute reduction in weekly seizure frequency from historical baseline</td>
<td>&lt;0.001</td>
<td>0.29 (-1.25–0.81)</td>
<td>0.91 (0.02–1.75)</td>
</tr>
</tbody>
</table>
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; LS mean, 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)

<table>
<thead>
<tr>
<th>Number (%) of patients</th>
<th>Placebo (n=103)</th>
<th>LEV (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one TEAE</td>
<td>62 (60.2)</td>
<td>65 (63.1)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>18 (17.5)</td>
<td>18 (17.5)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>10 (9.7)</td>
<td>10 (9.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (13.6)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (8.7)</td>
<td>4 (3.9)</td>
</tr>
</tbody>
</table>

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.

UCB Pharma SA.

Funding

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.

How directly applicable to population of the guideline?
All patients had a diagnosis of partial-onset seizures.

Internal Validity

The risk of selection and performance bias is unknown because there is no description of methods of randomisation, concealment of allocation or blinding. Risk of attrition bias is low. There were very few patients withdrawing from the study and an ITT analysis was conducted. Outcomes were measured in a valid and reliable way. Therefore, low risk of attrition or detection bias.

Xiao Z; Li JM; Wang XF; Xiao F; Xi ZQ; Lv Y; Sun HB;

23 December 2011
Page 132 of 364
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

Demographics

LEV, n=28 Placebo, n=28

Gender (male): 12 (42.9%) 12 (45.9%)
Age, years, mean±SD 32.8±11.2 (17-60) 32.5±11.2 (12-58)
Weight, kg, mean±SD 58.4±9.5 (43-82) 58.1±14.6 (41-102)
Asian 28 (100%) 28 (100%)

Epilepsy aetiology

Cause unknown 23 (82.1%) 17 (60.7%)
Age at onset: 18.6±9.4 (2-40) 16.3±11.2 (1-41)
Duration of epilepsy: 14.1±9.4 (2-40) 16.1±12.5 (2-48)
Baseline frequency of seizure: 4.9±7.3 (1-23.6) 5.6±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. Levetiracetam 1000mg/day (administered twice daily), increased to 2000mg/day after 2 weeks and 3000mg/day (maintenance dose) after 3 weeks

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 studies
Primary outcome: weekly frequency of partial seizures (logarithmically transformed)
Secondary:
- Absolute and % reduction in frequency/week
- 50% responder rate
- Number and % of seizure free patients and number of seizure free days/4 weeks.

Results
Proportion of seizure free participants:
LEV: 3/28 (10.7)
Placebo: 2/28 (7.1%)
P = NS

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

The proportion of participants having treatment withdrawn because of adverse events:
LEV: 0/28 (0%)
Placebo: 0/28 (0%)
P = NS

The proportion of participants having treatment withdrawn because of lack of efficacy:
LEV: 0/28 (0%)
Placebo: 0/28 (0%)
P = NS

Incidence of adverse events more than 10% in each arm:

<table>
<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>

Internal Validity
Randomisation code generated by study sponsor. Unclear risk of selection bias due to allocation concealment not clearly described. Low risk of performance bias as the blinding was adequate.
Appropriate statistical tests- log transformation was conducted to normalise data. Low attrition and detection bias.

Funding
UCB pharmacy, Netherlands

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.

How directly applicable to population of the guideline?
Uncertain – baseline frequency of epileptic episodes is a minimum of 4 /month. Is this the typical frequency(severity)?

Yamauchi T; Kaneko S; Yagi K; Sase S;

Reference number 362
Study Type Randomised Controlled Trial
RID: 406

Treatment of partial seizures with gabapentin: double-blind, placebo-controlled, parallel-group study

23 December 2011
### Patient Characteristics

Demographic and baseline disease characteristics†

<table>
<thead>
<tr>
<th>1800</th>
<th>Placebo</th>
<th>Gabapentin (mg/day) 1200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled patients</td>
<td>82</td>
<td>86</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (51.2)</td>
<td>37 (43.0)</td>
</tr>
<tr>
<td>Female</td>
<td>40 (48.8)</td>
<td>49 (57.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>18–44</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>45–64</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>≥65</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>31.8 ± 11.3</td>
<td>31.3 ± 10.6</td>
</tr>
<tr>
<td>Bodyweight (kg) (mean ± SD)</td>
<td>59.3 ± 11.5</td>
<td>59.4 ± 11.1</td>
</tr>
<tr>
<td>Type of seizure (n/%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP</td>
<td>44 (58.7)</td>
<td>44 (55.0)</td>
</tr>
<tr>
<td>CP</td>
<td>67 (89.3)</td>
<td>66 (82.5)</td>
</tr>
<tr>
<td>SG</td>
<td>25 (33.3)</td>
<td>21 (26.3)</td>
</tr>
<tr>
<td>Duration of epilepsy† (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19.5</td>
<td>19.8</td>
</tr>
<tr>
<td>Range</td>
<td>2.1–47.0</td>
<td>4.0–42.0</td>
</tr>
<tr>
<td>Baseline seizure (per 28 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>19.9</td>
<td>31.6</td>
</tr>
<tr>
<td>Median</td>
<td>9.7</td>
<td>11.2</td>
</tr>
<tr>
<td>Range</td>
<td>3.3–289.7</td>
<td>2.7–564.3</td>
</tr>
<tr>
<td>Concomitant AED, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>16 (19.5)</td>
<td>12 (14.0)</td>
</tr>
<tr>
<td>Two</td>
<td>66 (80.5)</td>
<td>74 (86.0)</td>
</tr>
</tbody>
</table>

**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.
Primary outcome: response ratio (RRatio).\[RRatio = \frac{T - B}{T + B},\] 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.

Efficacy results for the per-protocol set population

<table>
<thead>
<tr>
<th>Efficacy parameters</th>
<th>Gabapentin (n = 75)</th>
<th>Placebo (n = 80)</th>
<th>1200 mg/day (n = 35)</th>
<th>1800 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>% change in partial seizures†</td>
<td>Mean</td>
<td>2.6</td>
<td>-17.8</td>
<td>-22.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>-9.7</td>
<td>-21.2</td>
<td>-27.9</td>
</tr>
<tr>
<td>Responder rate‡, n (%)</td>
<td>5 (6.7)</td>
<td>13 (16.3)</td>
<td>7 (20.0)</td>
<td></td>
</tr>
<tr>
<td>Improvement in seizure frequency§, n (%)</td>
<td>Completely resolved</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Markedly improved</td>
<td>0</td>
<td>2 (2.5)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td></td>
<td>Moderately improved</td>
<td>5 (6.7)</td>
<td>11 (13.8)</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td></td>
<td>Slightly improved</td>
<td>17 (22.7)</td>
<td>22 (27.5)</td>
<td>13 (37.1)</td>
</tr>
<tr>
<td></td>
<td>No change</td>
<td>23 (30.7)</td>
<td>29 (36.3)</td>
<td>7 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Worse</td>
<td>30 (40.0)</td>
<td>16 (20.0)</td>
<td>8 (22.9)</td>
</tr>
</tbody>
</table>

† Percent change in partial seizures (PCH) was calculated by the formula: PCH (%) = \(\frac{100(T - B)}{B}\), 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).

Not reported.

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.

Yes. The sample size for the study was determined from the RRatio obtained in previous studies.

All patients enrolled in this study had refractory epilepsy with partial seizures.

The study has an unclear risk of selection bias as no details of allocation concealment or sequence generation method. Low risk of performance bias. There is a small risk of attrition bias: small numbers of patients withdrew before study end but they were not included in the efficacy analysis.
### 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, sd (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: 4/6/1/2, mean 2.48, sd 0.90
- Placebo: 1/7/1/4, mean 2.78, sd 0.80

**Specific AEDs used (carbamazepine/valproate/lamotrigine/phenytin):**
- 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)

### Results

- **Proportion of patients experiencing at least 50% reduction in complex partial seizures:**
  - Topiramate: 11/23
  - Placebo: 3/23
  (Auras or simple partial seizures were not included in analysis)

- **Proportion of patient having treatment withdrawn due to adverse events:**
  - Topiramate: 2/23
  - Placebo: 2/23

**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).

**Incidence of adverse events (>10% per treatment arm):**
- **Dizziness/somnolence:**
  - Topiramate: 4/23
  - Placebo: 2/23

- **Headache:**
  - Topiramate: 1/23
  - Placebo: 3/23

### Funding

- **Grant from Taipei Veterans General Hospital and Yen Tjing Ling Medical Foundation.**
- Topiramate and placebo tablets provided by Jassen Cilag Taiwan.
Topiramate (at 300mg) was more effective than placebo as an adjunct therapy in reducing complex partial seizures among patients refractory to stabilised AED treatments.

Internal Validity
Unclear risk of selection bias as the method of randomisation and allocation concealment was not clearly reported. Low/unclear risk of detection bias. Low risk of performance bias.

Does the study answer the question?

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.

How directly applicable to population of the guideline?
Direct
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

Reference number 4728

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.

Number of subjects n=59 (n=29 in Topiramate and n=30 in the valproate group)

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

<table>
<thead>
<tr>
<th></th>
<th>Topiramate (n = 24)</th>
<th>Valproate (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.7 (10.2)</td>
<td>39.4 (11.4)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>63</td>
<td>52</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.9 (17.5)</td>
<td>76.2 (18.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.2 (13.0)</td>
<td>172.1 (10.4)</td>
</tr>
<tr>
<td>Duration of epilepsy time since first seizure (years)</td>
<td>18.3 (12.4)</td>
<td>22.7 (16.0)</td>
</tr>
<tr>
<td>Median baseline seizure rate (all seizures)</td>
<td>5.9 per month</td>
<td>5.8 per month</td>
</tr>
<tr>
<td>CBZ average daily dose (baseline medication) (mg/d)</td>
<td>1070.8 (411.23)</td>
<td>1231.0 (409.79)</td>
</tr>
<tr>
<td>Study medication average dose during maintenance (ug/d)</td>
<td>251.1 TPM (101.8)</td>
<td>1384 VPA (377.0)</td>
</tr>
</tbody>
</table>

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.

Target dose is 200 to 400mg in the topiramate drug. Drug is introduced at 25mg and increased with weekly 25mg/d increments to a minimum of 200mg/d. Then individual titration up to 400mg/d or maximum tolerated dose.

Comparisons

The comparison is between topiramate and valproate up to their maximum tolerated doses as adjunctive therapy to carbamazepine.

Length of Study/ Follow-up Outcome measures studies

22 weeks: 2 week baseline phase, 12 week titration phase and 8 week maintenance phase.

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.
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.

Not reported.

Methods of randomisation are well described. However, participants and neurologists who administered the study drug were not blind to patient treatment: clinicians and patients were not.

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.

All patients who were enrolled had localization-related epilepsy with partial-onset seizures.

Methods of randomisation are well described. However, participants and neurologists who administered the study drug were not blind to treatment. Therefore, there is some risk of selection and performance bias. There were more patients who withdrew in the topiramate group but an ITT analysis was performed and so the risk of attrition bias is low. The investigators who performed the cognitive tests were kept blind to treatment although it is not clear if clinicians who recorded adverse events were kept blind to treatment. Therefore the risk of detection bias is unknown.

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

**Reference number** 4604
**Study Type** Randomised Controlled Trial
**RID:** 70

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

**Number of subjects**
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

<table>
<thead>
<tr>
<th>Gender</th>
<th>Total (n=247)</th>
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<tbody>
<tr>
<td>male</td>
<td>134 (54.3%)</td>
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<tr>
<td>female</td>
<td>113 (45.7%)</td>
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</table>

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Mean +/- SD</th>
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<tbody>
<tr>
<td></td>
<td>8.4 +/- 2.6</td>
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<table>
<thead>
<tr>
<th>Race</th>
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<tr>
<td>White</td>
<td>226 (91.5%)</td>
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<tr>
<td>Other</td>
<td>21 (8.5%)</td>
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</table>

Recruitment: Not described

Setting: 54 centres in Europe, South 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 studies 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).

Funding Parke Davis

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? No power calculation given. Sample sizes were 128 and 119.

How directly applicable to population of the guideline? See GRADE

Internal Validity Unclear risk of selection bias due to absence of reporting on allocation concealment or randomisation method. Unclear risk of performance bias as both groups were treated equally but no details of blinding. Although the drop out rates were comparable within the three groups, it is unclear the risk of attrition bias and its impact on the statistical power of the study.

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

Reference number 4701 Study Type Randomised Controlled Trial RID: 173

Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy
Number of subjects: 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 (IEEA 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

<table>
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<tr>
<th></th>
<th>OXC 600mg/day</th>
<th>OXC 200mg/day</th>
<th>OXC 2400mg/day</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>51.2</td>
<td>45.2</td>
<td>56.3</td>
<td>44.5</td>
</tr>
<tr>
<td>Mean age, yr (range):</td>
<td>34.6(15-65)</td>
<td>33.8(16-64)</td>
<td>35.2(15-66)</td>
<td>34.3(15-65)</td>
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<tr>
<td>Mean weight kg (range):</td>
<td>73.1(44-139)</td>
<td>70.5(45-135)</td>
<td>70.9(44-131)</td>
<td>70.2(35-120)</td>
</tr>
<tr>
<td>Median 28 days baseline Seizure frequency:</td>
<td>9.6</td>
<td>9.8</td>
<td>10.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Median 28 days baseline secondary generalised Seizure frequency:</td>
<td>3.5 (n=49)</td>
<td>2.0(n=68)</td>
<td>2.4(n=60)</td>
<td>3.5(n=51)</td>
</tr>
</tbody>
</table>

Recruitment: Not stated.


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 Outcome measures studies

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.

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

Proportion of seizure free participants
- OXC 600mg/day: 5/168 (3%)
- OXC 1200mg/day: 18/177 (10%)
- OXC 2400mg/day: 38/174 (22%)
- Placebo: 1/173 (0.6%)
- P value: all statistically significant vs placebo

Proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders)
- OXC 600mg/day: 20/168(26.8%)
- OXC 1200mg/day: 64/177(41.2%)
- OXC 2400mg/day: 116/174(50.0%)
- Placebo: 15/173(12.7%)
- P value: all statistically significant vs placebo
The proportion of participants having treatment withdrawn due to unsatisfactory treatment effect
OXC 600mg/day: 1/168 (0.6%)
OXC 1200mg/day: not reported
OXC 2400mg/day: not reported
Placebo: 22/173 (12.7%)

The proportion of participants having treatment withdrawn due to adverse events
OXC 600mg/day: 20/168 (11.9%)
OXC 1200mg/day: 64/177 (36.2%)
OXC 2400mg/day: 116/174 (66.7%)
Placebo: 15/173 (8.7%)

P value:

Incidence of adverse events >10%

<table>
<thead>
<tr>
<th></th>
<th>OXC 600mg/day</th>
<th>OXC 1200mg/day</th>
<th>OXC 2400mg/day</th>
<th>Total</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>n=168</td>
<td>n=177</td>
<td>n=174</td>
<td>n=519</td>
<td>n=173</td>
</tr>
</tbody>
</table>

Funding
Novartis

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 no power calculation although there was a large sample size. There was an overall 295/694 (42.5%) dropout rate. The dropout rate for the 2400mg arm was 128/174 (73.6%)

How directly applicable to population of the guideline?
See GRADE.

Method of randomisation allocation, concealment and blinding not reported. Very high overall dropout rates (42.5%). 73.6% drop out from 2400mg arm. Very high risk of attrition bias.

Ben-Menachem E; Gabbai AA; Hufnagel A; Maia J; Almeida L; Soares-da-Silva P;

Reference number 5077 Study Type Randomised Controlled Trial
RID: 276

Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy

2010 89 Epilepsy Res pgs 278 285
May

23 December 2011 Page 143 of 364
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)

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 generalisations) 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.

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 studies
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%);
somnia 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%).
BIAL - Portela & Co, SA.

**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.

**How directly applicable to population of the guideline?**
Direct.

**Internal Validity**
Modified ITT analysis as it was those who were randomised and administered at least one dose of study medication and had at least one postbaseline seizure frequency assessment.
Selection bias: unclear risk of bias - no details of allocation concealment.
Performance bias: unclear risk of bias - no details of blinding.
Attrition bias: high risk of bias - high drop out in all arms, especially eslicarbazepine and was very high for eslicarbazepinie 1200mg.
Detection bias: unclear risk of bias.

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

**Reference number** 4277  
**Study Type** Randomised Controlled Trial  
**RID:** 50

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

2005  
pgs 475 480

**Number of subjects**  
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
12 weeks treatment period.

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.

Both TID and BID were more efficacious than placebo in reducing the frequency of partial-onset seizures (p≤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≤0.001) and BID (43%; p≤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=9%) (D= discontinuation): Dizziness n=43 (D=7), somnolence n=31 (D=6), ataxia n=17(D=3), weight gain n=21(D=1), amphotropia n=10 (D=2), asthenia n=14 (D=2), Diplopa 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), amblyopias n=19 (D=1), weight gain n=17(D=0) and asthenia n=13 (D=1), diplopa n=15 (D=1) and thinking abnormal n=12 (D=3).

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

Supported by Pfizer inc.

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

For 80% power the number randomised was required to be 80 in each group to acquire 70 participants in each group. The number randomised was 98, 103 and 111. There was a high drop-out in the BID group.

Unclear risk of selection bias - no details of randomisation and allocation concealment methods. Attrition bias risk: The risk of drop out due to AE was 2.5 to 4 times higher in the treatment group compared to placebo. Reasons for withdrawal not fully accounted. Low risk of performance and detection bias.
dose > 10% for at least 1 month before enrolment. Exclusion criteria: none listed.

### Patient Characteristics

<table>
<thead>
<tr>
<th>Interventions/Test</th>
<th>Factor being investigated</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=96</td>
<td>n=96</td>
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<td>Mean age at first seizure, y (SD)</td>
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<td>23.9 (15.6)</td>
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<td></td>
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<tr>
<td>Unclassified</td>
<td></td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mean number of seizures/month (SD)</td>
<td></td>
<td>4.3 (4.2)</td>
<td>3.7 (2.9)</td>
</tr>
<tr>
<td>Antiepileptic medication, n (%)</td>
<td></td>
<td>Carbamazepine</td>
<td>43 (45)</td>
</tr>
</tbody>
</table>

### 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.

### Study week Daily dose, mg

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine</th>
<th>Topiramate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
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</tr>
<tr>
<td>3</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td>8–16</td>
<td>500</td>
<td>300</td>
</tr>
</tbody>
</table>

### 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 studies
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

<table>
<thead>
<tr>
<th>Lamotrigine, n= 67</th>
<th>Topiramate, n = 57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td></td>
</tr>
</tbody>
</table>

Combined cognitive scores
Combined score using the sum of the rank of changes for all cognitive tests

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

23 December 2011 Page 147 of 364
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 non-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).

Funding

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.

How directly applicable to population of the guideline?

Yes. 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

The risk of selection bias and performance bias is unknown because the methods of randomisation and concealment are poorly described. However, the baseline demographics and characteristics are similar in both study arms. There is a high risk of attrition bias because fewer outcome data were available for the topiramate group (59% vs. 70%).

The maximum dose of lamotrigine was compared with a medium dose of topiramate - indirectness. Risk of bias favoring lamotrigine in terms of efficacy, risk of bias favouring topiramate in terms of safety.

Bourgeois B;Leppik IE;Sackellaes JC;Laxer K;Lesser R;Messenheimer JA;Kramer LD;Kamin M;Rosenberg A;

Reference number 4627  Study Type Randomised Controlled Trial  RID: 97

Felbamate: a double-blind controlled trial in patients undergoing presurgical evaluation of partial seizures

1993  43  pg 693  696

Number of subjects

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-gravida, 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, and...
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 was variable was the time to the fourth seizure. Secondarily the number of patients having a fourth seizure was reported.

The results confirmed the anticonvulsant activity of felbamate and its ability to quickly and safely reduce the occurrence of frequent partial onset seizures.

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).

Wallace Laboratories

The results confirmed the anticonvulsant activity of felbamate and its ability to quickly and safely reduce the occurrence of frequent partial onset seizures.

No power calculation given and n=30 and n=34 sample sizes per group.

See GRADE

High risk of selection bias; the randomization procedure was only poorly reported and there was no description of allocation concealment. Unclear the risk of performance bias as the study's blindness was poorly addressed.
Brodie MJ; Richens A; Yuen AW;

Reference number 4808  Study Type Randomised Controlled Trial

Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group

1995 345  pg 476 479

Feb 25

Number of subjects 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 studies 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).

Supported by the Welcome foundation.

Similar efficacy for both LTG and CBZ. LTG seems to be better tolerated.

Funding

Does the study answer the question?

Effect due to factor in study?

No.

How directly applicable to population of the guideline?

Yes.

Internal Validity

Selection bias: high risk of bias - no details of randomisation or concealment method.
Performance bias: unclear risk of bias - no details of blinding although states double-blinded.
Attrition bias: unclear risk of bias - more patients in the carbamazepine group dropped out than the lamotrigine group. No ITT analysis reported.
Detection bias: unclear risk of bias - no details of the double-blinding and outcome measures were not precisely defined.

Chmielewska B; Stelmasiak Z;

Ref: 4731 Study Type Randomised Controlled Trial

Clinical evaluation of Gabitril and Lamictal for drug-resistant epilepsy in adults

2001 56 Ann Univ Mariae Curie Sklodowska [Med] pgs 35 42

Number of subjects

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.

23 December 2011 Page 151 of 364
Lamotrigine versus tiagabine adjunctive treatment. LTG 378mg/day vs TGB 43mg/day

Between treatments.

Efficacy: >50% reduction of seizure frequency;
Tolerability: % of patients with at least one treatment emergent AE;
Quality of life.

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%): 9/26 (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%)

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.

How directly applicable to population of the guideline? Direct.

High risk of performance bias as it was an open study;
Unclear risk of selection bias as study was randomised but no further details on randomization were given. No mention of allocation concealment. Unclear risk of attrition bias as no mention on drop outs.

Cramer J; Ryan J; Chang J; Sommerville K;

Reference number 4697 Study Type Randomised Controlled Trial RID: 170

The short-term impact of adjunctive tiagabine on health-related quality of life

2001 Suppl 3

Number of subjects CBZ+PHT n=101 vs CBZ+TGB n=105;
PHT+CBZ n=76 vs PHT+TGB n=67.

Inclusion/Exclusion 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.
TIAGABINE, PHENITOIN AND CARBAMAZEPINE.

RANDOMISED TO ADJUNCTIVE THERAPY.

BETWEEN TREATMENTS. CBZ+PHT vs CBZ+TGB OR PHT+CBZ vs PHT+TGB.

16 WEEKS DUAL THERAPY (DOUBLE BLIND PHASE).

QOL OUTCOMES.

ABBOTT LABORATORIES.

YES.

INTERNAL VALIDITY

QOL OUTCOMES.

16 WEEKS DUAL THERAPY (DOUBLE BLIND PHASE).

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/ TATIGABINE AND PHENYTOIN ADJUNCTIVE TO PHENYTOIN GROUPS.

TGB vs CBZ:
At least 50% reduction in seizure frequency: 14/67 (20.9%) vs 33/76 (43.4%).

TGB vs PHT:
At least 50% reduction in seizure frequency: 23/105 (21.9%) vs 28/101 (27.7%).


LESS MALES IN CBZ+PHT GROUP THAN CBZ+TGB GROUP AND MORE IN THE PHT+CBZ COMPARED TO THE PHT/TGB GROUP.

SELECTION BIAS - UNCLEAR/HIGH RISK OF BIAS - DETAILS OF RANDOMISATION AND ALLOCATION CONCEALMENT NOT GIVEN.

PERFORMANCE BIAS - UNCLEAR/HIGH RISK OF BIAS - NO DETAILS OF BLINDING GIVEN.

ATTENTION BIAS - UNCLEAR/HIGH RISK OF BIAS - NO DETAILS OF DROP-OUT GIVEN.

DETECTION BIAS - UNCLEAR/HIGH RISK OF BIAS - NO DETAILS OF BLINDING GIVEN.

DIRECT.

DEAN C; MOSIER M; PENRY K;
Patient Characteristics

<table>
<thead>
<tr>
<th>VGB</th>
<th>placebo</th>
<th>1g VGB</th>
<th>3g VGB</th>
<th>6g VGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>45</td>
<td>45</td>
<td>43</td>
<td>41</td>
</tr>
</tbody>
</table>

Sex
- Male: n(%)  
  - Placebo: 17(38)
  - 1g VGB: 19(42)
  - 3g VGB: 24(56)
  - 6g VGB: 23(56)

Age (yr)
- Mean (SD): 35(11)  
  - Placebo: 34(9)
  - 1g VGB: 34(9)
  - 3g VGB: 35(11)

Weight (kg)
- Mean (SD): 69(15)  
  - Placebo: 76(19)
  - 1g VGB: 72(17)
  - 3g VGB: 75(18)

Number (%) of concurrent AEDs
- One: 19(42)  
  - Placebo: 24(53)
  - 1g VGB: 23(53)

- Two: 26(63)  
  - Placebo: 20(44)
  - 1g VGB: 20(47)

- Three: 0(0)  
  - Placebo: 0(0)
  - 1g VGB: 0(0)

Onset age (yr)
- Mean (SD): 13(10)  
  - Placebo: 10(8)
  - 1g VGB: 14(10)

Duration of epilepsy (yr)
- Mean (SD): 22(11)  
  - Placebo: 24(9)
  - 1g VGB: 20(9)

Seizure frequency
- Median (range): 9(3-71)  
  - Placebo: 8.5(3-786)
  - 1g VGB: 8(1-228)
  - 3g VGB: 9(2-45)

Recruitment: Unknown.
Setting: 14 investigative sites in the United States.

Comparison is between 3 doses of vigabatrin (VGB) (1, 3 or 6 g per day) and placebo as adjunctive therapy to currently used AEDs.

The comparisons are between three doses of VGB and placebo, on top of currently used AEDs.

Length of Study/ Follow-up
- Outcome measures studies
  - 30 weeks: 12 weeks pre-treatment period, 6 weeks titration and 12 weeks maintenance phase.
  - 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,
Marion Merrell Dow.

The risk of selection and performance bias is unclear: unclear methods of randomisation or concealment. The risk of attrition bias is unknown. Although 14% of patients dropped out before study completion, no breakdown by study arm is presented. The risk of detection bias is unknown: no information on blinding but measurement of primary outcome appears to be rigorous.

Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>Baseline median (95% CI)</th>
<th>End study median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>45</td>
<td>9.0 (7.0, 10.5)</td>
<td>8.8 (6.0, 12.1)</td>
</tr>
<tr>
<td>1 g VGB</td>
<td>45</td>
<td>8.5 (6.0, 12.3)</td>
<td>7.7 (4.1, 11.5)</td>
</tr>
<tr>
<td>3 g VGB</td>
<td>43</td>
<td>8.0 (7.0, 10.5)</td>
<td>3.7 (2.5, 6.0)</td>
</tr>
<tr>
<td>6 g VGB</td>
<td>41</td>
<td>9.0 (7.0, 14.5)</td>
<td>4.5 (3.3, 6.0)</td>
</tr>
</tbody>
</table>

Treatment comparisons

<table>
<thead>
<tr>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear trend 0.0001</td>
</tr>
<tr>
<td>Placebo versus 1 g VGB 0.1263</td>
</tr>
<tr>
<td>Placebo versus 3 g VGB 0.0001</td>
</tr>
<tr>
<td>Placebo versus 6 g VGB 0.0001</td>
</tr>
<tr>
<td>3 g VGB versus 6 g VGB 0.8140</td>
</tr>
<tr>
<td>(Placebo and 1 g VGB) versus (3 g VGB and 6 g VGB) 0.0001</td>
</tr>
</tbody>
</table>

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.

Funding

Marion Merrell Dow.

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.

How directly applicable to population of the guideline?

The population is relevant because only patients with partial seizures were recruited.
Dodrill CB; Arnett JL; Deaton R; Lenz GT; Sommerville KW;

Reference number 4695  
Study Type  Randomised Controlled Trial  
RID: 168

Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood

2000 42  Epilepsy Res

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Variable</th>
<th>Baseline CBZ group</th>
<th>Baseline PHT group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PHT added (n=71)</td>
<td>TGB added (n=82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CBZ added (n=66)</td>
<td>TGB added (n=58)</td>
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<tr>
<td>Years of age Mean</td>
<td>33.34</td>
<td>37.07</td>
<td>40.42</td>
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<tr>
<td>Age at seizure onset</td>
<td>12.73</td>
<td>12.23</td>
<td>20.45</td>
</tr>
<tr>
<td>S.D.</td>
<td>10.78</td>
<td>10.40</td>
<td>15.84</td>
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<td>Gender F</td>
<td>47</td>
<td>45</td>
<td>29</td>
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<tr>
<td>Baseline complex partial seizure frequency (seizures 28 days)</td>
<td>N 70 81 66 57</td>
<td>Median 7 6 6 7</td>
<td></td>
</tr>
<tr>
<td>Baseline total partial seizure frequency (seizures 28 days)</td>
<td>N 70 81 66 58</td>
<td>Median 10 7 8 9</td>
<td></td>
</tr>
<tr>
<td>Baseline generalized tonic-clonic seizures (seizures 28 days)</td>
<td>N 23 24 20 22</td>
<td>Median 2 2 2 1</td>
<td></td>
</tr>
</tbody>
</table>

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.

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 studies
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 TGC as add-on therapy in patients receiving PHT.
Two statistically significant differences were found in the measures of abilities with improvements with TGC versus worsening with CBZ on tests of verbal fluency and perceptual: motor speed. For measures of adjustment and mood, treatment with TGC 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.

Sponsored by Abbott Laboratories.

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.

How directly applicable to population of the guideline?
All patients in this study were included because they suffered from partial seizures.

Internal Validity
It is not possible to judge the risk of bias in this study. This study is an analysis of a subset of patients (79%) who were randomized into treatment groups in two RCTs. No details of the original RCT are available.

Dodrill CB; Arnett JL; Sommerville KW; Shu V;

Reference number 4764
Study Type Randomised Controlled Trial
RID: 234

Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy

1997 48 pg$ 1025 1031

Number of subjects
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.
24 weeks: baseline period of 8 weeks and 4 week titration phase, followed by 12 week fixed dose phase.

Not clearly stated. This study compared changes from baseline testing with the testing at the end of the drug treatment period of the combined higher dose (32 and 56mg) tiagabine groups compared with placebo group for all psychological tests (n=11).

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).

Supported by Abbot Laboratories.

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.

No. All results could have occurred by chance. No statistical power calculation was performed. And no primary outcome measure specified.

The study included only patients with complex partial seizures.

There is a very high risk of bias in this study. For the purposes of this study 162 patients out of a total of 297 study subjects had neuropsychological testing. This was due to various administrative reasons: e.g. some pts entered the study before such testing was instituted. The sample is non random because for example, in 8 sites no neuropsychological testing was done at all.

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**Doedrill CB;Arnett JL;Sommerville KW;Sussman NM;**

**Reference number 4766**

**Study Type** Randomised Controlled Trial

**Evaluation of the effects of vigabatrin on cognitive abilities and quality of life in epilepsy**

1993 43  pgs 2501 2507

**Number of subjects**

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:**

See data entry for study by French et al, Reference Manager ID 4752.

**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**

23 December 2011  Page 158 of 364

Tests of cognitive abilities

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.

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.

Vigabatrin appears to have little impact upon tests of either cognitive abilities or quality of life.

See data entry for study by French et al, Reference Manager ID 4752.

Internal Validity

See reference 4752 for details of original RCT.

Dodrill CB; Arnett JL; Sommerville KW; Sussman NM;

Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy

1995 36

CGB 1g/day n=45; VGB 3g/day n=43; VGB 6g/day n=41; placebo n=45.

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) vs 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.

Setting: USA.

Recruitment: From 14 major medical centres.
Vigabatrin versus placebo. 1g, 3g or 6g vigabatrin.

Comparisons
Between treatment and placebo.

Length of Study/ Follow-up
Not reported.

Outcome measures
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-bewildernent, 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.

Funding
Marion Merrell Power.

Does the study answer the question?
Yes for cognitive outcomes and quality of life outcomes.

Effect due to factor in study?
No power calculation given and sample size was n=146 (n=40, n=36, n=38, n=32).

How directly applicable to population of the guideline?
Direct.

More females in placebo than the vigabatrin groups.

Selection bias - unclear risk of bias - no details of randomisation or allocation concealment.

Performance bias - low risk of bias.

Attrition bias - unclear/high risk of bias - higher drop-out in VGB 1g (20%) and VGB 6g (22%) than VGB 3g (12%) or placebo (11%).

Detection bias - low risk of bias.

Elger C; Bialer M; Cramer JA; Maia J; Almeida L; Soares-da-Silva P;

Funding
Marion Merrell Power.
Inclusion/Exclusion Criteria: 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. 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

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. Daily doses of ESL were increased at 4 week periods; 400mg, 800 and 1200mg.

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 studies

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

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 ESL once a day group (800mg) and 13% in the ESL 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.

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).

Does the study answer the question?

A higher proportion of seizure free patients found in the ELS treatment group taking once daily compared to placebo.

A significantly higher proportion of patients received ESL once daily had 50% or more reduction in seizure frequency compared to placebo.

No significant differences in reduction of seizure frequency were found between the ESL group twice daily and the placebo.

Funding

BIAL (Portela & C SA).

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.
**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**

<table>
<thead>
<tr>
<th>Reference number</th>
<th>4863</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Type</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>RID:</td>
<td>828</td>
</tr>
</tbody>
</table>

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

**Patient Characteristics**

Patient population was consisted of adults $\geq 18$ 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 $\geq 21$ 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/mmm$^3$, 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.

**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**

12 weeks then 4 weeks tapering off period.

**Outcome measures studies**

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 $> 25\%$ seizure exacerbation.
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%).

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%).

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%).

22% of patients in the placebo group showed exacerbation in seizure frequency than in any of the other ESL groups (<=12% in all groups).

**Funding**

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.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Unknown risk of selection bias as no adequate concealment of allocation is reported. Randomization was performed through generation of randomization codes (computerized). The randomization rate was 1:1:1:1 and the two groups were well matched for demographic and baseline disease characteristics. Low risk of performance bias as the study was double blind and all comparison groups received the same care apart the intervention. However, high risk of attrition bias (the responder rate in the ITT was significantly higher in the ESL 1200mg group and the ESL 800mg group compared the placebo. Low risk of detection bias. The three doses used were within the limits of usual therapeutic dosology.

**Fakhoury TA; Hammer AE; Vuong A; Messenheimer JA;**

**Reference number** 671  
**Study Type** Randomised Controlled Trial  
**RID:** 457

Efficacy and tolerability of conversion to monotherapy with lamotrigine compared with valproate and carbamazepine in patients with epilepsy

2004 5  
Aug

**Number of subjects**

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 clinician determined appropriate candidates for add-on therapy with lamotrigine, carbamazepine or valproate; and possible candidates for conversion to monotherapy with lamotrigine, carbamazepine, or valproate;

Exclusion criteria:

- Females only eligible if had negative urine or serum pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were incapable of bearing children.
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 (22%).

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
28 weeks (includes dose escalation 4 weeks, 8 weeks stabilisation, 8 week withdrawal phase, 8 week monotherapy phase).

Outcome measures
% of patients receiving sustainable monotherapy with study medication; % seizure fee 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%)

Funding
GlaxosmithKline.

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.

How directly applicable to population of the guideline? 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
Open study. Designed as two parallel arms (LTG vs CBZ and LTG vs VPA). No power calculation.
Selection bias - unclear/high risk of bias - no details randomisation or allocation concealment.
Performance bias - high risk of bias - unblinded study.
Attrition bias - high risk of bias as high drop-out rate in the LTG vs VPA ARM (over 20%).
Detection bias - high risk of bias - unblinded study.
Patient Characteristics

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Vigabatrin (n=22)</th>
<th>Placebo (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>29(17-59)</td>
<td>27(16-55)</td>
</tr>
<tr>
<td>Age at onset median</td>
<td>11(2-34)</td>
<td>10(1-22)</td>
</tr>
</tbody>
</table>

Twenty one women and 24 men, age range 15 to 61 years. N=35 had 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.

Comparisons

Vigabatrin is compared to placebo as adjunctive therapy to currently used AEDs.

Results

Seizure control

Seizure frequency at baseline and during double blind treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Weeks 12 to 20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPS</td>
<td>CPS</td>
</tr>
<tr>
<td>Placebo group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Back transformed mean</td>
<td>4.37</td>
<td>8.55</td>
</tr>
<tr>
<td>Range</td>
<td>0-55</td>
<td>0-124</td>
</tr>
<tr>
<td>Vigabatrin group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Back transformed mean</td>
<td>5.46</td>
<td>9.72</td>
</tr>
<tr>
<td>Range</td>
<td>0-91</td>
<td>0-38</td>
</tr>
</tbody>
</table>

* 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.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Vigabatrin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Mild depression</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Double vision</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Impaired memory</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

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.

Marion Merrell Dow.

Jawad S; Richens A; Goodwin G; Yuen WC;

Reference number 4757  
Study Type Randomised Controlled Trial  
Controlled trial of lamotrigine (Lamictal) for refractory partial seizures  
1989 30  
Number of subjects 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): 28.3 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 studies

>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.

Internal Validity
Unclear risk of selection bias (no details of randomization method and allocation concealment). Unclear risk of performance bias. Crossover study design low risk of attrition bias. The dose used was within the acceptable limits of usual therapeutic maintenance dose.

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

Reference number 4702 Study Type Randomised Controlled Trial RID: 174
Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized, controlled study
1995 52 Arch Neurol pg 989 996

Number of subjects 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. Vigabatrin group: during a 2-month titration phase, the daily dose of vigabatrin was increased to a mean level of 50mg/kg;
Carbamazepine group: during a 2-month titration phase, the daily dose of carbamazepine was increased to a plasma level of 35μmol/L

Comparisons Treatment versus treatment.

Length of Study/ Follow-up 12 months.
Outcome measures studies Efficacy: proportion of seizure freedom; proportion of responders; Safety: adverse events; visual evoked potential recordings and neuropsychological evaluation.

23 December 2011 Page 168 of 364
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.

Not reported.

Internal Validity

Selection bias: unclear risk of bias - no details of allocation concealment.
Performance bias: unclear/high risk of bias - no blinding.
Attrition bias: low risk of bias.
Detection bias: unclear/high risk of bias - no blinding.

Funding

Does the study answer the question?

Yes.

Effect due to factor in study?

No power calculation given. Sample size was 50 participants in each group.

How directly applicable to population of the guideline?

See GRADE.

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 (3g/daily).
Comparison is made on the seizure frequencies between Vigabatrin and placebo groups.

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.

>50% reduction in seizure frequency, adverse events, patient preference for drug/placebo.

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

Not mentioned.

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%.

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.

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 monotheapy (9 carbamazepine, 1 phenytoin, 1 valproate) and 13 were on two AEDs (10 carbamazepine, 6 primidone, 4 valproate, 4 phenytoin, 2 Phenobarbital.

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**
4 week run-in; 24 weeks treatment (2x 12 week treatment periods).

**Outcome measures studies**
>50% reduction in seizure frequency VGB compared to placebo; withdrawal due to adverse events; incidence of adverse events.

**Results**

<table>
<thead>
<tr>
<th>Outcome measures studies</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50% reduction in seizure frequency:</td>
<td></td>
</tr>
<tr>
<td>All seizures (n=19)</td>
<td></td>
</tr>
<tr>
<td>Phase 1: 9</td>
<td></td>
</tr>
<tr>
<td>Phase 2: 6</td>
<td></td>
</tr>
<tr>
<td>overall: 8</td>
<td></td>
</tr>
<tr>
<td>Partial seizures (n=17)</td>
<td></td>
</tr>
<tr>
<td>phase 1: 7</td>
<td></td>
</tr>
<tr>
<td>phase 2: 6</td>
<td></td>
</tr>
<tr>
<td>overall: 8</td>
<td></td>
</tr>
<tr>
<td>GTCs (n=12)</td>
<td></td>
</tr>
<tr>
<td>phase 1: 3</td>
<td></td>
</tr>
<tr>
<td>phase 2: 3</td>
<td></td>
</tr>
<tr>
<td>overall: 3</td>
<td></td>
</tr>
</tbody>
</table>

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.

**Withdrawal due to adverse events:** VGB 1/24 vs placebo 0/24.

**Funding**
Marrion merrell Dow.

**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.

**How directly applicable to population of the guideline?**
Direct.

**Internal Validity**
Selection bias: unclear/high risk of bias - no details of randomisation or allocation concealment.
Performance bias: low risk of bias.
Attrition bias: unclear/low risk of bias - 3 dropouts but unsure which arm they are from.
Detection bias: unclear risk of bias - no details of blinding of assessors.

**Meador KJ;Loring DW;Huh K;Gallagher BB;King DW;**
Reference number 4653 Study Type Randomised Controlled Trial RID: 123
Comparative cognitive effects of anticonvulsants

23 December 2011 Page 171 of 364
15 patients in three equal groups using a randomised triple crossover design

Inclusion: partial complex epilepsy
Exclusion: Not described

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).

Unknown, Georgia, USA

The neuropsychological effects of carbamazepine (CBZ), Phenobarbital (PB) and Phenytoin (PT)

Comparisons are made re the neuropsychological effects of carbamazepine (CBZ), Phenobarbital (PB) and Phenytoin (PT)

9 months; each crossover period was 3 months

The neuropsychological tests included: Digit Span, Selective Reminding Test, Digit Symbol, Finger Tapping, Grooved Pegboard, Choice Reaction Time, P3 evoked potential and Profile of Mood States.

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).

Ciba-Geigy Corporation

This study shows that patients receiving CBZ, PB and PT have comparable neuropsychological performance on most measures.

Due to small sample size this study should be repeated. However, the evaluation was very thorough.

See GRADE

High/unclear risk of selection bias - no details of randomisation and allocation concealment. High/unclear risk of performance bias - no details of blinding. High risk of attrition bias as almost 1/3 of patients in the sample dropped out of the study. No information on how this 1/3 distributed in the three groups.

Meador KJ; Loring DW; Hulihan JF; Kamin M; Karim R; CAPSS-027 S;

Reference number 602
Study Type Randomised Controlled Trial
RID: 41

Differential cognitive and behavioral effects of topiramate and valproate

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
Completers,*
ITT TPM VPA Placebo
n=34 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/day
Topiramate was initiated with 50 mg/d and escalated over 8 weeks to 400 mg/d or the maximum tolerated dose. Valproate was initiated with 250 mg/d and escalated to 2,250 mg/d or the maximum tolerated dose.

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
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
<table>
<thead>
<tr>
<th></th>
<th>TPM</th>
<th>VPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory difficulty</td>
<td>6 (18)</td>
<td>5 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Speech difficulty</td>
<td>4 (12)</td>
<td>2 (7)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Concentration/attention difficulty</td>
<td>3 (9)</td>
<td>3 (10)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (18)</td>
<td>4 (14)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Confusion</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Language problems</td>
<td>2 (6)</td>
<td>2 (7)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Other cognitive problems</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are n (%).

Funding
Ortho McNeil Pharmaceutical KJM
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.

How directly applicable to population of the guideline?

Patients had partial-onset seizures during the baseline phase.

Methods of randomisation and concealment of allocation are described and risk of selection and performance bias is low. Only 79% of patients in the topiramate group had neuropsychometric testing and were included in the analysis. There is a high risk of attrition bias and detection bias.

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

Reference number 4755

Study Type Randomised Controlled Trial

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

1994 35

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:

Inclusion criteria:
18-65 years old.
Simple or partial seizures (CPS, with or without secondarily generalised seizures) - ILAE classification 1981.

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.

Patient Characteristics

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.

By treatment sequence:

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.

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
Comparisons
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.
Seizure frequency.
Seizure days.
Number withdrawn.
Adverse events.

Statistical analyses found no evidence of a significant treatment-by-period interaction.

Proportion of responders (median seizure frequency reduction of 50% or higher compared to placebo during the lamotrigine maintenance period (percentage/range): 20% (13-27%).

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).

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%).

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%

Five occurred more frequently - ataxia, dizziness, diplopia, somnolence and rash (p<0.05) with lamotrigine than placebo.

Not mentioned in the study but HTA (2005) for adults says this was funded by GlaxoSmithKline.

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.

No power calculation given. Sample sizes: n=46 and n=52.

Direct. The dose used was within the limits of usual therapeutic dose.

Unclear risk of selection bias as no details given on randomisation and allocation concealment methods were given. The mean dose used was 317mg/day (>=400mg/daily) which is within the usual therapeutic dosage proposed (200-400mg/daily). Low risk of performance and attrition bias.
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).

Comparison of antiepileptic properties of carbamazepine (CBM or Tegretol) and clonazepam (CLP or Rivotril). 6mg 900 mg carbamazepine divided in three daily doses. For patients under 18 years, carbamazepine was given to 15 mg/kg.

Unknown

This study indicates clonazepam and carbamazepine to be equally effective in the treatment of newly diagnosed and previously untreated patients with psychomotor epilepsy.

Internal Validity

No details on method of randomisation or allocation concealment so the risk of selection bias is unclear. High risk of attrition bias as the drop out rates were high (26% and 41%) that would compromise the statistical power of the study.

Pina-Garza JE; Nordli DR; Rating D; Yang H; Schiemann-Delgado J; Duncan B;

Reference number: 5321

Adjunctive levetiracetam in infants and young children with refractory partial-onset seizures

2009 May

LEV n=60 and PLA n=56

23 December 2011
Pediatric patients aged 1 month < 4 years were eligible if they had partial-onset seizures inadequately controlled by one or two AEDs. Subjects must have experienced at least two partial onset seizures, with or without secondary generalisation, during each 7 day period during the 2 weeks prior to entering the study. Subjects aged 6 months to > 4 years must have had at least two partial onset seizures during baseline 48h video EEG accompanied by a corresponding clinical event.

Exclusion: a diagnosis of a treatable seizure etiology: status epilepticus that required hospitalization during the month before the baseline visit; current diagnosis of Lennox-Gastaut syndrom; epilepsy secondary to a progressive cerebral or neurodegenerative disease; a history of or the presence of pseudoseizures; previous use of levetiracetam; and clinically significant abnormal laboratory value or medical condition.

**Inclusion/Exclusion Criteria:**

**Recruitment:** Not reported

**Setting:** 62 centres in 13 countries

**Interventions/Test Factor being investigated**

48-h inpatient baseline video-EEG (electroencephalography) and a 5-day inpatient treatment period (1-day up-titration; 48-h evaluation video-EEG in the last 2 days). Children who experienced at least two partial-onset seizures during the 48-h baseline video-EEG were randomized to either levetiracetam [40 mg/kg/day (age 1 to <6 months); 50 mg/kg/day (age >6 months to <4 years)] or placebo.

**Comparisons**

Levetiracetam versus placebo.

**Length of Study/ Follow-up**

Up to 24 days

**Outcome measures studies**

Greater than 50% reduction in daily partial onset seizure frequency.

**Results**

116 patients were randomized [60 levetiracetam; 56 placebo; intent-to-treat (ITT) population], and 111 completed the study. The responder rate in average daily partial-onset seizures frequency (48-h video-EEG monitoring; primary efficacy variable) was 43.1% for levetiracetam [modified ITT (mITT) = 58] versus 19.6% for placebo (mITT = 51; p=0.013), with odds ratio for response 3.11 [95% confidence interval (CI), 1.22-8.26].

The median percent reduction from baseline in average daily partial-onset seizure frequency was 43.6% for levetiracetam and 7.1% for placebo with a median difference between treatment groups of 39.2% (95% CI, 17.5-62.2; p < 0.001). In general, levetiracetam was well tolerated. Treatment-emergent adverse events were reported by 55.0% levetiracetam- and 44.6% placebo-treated patients (ITT population).

**Funding**

UCB sponsored

**Does the study answer the question?**

Add on evidence for LEV in young children with partial seizures.

**Effect due to factor in study?**

Sample size calculated based on the primary efficacy variable of responder rate to detect a 26.5% difference between the responder rates in the two treatment groups, assuming that 40% of the levetiracetam-treated and 13.5% of the placebo-treated participants responded to treatment.

**How directly applicable to population of the guideline?**

Direct trial

**Internal Validity**

No adequate details on randomisation and blinding. Short treatment and evaluation period.
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.

Withdrawal because seizure frequency exceeded escape criteria; adverse events:

Not reported. This study gives withdrawal numbers and adverse events only and is a very small sample size.

Internal Validity
Selection bias: high risk - mention of randomisation but no method mentioned and no details of allocation concealment.
Performance bias: double-blinded but no details of methods. Very small sample and unbalanced.
Attrition bias: high risk - high drop-out as only three completed study.

Patient Characteristics
Diagnosis of epilepsy with at least six complex partial seizures in the 8 weeks before screening and were undergoing evaluation for epilepsy surgery.

Recruitment:
At a single centre in the UK. Undergoing evaluation for epilepsy surgery.

Interventions/Test / Factor being investigated
Tiagabine versus placebo. 2 achieved 66mg/day and a third reached 42mg/day.

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 studies
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;

Funding
Not reported.

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.

How directly applicable to population of the guideline?
Direct.

Schachter SC;
Detection bias: double-blinded but no details of methods. Presurgery study (Binnie et al) reported in this review of 3 studies, however it stated that this study was unpublished and the other two studies were either not randomised or dosage studies.

### 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.

### Inclusion/Exclusion Criteria:

- **Inclusion criteria:**
  - Completed an evaluation for epilepsy surgery;
  - 2-10 partial seizures within 48 hours of randomisation, including at least one 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 2 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.

### Recruitment:

- Patients who were to undergo pre surgical evaluations.

### Setting:

- Not reported.
Oxcarbazepine versus placebo. OXC 2400 mg/day. (1200mg twice daily).

Between treatment and placebo comparison.

10 days treatment. Patients could enter an open-label extension trial.

Primary: time to meeting one of the exit criteria. Secondary % of patients who met one of the exit criteria.

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

Sponsored by Ciba-Geigy Corporation (Novartis Pharmaceuticals Corporation)

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.

How directly applicable to population of the guideline?
Direct.

Unclear the risk of selection bias as study did not report allocation concealment.
The validity of the monotherapy design used was compromised as lorazepam could be administered as add on therapy if necessary to maintain seizure frequency in a safe range.
Performance bias - low risk of bias.
Attrition bias - low risk of bias.
Detection bias - low risk of bias.

Schmidt D; Jacob R; Loiseau P; Deisenhammer E; Klinger D; Despland A; Egli M; Bauer G; Stenzel E; Blankenhorn V;

Reference number 1113
Study Type Randomised Controlled Trial
RID: 551
Zonisamide for add-on treatment of refractory partial epilepsy: a European double-blind trial

1993 May
Epilepsy Res
pp5 67 73

Number of subjects Zonisamide group n=71;
Placebo group n=68;

23 December 2011 Page 181 of 364
**Patient Characteristics**

**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;

**Inclusion/Exclusion Criteria:**

- 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 studies**

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**

>=50% decrease in number of seizures:

Zonisamide versus placebo:

- 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).

10 patients (1.5%) treated with zonisamide had a 75% reduction in seizure frequency.

**Funding**

Not reported.

**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?**

No power calculation was given but the sample size was 139 participants.
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.

Randomisation by blocks of 4 during the 12-week double-blind phase. Unclear risk of selection bias as study was randomized but no allocation concealment was mentioned. Low risk of attrition and detection bias.

Sethi A; Chandra D; Puri V; Mallika V;

Reference number 903  Study Type Randomised Controlled Trial  RID: 502

Gabapentin and lamotrigine in Indian patients of partial epilepsy refractory to carbamazepine

2002 Sep 50  Neurol India  pgs 359 363

Number of subjects 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

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.

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.

Recruitment:

Not reported.

Setting:

India.

Interventions/Test Factor being investigated

Gabapentin and lamotrigine as adjunctive therapy to carbamazepine. Target dose not reported. Gabapentin was administered in a dose of 300 mg on day one, followed by 300 mg twice daily on day 2. there after an increment of 300 mg was made daily till seizures were controlled or the toxic effect appeared. The seizures were called as controlled if there was 50 % reduction in the seizures frequency or total control of seizures. Lamotrigine was added to the treatment regimen in a dose of 50 mg per day for first two weeks followed by 50 mg twice daily for next 2 weeks. Subsequently, at every two weeks interval, increase of 50 to 100 mg per day was made until the similar criteria for seizures control were achieved.

Comparisons

Comparisons are made between gabapentin and lamotrigine as adjunctive therapy to carbamazepine.

Length of Study/ Follow-up Outcome measures studies

Add on therapy was administered for 12 weeks. Length of baseline period and titration period not reported. It is unclear whether the add-on period included a titration phase.

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

Primary outcome.

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.

Subgroup analysis

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).

Adverse events

The most commonly occurring adverse events were dizziness, headache and drowsiness in both groups. However, skin hypersensitivity reaction only occurred in the lamotrigine group.

Unknown. 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.

The study population consisted of patients with partial seizures whose seizures were refractory to carbamazepine.

No. No statistical power calculations were conducted.

Risk of bias unknown. Randomisation, concealment of allocation not described. The baseline characteristics which are reported appear to be similar in each group. Unlikely risk of attrition bias as no participants dropped out. Unclear performance and detection bias as no details on blinding.

Sun MZ; Deckers CL; Liu YX; Wang W;

Comparison of add-on valproate and primidone in carbamazepine-unresponsive patients with partial epilepsy

2009 18 Mar

n=136.
VPA: n=68 vs PRM n=68.

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, SGTC5, SPS.

**Recruitment:**

Neurologists from two hospitals identified eligible patients.

**Setting:**

Shanxi medical university, China.

**Interventions/Test /Factor being investigated**

Sodium valproate versus primidone. Titrated in 3 steps: VPA: 200mg/day; 400mg/day and 600mg/day; PRM: 250mg/day; 500mg/day; 750mg/day. Average dosages were 583mg/day for VPA and 596mg/day PRM. Max dosages used in maintenance period were 1500mg/day PRM and 1600mg/day VPA.

**Comparisons**

Comparisons between treatments.

**Length of Study/ Follow-up**

Titration period (of flexible length) maintenance period doses held stable 3-months.

**Outcome measures studies**

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.

**Funding**

Not reported.

**Does the study answer the question?**

Yes.

**Effect due to factor in study?**

Sample size calculation done on proportion of patients seizure free. 61 patients were required in each group for a power of 80% and n=68 and n=68 were randomised in each group and n=63 and n=57 completed the trial. No

**How directly applicable to population of the guideline?**

Direct.

**Internal Validity**

Selection bias: unclear/high risk of bias - no details of randomisation or allocation concealment.
- Performance bias: high risk of bias - no blinding (open study).
- Attrition bias: low risk of bias.
- Detection bias: high risk of bias - no blinding (open study).

**Reference number**

4713

**Study Type**

Randomised Controlled Trial

**Vigabatrin in the treatment of epilepsy: a double-blind, placebo-controlled study**

1986 27

**pgs 717 723**

23 December 2011  Page 185 of 364
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.

FundingDoes the study answer the question?
Not reported.

Setting: Outpatients at an epilepsy clinic in Italy.

Interventions/Test /Factor being investigated: Vigabatrin as add-on therapy. Two doses: 2.0g daily for patients weighing <=65kg and 3.0g daily for patients weighing >65kg.

Comparisons: The comparison is between Vigabatrin as add-on therapy and placebo.

Length of Study/ Follow-up: 14 weeks: two periods of 7 weeks (crossover) one period on placebo and the other on Vigabatrin.

Outcome measures studies: 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

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.
How directly applicable to population of the guideline?

17 of the 20 patients who completed the study suffered from partial seizures and three had generalized seizures.

Internal Validity

Very little description is given of randomisation or concealment of allocation methods. Therefore, risk of selection and performance bias is unclear. This is a crossover trial where 3 patients dropped out in total. Main outcome (seizures) was measured in a standard manner. Risk of attrition bias and detection bias is minimal. The dose used in the study (2-3g/daily) was the usual therapeutic dose for this drug.

Tassinari CA; Michelucci R; Ambrosetto G; Salvi F;

Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy

1987 44 Arch Neurol

Number of subjects

N=31 (crossover), 30 patients suffered from partial epilepsy, 1 patient had progressive myoclonic epilepsy.

Inclusion/Exclusion Criteria:

Inclusion criteria: patients with any type of epilepsy, provided they were taking no more that 4 concomitant antiepileptic drugs and had at least four documented seizures per month while receiving optimal doses of current antiepileptic drugs. No exclusion criteria were defined.

Patient Characteristics

15/31 were females and 16/31 were males, aged 10-58 years (mean 28.9, sd 11.5). 15/30 patients with partial epilepsy had complex partial seizures with or without secondary generalized seizures, 8/30 had complex partial associated with atonic seizures, and 7/30 had various partial seizure types. On this basis, group 1 was consisted of the 15 patients with complex partial seizures and the group 2 included the other 15 with various seizure types.

Recruitment:

Unknown.

Setting:

a clinic (no further information).

Interventions/Test Factor being investigated

Vigabatrin (2.3 gr/d) against placebo. Vigabatrin was administered twice daily with the dose (2 or 3 g/d) stratified according to body weight (40-60 kg, 1 g twice daily, >=61 kg twice daily).

Comparisons

Comparison are made between the group of patients receiving Vigabatrin compared to placebo and separate comparisons between the two groups of patients (based on different seizure types) and the comparison.

Length of Study/ Follow-up

2 month run in period (only preexisting antiepileptic medications were given) followed by 6-month cross over treatment with vigabatrin and placebo. 1 month after the cross over period, all patients received placebo.

Outcome measures studies

> 50% seizure frequency, adverse events.

Results

For the sample with all types of seizures (N=30), 10 of them (33%) had experienced >50% in seizure frequency during Vigabatrin treatment compared to placebo. 6/15 (40%) patients in group 1 (patients with complex partial seizures) and 4/15 (26.7%) in the group 2 (with various seizure types) had >50% reduction in seizure frequency compared to placebo groups. For the group 1 there was a statistically significant treatment effect whereas for the group 2 this was not the case.

Withdrawal due to adverse events:

Vigabatrin: 1/31
Placebo: 0/31
Vigabatrin was supplied by Merrel Dow Research Institute, Strasbourg Center, France.

Yes. Vigabatrin showed a significant treatment effect for the group of patients with complex partial seizures but not for the whole sample and the group 2 (various seizure types). The proportion of patients with >50% reduction in seizure frequency compared to placebo were 33.3%, 40% and 26.7% in the whole sample, the group with complex partial seizures and the group with other types respectively.

No patient withdraw due to experience of adverse events.

Based on the unclear risk of selection bias and the absence of pre consideration of sample size based on the statistical power of the study, it is uncertain whether the effect was due to the study intervention.

Unclear risk of selection bias as the randomization procedure and the allocation concealment are poorly reported. Performance bias is low as the study was conducted under double blind conditions. Low attrition bias. Although the doses used (2.3 gr/d) were within the acceptable limits of usual dose for adults and were adjusted according to patient's weight, some patients in the sample were children for whom the limits of usual therapeutic dose should have been lower.

**US Gabapentin Study group no.5**

**Reference number** 4621  
**Study Type** Randomised Controlled Trial  
**RID:** 86

Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study.

1993 43

**Number of subjects** 306 patients total: 98 placebo, 53 received 600 mg gabapentin, 101 received 1200 mg gabapentin, 54 received 1800 mg gabapentin.

**Inclusion/Exclusion Criteria:**

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.

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.

**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. Three doses of gabapentin (600 mg, 1200 mg and 1800 mg) and placebo

**Comparisons**

Comparison is made between three doses of gabapentin (600 mg, 1200 mg and 1800 mg) and placebo.

23 December 2011  
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12 week baseline period; 12 week double blind phase

Primary outcome: Number of seizures per 28 days
Secondary outcomes: Response ratio (RRatio); percent change in seizure frequency and responder rate.

**Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>600 mg GBP</th>
<th>1200 mg GBP</th>
<th>1800 mg GBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response ratio</td>
<td>-0.025</td>
<td>-0.151</td>
<td>-0.118</td>
<td>-0.233</td>
</tr>
<tr>
<td>Adjusted mean</td>
<td>0.022</td>
<td>0.037</td>
<td>0.027</td>
<td>0.034</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value compared to placebo</td>
<td>0.007</td>
<td>0.023</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Responder rate</td>
<td>8.4%</td>
<td>18.4%</td>
<td>17.6%</td>
<td>26.4%</td>
</tr>
<tr>
<td>(percent of patients with at least 50% reduction in seizure frequency from baseline to treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value compared to placebo</td>
<td>0.103</td>
<td>0.080</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Median percent change in seizure frequency</td>
<td>-5.9</td>
<td>-24.3</td>
<td>-20.0</td>
<td>-31.9</td>
</tr>
</tbody>
</table>

**Funding**

Park-Davis

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.

**Length of Study/ Follow-up**

Unclear risk of selection bias as the randomization procedure and the allocation concealment were not described. Low risk of attrition bias. Low risk of performance and detection bias.

**Internal Validity**

For 80% power sample size was calculated at n=180 (90 in each group - gbp 1200mg and placebo groups) - this was reached in these groups n=101 and n=98. The other groups were smaller sample sizes and did not reach 80% power.

**How directly applicable to population of the guideline?**

See GRADE

**Effect due to factor in study?**

Unclear risk of selection bias as the randomization procedure and the allocation concealment were not described. Low risk of attrition bias. Low risk of performance and detection bias.

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**Zamponi N; Cardinali C;**

**Reference number** 4607  **Study Type** Randomised Controlled Trial  **RID:** 73

Open comparative long-term study of vigabatrin vs carbamazepine in newly diagnosed partial seizures in children

1999 56

**Number of subjects**

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 6 months 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.
Vigabatrin 50-60mg/kg/day or carbamazepine controlled release 15 to 20mg/kg per day. VGB starting dose 10-15mg/kg/day increased progressively at 2-3 day intervals. CBZ 5mg/kg day progressively increased at 3-4 day intervals.

Vigabatrin versus carbamazepine controlled release.

2 years (at 1,3,6,12,18,24 months). Withdrawal due to adverse events; adverse events.

Not reported. No, it is unclear and only reports adverse events clearly.

Internal Validity
Open study. Selection bias - unclear/high risk of bias: no details of randomisation or allocation concealment. Performance bias - high risk of bias - open study. Attrition bias - unclear/high risk of bias - higher drop-out in the CBZ group (over 20%). Detection bias - high risk of bias - open study. Contamination: In 30 cases vigabatrin was administered as first-choice drug and 8 cases it replaced another AED which had been started less than 1 month before. In 6 cases the previous therapy was carbamazepine which had been discontinued due to early appearance of a rash (4 patients) or lack of efficacy (2 patients).

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. VGB starting dose 10-15mg/kg/day increased progressively at 2-3 day intervals. CBZ 5mg/kg day progressively increased at 3-4 day intervals.

Comparisons
Vigabatrin versus carbamazepine controlled release.

Length of Study/ Follow-up Outcome measures studies
2 years (at 1,3,6,12,18,24 months). 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.

Funding
Not reported.

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.

How directly applicable to population of the guideline?
Mixed population as some had the drug as first line and others had it as refractory treatment, although said all were newly diagnosed.

Open study.

Zhou B; Zhang Q; Tian L; Xiao J; Stefan H; Zhou D;

Reference number 169 Study Type Randomised Controlled Trial RID: 357
Effects of levetiracetam as an add-on therapy on cognitive function and quality of life in patients with refractory partial seizures
2008 12 Pgs 305 310
23 December 2011 Page 190 of 364
n=28 (n=14 in the LEV group and n=14 in the placebo group)

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.

Demographics of the LEV and placebo groups

<table>
<thead>
<tr>
<th>Demographic</th>
<th>LEV group (N = 13)</th>
<th>Placebo group (N = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.2 ± 11.1</td>
<td>31.3 ± 9.8</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>53.8%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Age at epilepsy onset (years)</td>
<td>18.5 ± 10.1</td>
<td>14.6 ± 7.5</td>
</tr>
<tr>
<td>Duration of epilepsy (years)</td>
<td>8.7 ± 6.4</td>
<td>16.5 ± 7.2</td>
</tr>
<tr>
<td>Seizure frequency at baseline (No. of seizures/week)</td>
<td>6.55 ± 10.79</td>
<td>6.15 ± 11.20</td>
</tr>
<tr>
<td>Education (years)</td>
<td>8.4 ± 3.9</td>
<td>8.2 ± 3.4</td>
</tr>
<tr>
<td>Number of antiepileptic drugs</td>
<td>1</td>
<td>4 (30.7%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>9 (69.3%)</td>
</tr>
</tbody>
</table>

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.

Target of 1500mg twice daily. Titration from 500mg twice daily in the first two weeks, 100mg twice daily in weeks 3 and 4 and 12 weeks at the maximum dose of 1500mg twice daily.

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 studies 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.

Funding 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.
All patients who were enrolled were diagnosed with partial-onset seizures.

There is very little information in this study about allocation concealment and blinding methods. The risk of selection and performance bias is unknown. Withdrawals from the treatment group is relatively low but an intent to treat analysis was not performed. The risk of attrition bias is unknown as is the risk of detection bias.

The study was blinded for the short-term treatment phase (12 weeks) but unblinded for the long-term phase (24 weeks). The study goal was to see the effects of adjunctive levetiracetam on cognitive function and QOL.

**Question:** How effective and cost-effective are anti-epileptic drugs for primary generalised tonic-clonic seizures
Grading: 1++  High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

Tudur Smith C; Marson AG; Chadwick DW; Williamson PR;

Reference number 5292  Study Type Meta-analysis  RID: 978

Multiple treatment comparisons in epilepsy monotherapy trials

2007 8  pgs 34


table

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>RCT (double blinded, single blinded and unblinded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion Criteria:</td>
<td>Patient Characteristics</td>
</tr>
<tr>
<td>Recruitment:</td>
<td>Setting:</td>
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<tr>
<td>Interventions/Test / Factor being investigated</td>
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<tr>
<td>Comparisons</td>
<td></td>
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<tr>
<td>Length of Study/ Follow-up</td>
<td>Outcome measures studies</td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td></td>
</tr>
<tr>
<td>Does the study answer the question?</td>
<td>MRC funded work related to original systematic reviews.</td>
</tr>
<tr>
<td>Effect due to factor in study?</td>
<td>In patients with generalised onset tonic clonic seizures valproate or phenytoin had the best combination of seizure control and treatment failure. For results see Appendix O. This directly related to our question for generalised tonic clonic seizures.</td>
</tr>
<tr>
<td>How directly applicable to population of the guideline?</td>
<td></td>
</tr>
</tbody>
</table>

Individual patient data (IPD) came from the 8 Cochrane systematic reviews and the SANAD trial. The use of IPD data is regarded as the gold standard therefore it is a very well conducted meta-analysis. The quality was assessed in the individual cochrane reviews. Internal consistency was explored.
**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;**

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
<th>RID: 197</th>
</tr>
</thead>
<tbody>
<tr>
<td>A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997 27</td>
<td>Epilepsy Res</td>
<td></td>
<td>PGS 195 204</td>
</tr>
</tbody>
</table>

**Number of subjects:**
- Total: 287 (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**

<table>
<thead>
<tr>
<th>Age (mean; range)</th>
<th>Gender (M/F)</th>
<th>Race (Cauc/B/Other)</th>
<th>Body wt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OXC (n=143)</td>
<td>27.1(16-63)yrs</td>
<td>82/61</td>
<td>63.6(41-104)kg</td>
</tr>
<tr>
<td>PHT (n=144)</td>
<td>26.6(15-91)yrs</td>
<td>92/52</td>
<td>64.9(43-101)kg</td>
</tr>
</tbody>
</table>

**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.
- 300 mg OXC or 100 mg PHT.

**Comparisons**
- Oxcarbazepine vs. phenytoin

**Length of Study/ Follow-up Outcome measures studies**
- A flexible titration period of 8 weeks followed by 48 weeks of maintenance treatment.
- 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**

<table>
<thead>
<tr>
<th>Seizure frequency per week: Mean/median</th>
<th>OXC (n=118)</th>
<th>PHT (n=119)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean/median</td>
<td>0.08/0</td>
<td>0.06/0</td>
<td>p=0.72</td>
</tr>
<tr>
<td>Number of seizures</td>
<td>3.57/0</td>
<td>2.13/0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No seizures</td>
</tr>
<tr>
<td>1 seizure</td>
</tr>
<tr>
<td>2-15 seizures</td>
</tr>
<tr>
<td>16-50 seizures</td>
</tr>
<tr>
<td>More than 50 seizures</td>
</tr>
</tbody>
</table>

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).

**Funding**
- International Adult Oxcarbazepine/Phenytoin Trial Group and Novartis Pharma

23 December 2011  
Page 194 of 364
This trial provides support for the efficacy and safety of OXC as first line treatment in adults with PS.

The power calculation required N=182 in the maintenance period. 287 were randomised however there was a very high drop-out.

Unlikely risk of selection bias, as study had good randomization process. High risk of attrition bias as high drop outs. Low risk of performance bias as study was double blinded. Low risk of detection bias.

Does the study answer the question? Effect due to factor in study?
See GRADE

Unlikely risk of selection bias, as study had good randomization process. High risk of attrition bias as high drop outs. Low risk of performance bias as study was double blinded. Low risk of detection bias.

Biton V;Di MJ;Shukla R;Lee YY;Poverennova I;Demchenko V;Saiers J;Adams B;Hammer A;Vuong A;Messenheimer J;

Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study

Reference number 5303 Study Type Randomised Controlled Trial RID: 881

Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study
2010 19
Nov

Number of subjects All patients
N: 153

Inclusion/Exclusion Criteria:
Inclusion criteria:
≥13 years of age
Confident diagnosis of epilepsy with primary generalised tonic clonic (PGTC) seizures for ≥24 weeks before the baseline phase of the study.
Historical or prospective electroencephalographic evidence of either spike and wave discharges consistent with PGTC seizures or at least 2 EEGs with no indication of focal abnormalities.
Documented history of PGTC seizures with or without other generalised seizure types with no focal onset and at least one PTGC seizure during the 8 consecutive weeks before the baseline phase.
If reliably documented, historical seizure data could be used to replace up to 4 weeks if data from the baseline phase.
Receiving a stable regimen of one or two AEDs for at least 4 weeks before the beginning of the baseline phase.

Exclusion criteria:
History of partial seizures or interictal expression of partial seizures on EEG
Status epilepticus during or within 24 weeks before the start of the baseline phase
Chronic treatment with 3 or more AEDs
Current or previous use of lamotrigine
Current use of felbamate
Adherene to the ketogenic diet
Pregnancy or planned pregnancy during the study or within 3 weeks after the last dose of study medication

Patient Characteristics
Patients with primary generalised tonic clonic seizures
Group 1 (lamotrigine XR)
N: 70
Age (mean): 29.4
Sex, n (%)
Male: 38 (54)
Female: 32 (46)
Mean (SD) age at first seizure, years: 16.5 (11.3)
Drop outs: 4 (1 due to adverse events)
Group 2 (placebo)
N: 73
Age (mean): 28.4
Sex, n (%): Male: 35 (48)
Female: 38 (52)
Mean (SD) age at first seizure, years: 14.8 (9.8)

Recruitment: Not reported.
Setting: multi-centre

Interventions/Test /Factor being investigated
Comparisons Length of Study/ Follow-up
Outcome measures studies
Recruitment: Not reported.
Setting: multi-centre
Interventions/Test /Factor being investigated: adjunctive lamotrigine XR
8 weeks baseline phase
*7 week escalation phase during which lamotrigine XR was introduced and titrated to its target dose (200mg/day OD for patients on valproate with or without another AED; 500mg/day OD for pts on an enzyme-inducing AED with or without another AED other than valproate; 300mg/day OD for pts on an AED other than valproate and enzyme-inducing AEDs.
*12 week maintenance phase during which dosages of study medication and concomitant AEDS were maintained.

Comparisons: adjunctive lamotrigine XR v placebo

Length of Study/ Follow-up: at the end of maintenance phase
Outcome measures studies: seizure frequency, investigator and patient ratings, adverse events

Results

Median % decrease in weekly frequency of PTGC seizures (escalation and maintenance phases)
Group 1: 75.4%
Group 2: 32.1%
Median difference: 31.6%
p value: <0.0001

% change from baseline in weekly PGTC seizure frequency (escalation phase)
Group 1: 161.9%
Group 2: 20.6%
Median difference: 25.7%
p value: <0.0001

% change from baseline in weekly PGTC seizure frequency (maintenance phase)
Group 1: 89.7%
Group 2: 33.3%
Median difference: 35.8%
p value: <0.0001

Proportion of patients with ≥50% reduction in PGTC seizure frequency (escalation and maintenance phases)
Group 1: 69.6%
Group 2: 31.9%
p value: <0.0001

Proportion of patients with ≥50% reduction in PGTC seizure frequency (escalation phase)
Group 1: 55.1%
Group 2: 31.9%
p value: 0.0067

Proportion of patients with ≥50% reduction in PGTC seizure frequency (maintenance phase)
Group 1: 75.0%
Group 2: 41.4%
P value: <0.0001

% of patients with 100% reduction in PGTC seizure frequency (escalation and maintenance phases)
Investigator and patient ratings
Number of pts showing improvement (mild/moderate/marked)
lamotrigine XR: 84%
placebo: 54%
p value: 0.0005

Seizure frequency
lamotrigine XR: 87%
placebo: 69%
p value: 0.0420

Seizure duration
lamotrigine XR: 82%
placebo: 54%
p value: 0.0005

Seizure intensity
lamotrigine XR: 85%
placebo: 58%
p value: 0.0012

Adverse experiences
lamotrigine XR: 41%
placebo: 23%
p value: 0.0197

Improvement in seizure control
lamotrigine XR: 87%
placebo: 74%
p value: NS

Funding
GlaxoSmithKline

Does the study answer the question?
Yes.

Effect due to factor in study?
For 90% power a sample size of n=128 was required, which was met at randomisation and completion.

How directly applicable to population of the guideline?
direct

Internal Validity
No details of placebo medication. Unclear randomisation method and allocation concealment.

Biton V;Montouris GD;Ritter F;Riviello JJ;Reife R;Lim P;Pledger G;

Reference number 4708 Study Type Randomised Controlled Trial RID: 179
A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group
1999 52

Number of subjects 80 patients in total, 39 in Topiramate group, 41 in placebo group

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In the Topiramate group 24 out of 39 were male. The mean age was 26.8 ± 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 ± 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 ± 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 ± 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. Dosage based on weight: Topiramate titrated to target dosages of 175, 225 or 400mg/day (in 2 divided doses).

**Comparisons**

Matching placebo.

**Length of Study/ Follow-up**

8 weeks up-titration. 12 weeks stabilisation period.

**Outcome measures studies**

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**

20 week trial, with 8 weeks of titration and 12 week stabilization period.

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.

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 8.6 mg/kg/day.
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.

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.

All generalised seizures: In the Topiramate group 2 out of 39 became seizure free compared to 0 out of 41 in the placebo group.

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.

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.

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.

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.

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.

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.

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.

Not reported

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?
Yes. For 80% power n=26 were required and the number randomised was n=41 and n=39.

How directly applicable to population of the guideline?
Yes.

Selection bias: low risk of bias
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.
### 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  
- **Seizure classification:** tonic-clonic 100% vs 100%, absence 31% vs. 34%, myoclonic 29% vs. 27%. Other (clonic, tonic, atonic, unclassified) 15% vs. 17%.  
- **Number of subjects:** 184 entered into baseline 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).  
- **Recruitment:** Not reported.  
- **Setting:** USA. No further details provided.  
- **Comparisons:** Comparison between treatment (lamotrigine) and placebo.
Funded by GlaxoSmithKline, manufacturer of Lamotrigine.

Authors conclude that adjunctive lamotrigine is effective at controlling PGTC seizures and all generalised seizures in patients treated with lamotrigine compared to placebo (p<0.05).

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).

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).

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).

Lamotrigine versus placebo:

>50% 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;

Effect due to factor in study?

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%.

The results are more favourable for adults, but the sample sizes for 2 to 12 year olds were too small to permit definite conclusions.

How directly applicable to population of the guideline?

Direct.

Authors report study was randomised and double-blinded, but no details provided. 38 study sites enrolled patients, no further details provided.

Baseline demographic data and patient characteristics provided and states no significant differences.

Enrolment stratified by age to ensure comparability between treatment groups.

Selection bias: high risk of bias - does not mention method of allocation concealment or randomisation.

Performance bias: unclear/unknown risk of bias - method of blinding not given.

Attrition bias: low risk of bias.

Detection bias: unclear/unknown risk of bias - blinding details not given.
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 generalised tonic clonic seizures (without focal features):

- **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 dosage 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 vs 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 studies**

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.

Funding

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

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.

How directly applicable to population of the guideline?
Yes.

The statistician set up a randomisation plan where each patient was allocated three drugs depending on first, second and third preference for each patient (drug A carbamazepine, drug B sodium valproate and drug C phenytoin. When a patient was selected for study the drug of first preference was selected on a sequential basis from the randomisation list by a secretary in the department of neurology. Low risk of selection bias as the randomization procedure and the allocation concealment were adequately addressed. High risk of performance bias as the study was not blinded. Low risk of attrition bias as an ITT analysis was performed and compensated for the unequal proportions of drop out rates. Low risk of detection bias (outcome measures were valid and reliable).

Patients who dropped out were analysed as patients with poor control for ITT.
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.

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.

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.

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.

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.

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.

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.

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.

Funding
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.

For 80% power the sample size required in maintenance period was n=182. The number randomised was n=97 and n=96 (total n=193) however only n=161 (total) reached the maintenance period.

Internal Validity
Low risk of selection bias. Performance bias low risk as study was double blinded. High risk of attrition bias as study had high number of drop outs. Low risk of detection bias.
The mean age was 21.1 years in the valproate group and 20.6 in the Phenytoin group.

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.

Not reported. No significant difference in the efficacy or safety of valproate and Phenytoin in the treatment of primary GTCS.

Internal Validity

Selection bias: high risk of bias - no details of randomisation or concealment method. Groups differed at baseline as the VPA group had seventeen participants with other generalised seizure types, compared to only one in the PHT group

Attrition bias: unclear - similar percentage (30% in each group) dropped out but different reasons given.

Recruitment: Not reported. 16 participating centres.

Setting: Outpatient setting.

Interventions/Test / Factor being investigated

Pharmacological interventions. Valproate versus Phenytoin.

Comparisons

Valproate versus Phenytoin.

Length of Study/ Follow-up

6 months.

Outcome measures studies

Seizure recurrence rates, serum drug levels and adverse events.

Funding

Does the study answer the question?

No significant difference in the efficacy or safety of valproate and Phenytoin in the treatment of primary GTCS.

How directly applicable to population of the guideline?

Yes.

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).

Effect due to factor in study?

No. There was no power calculation and a high drop out in both arms.

Attrition bias: unclear - similar percentage (30% in each group) dropped out but different reasons given.
### Patient Characteristics

**Number of subjects**: 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**

9 week crossover study, week 5 washout period.

**Outcome measures studies**

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.

**Funding**

Not reported.
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.

Selection bias: high risk of bias - randomisation and allocation concealment were poorly addressed.
Performance bias: unclear/unknown risk of bias - trial states it was double blinded and randomised but is unclear as to how this was done.
Attrition bias: low risk of bias.
Detection bias: unclear/unknown risk of bias - outcomes not clearly defined and blinding unclear.

Does the study answer the question? No. No power calculation was given and there were only 12 participants.

How directly applicable to population of the guideline? Yes.

Internal Validity

Rationale for inclusion of the study

Brodie MJ; Richens A; Yuen AW;

Reference number 4808 Study Type Randomised Controlled Trial RID: 706

Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group

1995 345
Feb 25

Reference number 4808

Study Type Randomised Controlled Trial

Number of subjects 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 studies 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).

Funding

Supported by the Welcome foundation.

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 power calculation given. Sample sizes were n=131 and n=129.

How directly applicable to population of the guideline?

Yes.

Internal Validity

Selection bias: unclear/high risk of bias - no details of randomisation or concealment method.
Performance bias: low risk of bias.
Attrition bias: unclear risk of bias - more patients in the carbamazepine group dropped out than the lamotrigine group. No ITT analysis reported.
Detection bias: unclear risk of bias - outcome measures were not precisely defined.
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. 300 mg sodium valproate

Comparisons:
Oxcarbazepine versus sodium valproate.

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

Outcome measures studies:
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-
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.

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.

None reported

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.

The final sample size had the statistical power to detect an effect of the study intervention.

Unclear risk of selection bias due to absence of reporting of allocation concealment and randomisation method. Low risk of performance bias as study was double blinded. High risk of attrition bias. Low risk of detection bias.

Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. ICBERG (International Community-based Epilepsy Research Group)

N=302, 129 females.

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).

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.

Generalised tonic-clonic seizures: n=179
Secondarily generalised seizures: n=61
Partial with secondary generalisation: n=54
Generalised tonic-clonic and other generalised seizures: n=8

Via Health Worker and invitation to attend an epilepsy clinic at Nakuru Provincial General Hospital.

Epilepsy Clinic in Kenya
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.

6-10 year olds (1st Maintenance)
CBZ- 400mg
PB-30 mg

11-15 year olds (1st maintenance period)
CBZ- 500mg
PB- 45mg

>16 years old (1st Maintenance)
CBZ- 600mg
PB- 60mg

Comparisons
Carbamazepine versus phenobarbitone.

Length of Study/ Follow-up
Up to 12 months

Outcome measures
Seizure freedom, reduction/increase in seizure frequency, and adverse events.

Results
Seizure freedom at 6 to 12 months:
CBZ (n=126): 65 (52%)
PB (n=123): 67 (54%)

>50% reduction in seizures
CBZ (n=126): 37 (29%)
PB (n=123): 28 (23%)

N=249 (82%) completed the 12 month follow-up. The difference in drop-out rates between the two AEDs is non-significant.

Funding
Ciba Geigy for financial and logistic support and the National Society for Epilepsy for logistic support.

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, high drop out, unclear methodology, therefore may be biased.

How directly applicable to population of the guideline?
Study conducted in a Kenyan population.

Internal Validity
No ITT analysis. No mention of blinding.
Selection bias: unclear risk of bias - no details of randomisation and allocation concealment.
Performance bias: unclear risk of bias - no mention of blinding.
Attrition bias: high risk of bias.
Detection bias: unclear risk of bias - no mention of blinding.
Comparison of sodium valproate and phenytoin as single drug treatment in generalised and partial epilepsy

1991  39  J Assoc Physicians India  

Number of subjects 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 studies Seizure reduction: excellent (100% reduction), good (75-99% reduction), fair (50-74% reduction) and poor (less than 50% reduction).

Results

<table>
<thead>
<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</td>
<td>3</td>
<td>1(33.3%)</td>
<td>2(66.7%)</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Phenytoin Response

<table>
<thead>
<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(1005)</td>
<td>--</td>
</tr>
<tr>
<td>Sec. gen. of Partial</td>
<td>4</td>
<td>--</td>
<td>1(25%)</td>
<td>3(75%)</td>
<td>--</td>
</tr>
</tbody>
</table>

Funding Unknown

Does the study answer the question? It appears that while sodium valproate and Phenyltoin were equally effective in controlling generalised epilepsy, valproate was a better drug for controlling partial seizures.

Effect due to factor in study? No. There was no power calculation and the methodology was not adequate.

How directly applicable to population of the guideline? See GRADE

Internal Validity Selection bias: high risk of bias - no allocation concealment or randomisation method and groups not comparable at baseline.
Performance bias: high risk of bias - no blinding reported.
Attrition bias: low risk of bias.
Detection bias: High risk of bias - The actually measurement technique for seizure

23 December 2011  Page 213 of 364
frequency was not described. There was no blinding reported.

Steiner TJ; Dellaportas CI; Findley LJ; Gross M; Gibberd FB; Perkin GD; Park DM; Abbott R;

Reference number 4705 Study Type Randomised Controlled Trial RID: 176

Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin 1999 40 pgs 601 607

Number of subjects 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

<table>
<thead>
<tr>
<th></th>
<th>LTG, n=86</th>
<th>PHT, n=95</th>
<th>All, n=181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (%)</td>
<td>55/45</td>
<td>57/43</td>
<td>56/44</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>28 (13-70)</td>
<td>27 (13-74)</td>
<td>28(13-74)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Age at first seizure (yr)</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

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. Capsules of high and low strengths of both drugs: LTG 50 and 25mg; PHT 100 and 50mg, once daily at night; the doses for the first 2 weeks were LTG 100mg, and PHT 200mg and these were increased to 150 and 300mg, respectively for the second 2 weeks, then the dose of either drug could be increased by one capsule if seizure control was inadequate and no clinically significant adverse events.

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 studies 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

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.

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%.

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
LTG and PHT monotherapy were similarly effective against these seizure types in patients with...PHT.

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

PHT:
- Asthenia 28/95*
- Rash 12/95
- Headache: 9/95
- Dizziness: 8/95
- Somnolence: 6/95*
- Ataxia: 0/95

* P<0.05

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.

Funding

Wellcome Foundation Ltd.

Effect due to factor in study?

90% power calculation required n=86 in each group. The number randomised was n=86 and n=95. However there was a 15% and 19% drop-out.

How directly applicable to population of the guideline?

See GRADE

Selection bias: high/unclear risk of bias - no details of randomisation method or allocation concealment.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: unknown risk of bias - diaries used to assess seizure frequency.

Turnbull DM; Howel D; Rawlins MD; Chadwick DW;

Reference number: 4672

Study Type: Randomised Controlled Trial

Which drug for the adult epileptic patient: phenytoin or valproate?

1985 290 Br Med J (Clin Res Ed) pgs 815 819

Number of subjects 140 in total sample with 70 in each arm, valproate and Phenyltoin 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.

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### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Valproate (70 patients)</th>
<th>Phenytoin (70 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>16-69 (30 median)</td>
<td>16-70 (30 median)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Male</td>
<td>34</td>
<td>39</td>
</tr>
</tbody>
</table>

### Recruitment

Unknown.

### Setting

Dept of Neurology, Royal Victoria Infirmary.

### Interventions/Test

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

Achievement of a two year remission and 'time to first seizure'.

### Results

<table>
<thead>
<tr>
<th>Outcome measures studies</th>
<th>Valproate</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>No achieving 2 year remission</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>No controlled for &lt;2 years</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>No continuing to have seizures</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Idiosyncratic adverse effect</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>requiring drug withdrawal</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Non-compliant or lost to follow-up</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

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.

### Funding

Sanofi

### 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?

No power calculation given but sample size was 70 in each arm.

### How directly applicable to population of the guideline?

See GRADE

### Internal Validity

Selection bias: unclear/high risk of bias - allocation concealment and method of randomisation not reported.

Performance bias: high risk of bias - does not report binding.

Attrition bias: unclear/unknown risk of bias - no ITT analysis.

Detection bias: high risk of bias - no binding reported, unusual outcomes - no. achieving 2 year remission and no. controlled for under 2 years.
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)

Reference number: 4628  
Study Type: Randomised Controlled Trial  
Funding: Labaz, Warner-Lambert Pharmaceuticals.

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.

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.

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.

23 December 2011  
Page 218 of 364
In the table that gave details of the results of response to treatment, there is a mistake as group B have 15 patients rather than 14. This is because patient 9 is counted for group A and group B.

Selection bias: High risk of bias - no details of randomisation, no mention of concealment of allocation.
Performance bias: High risk of bias - no blinding to treatment allocation.
Attrition bias: Low risk of bias.
Detection bias: Unknown risk of bias - Five patients did not have telemetry to assess seizure frequency prior to treatment as it was not available in the department when they entered the study.

Coppola G; Auricchio G; Federico R; Carotenuto M; Pascotto A;

Reference number 660
Study Type Randomised Controlled Trial
RID: 456

Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: an open-label, randomized, parallel-group study
2004 45

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 (e.g. juvenile myoclonic epilepsy);
  - other types of epileptic seizures;
  - stimulus-sensitive absences: photosensitive, pattern-sensitive, self-induced pattern-sensitive;
  - irregular, arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency;
  - central-temporal or occipital focal EEG discharges or abnormal background EEG activity;
  - known or suspected 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;
Gender: 17 male; 21 female;
Age: range (mean): 3 to 13 years (7.5 years);
Disease status: all had newly diagnosed childhood or juvenile typical absence seizures;
mean duration of epilepsy 6 months (range 1-17 months); family history of epilepsy in 44.7% of patients and history of febrile seizures in 6% (15.8%); neurologica and neuropsychological 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.

LTG: daily dose 0.5mg/kg - 2 weeks (2 divided doses), then 1.0mg/kg/day - 2 weeks.
Afterwards dosage increased by 1mg/kg/day increments every 5 days until seizures controlled or intolerable adverse events occurred, or maximum 12mg/kg/day. VPA was given as 200mg enteric-coated non-sustained release tablets or some times by liquid formulation (40mg/ml) - initially at 10mg/kg/day which increased by 5mg/kg/day every 3 days until seizures controlled or intolerable side effects. The maximum was 30mg/kg/day (in 3 divided doses).

The patients were then randomised to either LTG or VPA.

Comparisons
LTG monotherapy versus VPA monotherapy.

Length of Study/Follow-up
If interrupted the full up titration schedule was reached around 75 days after the start of treatment.
The patients were seen at monthly intervals for 12 or less months and exited if not satisfactorily controlled at highest dosage.

Outcome measures/studies
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 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 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).

Funding
States that the study was not sponsored by any commercial organisation.

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.

How directly applicable to population of the guideline?
Direct.
Internal Validity

An open-label, randomised, parallel-group design.

Selection bias - High risk of bias - randomisation was adequate: code not available to physician and randomisation list controlled by an external investigator; no mention of allocation concealment; there were more girls and shorter duraion of epilepsy in the LTG group.

Performance bias - high risk of bias - no blinding;

Attrition bias - unclear/unknown bias - more in the LTG group dropped out (32% versus 16%) due to lack of efficacy;

Detection bias - low risk of bias - there were independent expert electroencephalographers who were unaware of the randomisation to which drug; there was a precise definition of outcome and valid and reliable methods were used to determine the outcome.

Martinovic Z;

Reference number 4896 Study Type Randomised Controlled Trial RID: 291

Comparison of ethosuximide with sodium valproate as monotherapies of absence seizures

1983 pg 301 305

Number of subjects 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. EMI essay method assessed drug plasma concentrations, dosage adjusted in accordance with these, increased later if not seizure-free.

Ethosuximide 250mg twice daily; sodium valproate 150mg 3 times daily.

Therapeutic dosage and range of ESM and VPA plasma concentration:

ESM (8 patients): 15-28mg/kg, therapeutic plasma range 51-114ug/ml. VPA (7 patietns): 25-36mg/kg, 68-131 ug/ml. Values after 3-15 days of the first complete seizure control.

Comparisons Ethosuximide versus sodium valproate.

Length of Study/ Follow-up For periods of 1 to 2 years.

Outcome measures studies Seizure control; improvement 50-75%; time to seizure control; adverse events.

Results If parents did not cooperate fully from the trial the children were not retained in the study, six patients were not included.

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).
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.

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.

Not reported.

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.

No power calculation but sample size very small.

Randomisation is mentioned but method not explained. Preliminary report as followup continuing. Part of a larger project (Radojicic and Martinovic).

Selection bias: Unclear/high risk of bias – no allocation concealment or randomisation details.
Performance bias: High risk of bias – no blinding of treatment allocation.
Attrition bias: High risk of bias - very small sample and then 6 incomplete information.
Detection bias: Unknown risk of bias – no blinding.

Valproic acid versus ethosuximide in the treatment of absence seizures

Reference number 4665  Study Type Randomised Controlled Trial  RID: 135

Valproic acid versus ethosuximide in the treatment of absence seizures

1982 32  pgs 157 163

Number of subjects 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).

Inclusion/Exclusion Criteria:
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: 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.
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. Group one (first 23 patients) VPA 15 to 20 mg/kg, increased at 5 days to maximum 30 mg/kg (if the 12-hour telemetered EEG still showed generalised spike-wave discharges. ESM 250 to 1500 mg daily. Group 2 (another group of 22 patients) VPA 12.5 to 20 mg/kg. ESM 250 to 1500 mg daily.

Group 1: Valproic acid (VPA) and placebo ethosuximide (ESM) then ethosuximide and valproic acid placebo. Group 2: vice versa.

NINCDS- National institute of neurological and communicative disorders and stroke. 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.

Results

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.
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.

Patients were initially in hospital for the first 10 days and were then followed every 2 weeks for each drug.
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.
Patients who did not respond to the first drug or who has serious adverse effects crossed over to the second drug.

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.

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 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.

Funding
NINCDS- National institute of neurological and communicative disorders and stroke.
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.

How directly applicable to population of the guideline?

Direct.

InternalValidity

Selection bias: Unclear/high risk of bias - no details of randomisation, of allocation concealment.
Performance bias: Unclear risk of bias - no details of blinding given; groups were split into two groups with slightly different starting dosage. Monotherapy and adjunctive therapy mixed within groups.
Attrition bias: high risk of bias - patients who were successful on the first treatment did not cross over.
Detection bias: Unknown risk of bias - outcome is 80% reduction in seizure frequency for crossover patients.

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

Reference number: 4668

Study Type: Randomised Controlled Trial

RID: 138

2005 14

pgs: 597 605

Number of subjects:
- 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. LTG monotherapy was started with 25mg once a day for weeks 1 and 2 then escalated to 50mg once a day in week 3 and 4. From week 5 on, 100mg once a day or 50mg b.i.d were established. The CBZ started with a daily dose of 200-400mg in adults and with 200-300mg in patients between 11 and 15 years. The recommended maintenance dose was 600-1200mg in adults and 600-1000mg in persons between 11 and 15 years. For VPA, a dose of 5-10mg/kg body weight was given initially and increased every 4-7th day by approximately 5mg/kg. The recommended daily maintenance dose was 600-1200mg for children between 6 and 14 years or persons with a body weight of 20-40mg, 600-1500mg for adolescents from 14 years on or for persons with a body weight between 40 and 60kg, and 1200-2100mg for adults and persons weighing at least 60 kg.

Comparisons:
- LTG versus CBZ or VPA.

Length of Study/ Follow-up:
- 24-26 weeks.

Outcome measures studies:
- 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

23 December 2011
Question: How effective and cost-effective are anti-epileptic drugs for Childhood absence epilepsy
A multicenter, randomized, placebo-controlled trial of levetiracetam in children and adolescents with newly diagnosed absence epilepsy

LEV n=38 and PLA n=21

Inclusion: 1) age between 4 and 16 years; 2) a recent diagnosis of childhood or juvenile absence epilepsy, as defined by the ILAE; 3) EEG evidence of regular, synchronous and symmetrical spike-wave paroxysmal discharges with a frequency of about 3 Hz and duration of at least 4s, occurring spontaneously or during hyperventilation; 4) a history of clinically evident spontaneously occurring absence seizures impacting on functional abilities; and 5) written informed consent. Exclusion: 1) history of generalised tonic-clonic seizures; 2) clinical or EEG findings inconsistent with a diagnosis of childhood or juvenile absence epilepsy; 3) previous treatment with AEDs (except for earlier treatments for other indications such as febrile seizures, or brief exposures to other AEDs prior to diagnostic assessment; 4) renal disorders; 5) clinical significant hepatic or renal disorders; 6) history of hypersensitivity reactions to study products or structurally related substances; and 7) any condition that was expected to impact negatively on subjects health or study procedures.

Seizure freedom, Adverse events

Nine of 38 patients (23.7%) were responders in the levetiracetam group, compared with one of 21 (4.8%) in the placebo group (p = 0.08). Seven of 38 patients (18.4%) were free from clinical and EEG seizures during the last 4 days of the trial (including 24-h EEG monitoring on day 14) compared with none of the patients treated with placebo (p = 0.04). Seventeen patients remained seizure-free on levetiracetam after 1 year follow-up. Of the 41 patients who discontinued levetiracetam due to lack of efficacy (n = 39) or adverse events (n = 2), 34 became seizure-free on other treatments

Supported by an UCB grant

Although superiority to placebo just failed to reach statistical significance for the primary end point, the overall findings are consistent with levetiracetam having modest efficacy against absence seizures.

Required sample size of n=40 and n=20 however actual randomised was n=38 and n=21.
Internal Validity

Overall reasonable well conducted randomized placebo controlled trial. Both arms comparable at baseline. Very short study duration and small sample size.

How directly applicable to population of the guideline?

Relevant to clinical question

Question: How effective and cost-effective are anti-epileptic drugs for Infantile spasms
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 development test:
  - normal: 2 vs 1.
  - 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.
There was a five day double-blind period. Those patients continuing with the study entered a 24-week open phase. Outcomes: cessation of spasms; reduction in spasms; resolution of hypsarrhythmia; relapse rates.

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.

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.

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.
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;

Reference number 604  Study Type Randomised Controlled Trial  RID: 42
Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms

2003  18  pgs 165 170

Number of subjects  
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 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 studies
Cognitive and motor development; language; autistic symptomology; cessation of spasms; resolution of hypsarrhythmia.

Results
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.

All patients had resolution of spasms and hypsarrhythmia on EEG safer 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.

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.

Supported in part by Bloorview Children's Hospital Foundation.

Funding
Does the study answer the question?
Partially regarding outcomes of cessation of spasm and cognitive outcomes.

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.

Effect due to factor in study?
No, study too small and methodology was unclear.

How directly applicable to population of the guideline?
Direct.

Internal Validity
The authors state that the patients were stratified based on whether the patient was assessed as idiopathic or symptomatic and by sex and this formed 4 cells and then these cells were randomised between ACTH and vigabatrin. Open study. The psychologists who evaluated the infant outcomes were blinded to the study medication. Full demographics not shown, do not know if groups were statistically different at baseline.

Baram

Reference number 1
Study Type Randomised Controlled Trial
High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study 1996 97 Pediatrics

23 December 2011 Page 233 of 364
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.

Results
Cessation of seizures:
ACTH: 13/15 86.6% responded by EEG and clinical criteria; seizures stopped in an additional infant (EEG remained hypersarrhythmic 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.

Funding
Not reported.
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?
No allocation concealment details and no power calculation given.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Computer-generated random-number list. The investigators were blinded to treatment whereas the patients were not.

Chiron C; Dumas C; Jambaque I; Mumford J; Dulac O;

Reference number 4616
Study Type Randomised Controlled Trial
Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis
1997 26

Number of subjects 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.

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Adverse events were reported to or noted by the investigator.

Comparison between treatments: vigabatrin vs hydrocortisone.

Comparison between treatments: vigabatrin vs hydrocortisone or cross-over (responders).

Cessation of spasms; resolution of hypsarrhythmia; relapse rates; adverse events.

Cessation of spasms:

After 1 month: 11/11 vigabatrin and 5/11 hydrocortisone patients were spasm-free (p<0.01).

The 6 non-responders to hydrocortisone and one infant who had severed side effects after hydrocortisone were crossed over to vigabatrin:

All 7 responded to vigabatrin.

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.

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.

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.

Not reported.

Yes as it includes cessation of spasms, psychomotor evaluation and adverse events.

Vigabatrin was withdrawn over a 24 hour period and hydrocortisone was tapered off over 2 weeks.

Vigabatrin was withdrawn over a 24 hour period and hydrocortisone was tapered off over 2 weeks.

The authors concluded that vigabatrin should be considered as the first choice treatment for infantile spasms due to tuberous sclerosis.

No as only 22 participants and an open study with unclear methodology.

Direct.

unclear the risk of selection bias, as authors stated that study was randomized but no details on randomization or allocation concealment were given. The two groups were comparable at the beginning of the study.

High risk of performance bias as study was unblinded. Low risk of detection and attrition bias.
Infantile spasms. Comparative trial of nitrazepam and corticotropin

1986 Arch Neurol

**Number of subjects**
- 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 studies**
- 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].

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.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Unclear risk of selection bias: No details of allocation concealment. Although the randomization process was conducted by a computer randomization system of producing codes, the authors stated that the nitrazepam treatment group was slightly larger and these patients were slightly older and had fewer spasms at baseline, however the two treatment groups were roughly comparable.
Unclear risk of performance bias; the only blinding mentioned was of the outcome assessors.
No ITT was performed - 4 who dropped out at 14 to 22 days of treatment were included in the analysis; 3 who dropped out due to side effects were not included in ITT; and one with wrong diagnosis was not included in analysis.
The 8 centres were analysed together as the authors state that they were roughly comparable although varying considerably in size and because scored by a single individual who was unaware of the treatment given.
Different administration: the ACTH group received corticotropin gel as a single daily intramuscular dose whereas the nitrazepam was two doses of pills (not specified but assume pills).
Unclear the risk of attrition bias; 8/25 in ACTH but none in nitrazepam group.

Hrachovy RA; Frost JD; Kellaway P; Zion TE;

Reference number 49
Study Type Randomised Controlled Trial
RID: 94

Double-blind study of ACTH vs prednisone therapy in infantile spasms

1983 103 J Pediatr pgs 641-645

Number of subjects Total: 24 infants.
ACTH arm: 12 patients.

Inclusion/Exclusion Criteria:
Patients with infantile spasms and hypsarrhythmic EEG patterns on serial 24-hour video and polygraphic monitoring.

23 December 2011 Page 238 of 364
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;

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**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.

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**Outcome measures/studies**

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.

---

**Funding**

Grant NS11535 and Contract NS-9-2321 from the National Institute of Neurological and Communicative Disorders and Stroke.
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.

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.

Unclear risk of selection bias: authors mentioned that the two groups were randomized but no details given of the process and no baseline evaluation of differences between the two groups has been given. In addition, no mention of allocation concealment. Authors state that study is double-blinded but no details given of the process. Low risk of attrition bias as no participant dropped out.

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
<th>RID:</th>
</tr>
</thead>
<tbody>
<tr>
<td>4649</td>
<td></td>
<td></td>
<td>119</td>
</tr>
<tr>
<td>The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial</td>
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<tr>
<td>2004 364</td>
<td>pg5 1773 1778</td>
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</tbody>
</table>

**Number of subjects**

Total: 107 patients.
Vigabatrin: 52.
Hormonal treatment - prednisolone: 30; tetracosactide: 25.

**Inclusion/Exclusion 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 trial 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.

23 December 2011
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. The local investigator reviewed diaries on day 14. Diaries and the investigator's report were used to confirm the days on which spasms occurred.

Comparisons
Comparisons between treatments.

Length of Study/ Follow-up
Follow-up 14 days then every 3 months until aged 14 months.

Outcome measures studies
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%, X2=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%).

Funding
Grant from the Bath Unit for Research in Paediatrics.
FJKOC was supported by the wellcome trust and AL an d EH by Cow and Gate.

Does the study answer the question?
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.

How directly applicable to population of the guideline?

Direct for the prednisolone and Vigabatrin interventions but not applicable for the tetracosactide intervention. The population is of direct interest.

Internal Validity

There was central allocation of randomised treatment. Treatments were allocated by stratified block randomisation. Low risk of selection bias; an independent statistician generated random numbers by using SPSS and allocation sequences. Allocations were concealed in opaque envelopes at the trial centre. The participants were stratified by 16 strata using three variables: sex, age at randomisation and presence or absence of factors that would increase the risk of developmental delay. High risk of performance bias as study was unblinded. Low risk of attrition bias; 1 discontinued from prednisolone, 1 discontinued from tetracosactide and 2 received prednisolone; 1 of Vigabatrin group received prednisolone. All were ITT analysed.

Omar FZ; Al-AbdulWahab NO; Ali BM; Karashi FA; Al-Musallam SA;

Reference number 3134 Study Type Randomised Controlled Trial RID: 646

Vigabatrin versus ACTH in the treatment of infantile spasms

2002 7 pg$ 18 21

Number of subjects
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 hypsarrhythmia 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.
Complete history taken form 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 studies 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.

Response was more appreciated in the vigabatrin group with a known etiology.

Funding
Not reported.

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.

No. The methodology is unclear. No power calculation was given and sample size was small.

Effect due to factor in study? Direct.

How directly applicable to population of the guideline? Direct.

Internal Validity
Unclear risk of selection bias as it was mentioned that the two groups were randomized but no details were given on randomization and on allocation concealment. High risk of performance bias as study was unblinded. Low risk of attrition bias and detection bias.

Vigevano F; Cilio MR;

Reference number 4613 Study Type Randomised Controlled Trial RID: 79
Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study

1997 38 pgs 1270 1274
<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Total: 42 infants. Vigabatrin arm: 23. ACTH arm: 19.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion Criteria:</td>
<td>Inclusion: Newly diagnosed and previously untreated infantile spasms.</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>Vigabatrin vs ACTH</td>
</tr>
<tr>
<td>Gender:</td>
<td>Males: 14 vs 7. Females: 9 vs 12.</td>
</tr>
<tr>
<td>Age at onset:</td>
<td>2.5-9 months (mean 5.8) vs 2-9 months (mean 5.3).</td>
</tr>
<tr>
<td>Setting:</td>
<td>Italy. Not reported where.</td>
</tr>
<tr>
<td>Interventions/Test /Factor being investigated</td>
<td>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.</td>
</tr>
<tr>
<td>Effect due to factor in study?</td>
<td>No. No power calculation and methodology is limited, it is open and has no statement of concealed allocation.</td>
</tr>
</tbody>
</table>

**Results**

Vigabatrin vs ACTH:

- Cessation of spasms: 11 (48%) vs 14 (74%), p=0.12.
- Phase 1 and Phase 2 results:
  - 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.

**Length of Study/ Follow-up**

- Follow-up of study was 40 days: 20 days for phase 1 and 20 days for phase 2.
- No outcome measures explicitly stated. Cessation of spasms; adverse events.

**Funding**

- Not reported.

**Does the study answer the question?**

- Partially. It has cessation of spasms and adverse events reported.

**Effect due to factor in study?**

- 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.
Unclear risk of selection bias: authors stated that study was randomised but no further details given and no allocation concealment was reported. The two groups were comparable in terms of age, gender and cryptogenic/symptomatic type of spasms at the beginning of the trial.
Unclear the risk of performance bias as study was not reported to be open or double blinded. Low risk of attrition bias.
The study provide very little information regarding the study design that does not allow assessment of its internal validity.

Vigabatrin was twice daily dosage and ACTH was single morning dosage. Different modes of administration, ACTH was depot, assume that vigabatrin was pills.
The children's HTA (2006) comments that the trial design compared strategies rather than treatments.

Question: How effective and cost-effective are anti-epileptic drugs for Benign rolandic epilepsy/benign epilepsy with centrotemporal spikes (BECTS)
Sulthiame as monotherapy in children with benign childhood epilepsy with centrotemporal spikes: a 6-month randomized, double-blind, placebo-controlled study. Sulthiame Study Group

**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.

**Interventions/Test Factor being investigated**

Sulthiame (STM).5 mg/kg/day in three administrations.

**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 studies**

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: 21/35 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 (80.8%) 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.

**Funding**

Not reported.

**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.
Internal Validity

Low risk of selection, detection, performance and attrition bias. Study was randomized with allocation concealment, double blinded, with reliable outcome measures and low drop outs.

How directly applicable to population of the guideline?

Direct.
Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign epilepsy of childhood with centrotemporal spikes (BECTS): an open-label, parallel group trial

<table>
<thead>
<tr>
<th>Reference number</th>
<th>271</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
<th>RID: 389</th>
</tr>
</thead>
</table>

**Levetiracetam or oxcarbazepine as monotherapy in newly diagnosed benign epilepsy of childhood with centrotemporal spikes (BECTS): an open-label, parallel group trial**

- **Number of subjects**: 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 caregivers. 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. LEV was titrated up to 20-30 mg/kg/once or twice a day and OXC up to 20-35 mg/kg once or twice a day.
- **Comparisons**: Between levetiracetam and oxcarbazepine.
- **Length of Study/ Follow-up**: Mean follow up period of 18.5 months (range 12-24 months).
- **Outcome measures studies**: 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).
- **Funding**: Not reported.
- **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 OX had treatment withdrawn due to adverse events and a higher proportion of children in OXC withdrawn due to lack of efficacy compared to LEV.
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.

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).

High risk of selection bias as no allocation concealment was reported and high risk of performance bias as study was no blinded. The study was an open label trial.

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;

Reference number 1556 Study Type Randomised Controlled Trial RID: 581

The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign rolandic epilepsy

2007 48

Number of subjects 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 anti-epileptic 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.

Interventions/Test Factor being investigated Topiramate versus carbamazepine.

Average (sd) dose for the TPM group was 3.4 (1.6) mg/kg/day and for the CBZ group was 21.6 (3.2) mg/kg/day.

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 studies 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

By a grant of JANSSEN, KOREA LIMITED, a Johnson & Johnson company.

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.

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.

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).

High risk of selection bias as no allocation concealment was reported. Unclear risk of performance bias as study was single blinded.

Question: How effective and cost-effective are anti-epileptic drugs for Severe myoclonic epilepsy of infancy (SMEI)
Chiron C; Marchand MC; Tran A; Rey E; d’Athis P; Vincent J; Dulac O; Pons G;

Reference number: 4631

**Study Type:** Randomised Controlled Trial

**Funding:** Biocodex, France.

**Grading:** 1+ Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

**Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial.**

**STICLO study group**

2000 356

**Number of subjects:**

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 1/20 on 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 studies**

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/Ml): 3/21 in stiripentol and 0/20 in placebo
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.

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).

Unclear the risk of selection bias due to absence of allocation concealment. Low risk of detection and performance bias. Unclear the risk of attrition bias due to higher drop rate in placebo.

Question: How effective and cost-effective are anti-epileptic drugs for Lennox-Gastaut syndrome
Motte J; Trevathan E; Arvidsson JF; Barrera MN; Mullens EL; Manasco P;


1997 337

 pg5 1807 1812

Reference number 4614

Study Type Randomised Controlled Trial

Randomised Controlled Trial


1997 337

pg5 1807 1812

Number of subjects 169 in total

Lamotrigine:79; Placebo:90

Recruitment: Not reported.

Setting: Not reported

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 valproate

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 valproate, 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 valproate, 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.

Interventions/Test Factor being investigated Lamotrigine added to patients standard antiepileptic drugs.

Lamotrigine 100-200 mg for patients concomitantly receiving valproate and 300-400 mg for patients who were not receiving valproate.

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 studies Number of patients who had greater than 50% reduction in the frequency of seizures, adverse events.

Results The study reported that valproate 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 valproate. 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 valproate: 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 my, for weeks 9 to 16 they were given 50 to 100 mg.

23 December 2011 Page 253 of 364
For patients weighing more than 25 kg and who were taking valporate; 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 valporate; 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 valporate; 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.

Glaxo Wellcome

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.

This was a well conducted double blind randomized study. However, no prior consideration of statistical power has been made.

Effect due to factor in study?
Direct.

How directly applicable to population of the guideline?
Direct.


Sachdeo RC;Glauser TA;Ritter F;Reife R;Lim P;Pledger G;

Reference number 4606
Study Type Randomised Controlled Trial
A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate YL Study Group
1999 52

Number of subjects 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

23 December 2011 Page 254 of 364
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 entry 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).

Funding
R.W Johnson Pharmaceutical Research Institute and PHS grant.

Results
Placebo n=50 and Topiramate n=48.

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.

Results were given for 97 participants.
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 ≥50% reduction in drop attacks compared to 7/49 (14%) of the control group (p=0.071). A ≥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.

The percentage of patients with ≥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.

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.

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% fatigue; 10% dizziness; 10% weight loss.
<table>
<thead>
<tr>
<th>Does the study answer the question?</th>
<th>Yes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect due to factor in study?</td>
<td>No risk of bias but small sample size n=112. For a power of 80% the sample size was required to be 40 patients in each group and n=50 and n=48.</td>
</tr>
<tr>
<td>How directly applicable to population of the guideline?</td>
<td>Direct.</td>
</tr>
</tbody>
</table>
**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;

<table>
<thead>
<tr>
<th>Reference number</th>
<th>901</th>
<th>Study Type</th>
<th>Randomised Controlled Trial</th>
<th>RID: 500</th>
</tr>
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</table>

Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. [see comment]

2008 May 20  pg$ 1950 1958

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>138 in total  Rufinamide: 74; Placebo: 64</th>
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<tr>
<th>Inclusion/Exclusion Criteria:</th>
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<tbody>
<tr>
<td>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 (&lt;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</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
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</thead>
<tbody>
<tr>
<td>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 valporate, 30 had used lamotrigine, 20 topiramate, 14 clonazepam and 12 carbamazepine.</td>
</tr>
<tr>
<td>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 valporate, 19 had used lamotrigine, 17 topiramate, 7 clonazepam and 12 carbamazepine.</td>
</tr>
</tbody>
</table>

| Recruitment: |
| Not reported |

| Setting: |
| Not reported |

| Interventions/Test / Factor being investigated |
| Rufinamide versus placebo. |
| Rufinamide, the target dose of 45mg/kg was achieved by 65 patients (87.8%); Placebo, the target dose of 45mg/kg was achieved by 64 patients (all patients) |

| Comparisons |
| Treatment versus placebo |

| Length of Study/ Follow-up |
| 14 day titration period; 70 day maintenance period. |

| Outcome measures studies |
| 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-atonic 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.

Funding
None reported

Does the study answer the question?
Yes.

Effect due to factor in study?
Power calculation required n=64 in each arm for 91.3% power. N=74 and n=64 were randomised and n=64 and n=59 completed the study.

How directly applicable to population of the guideline?
Direct.

Selection bias: unclear risk of bias as no details of allocation concealment given.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.

Lahat E; Goldman M; Barr J; Bistritzer T; Berkovitch M;

Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study [see comment]

Reference number 48
Study Type Randomised Controlled Trial

Number of subjects 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
**Outcome measures studies**

Cessation of seizures within a given time frame (7-10 minutes), and seizure-recurrence at 1 hour.

**Results**

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.

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 8.0 minutes [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.

**Funding**

None listed.

**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.

**How directly applicable to population of the guideline?**

Direct study

Selection bias: low risk of bias.

Performance and detection bias: unclear risk of bias as the study is unblinded, however it is an emergency treatment.

Attrition bias: low 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

Number of subjects: 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

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 ≥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.

Funding: Funded with grants from the voluntary sector.

Does the study answer the question? Yes.
Effect due to factor in study?

No power calculation given and small sample.

How directly applicable to population of the guideline?

Yes.

Internal Validity


The Felbamate Study Group in Lennox Gastaut syndrome;

Reference number 4676  Study Type Randomised Controlled Trial  RID: 146

Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome).

1993 328  pgs 29 33

Number of subjects 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) The maximum dose of Felbate was either 45 mg per kilogram per day or 3600 mg daily, whichever represented the lower dose.

Comparisons between Felbamate and placebo.

Length of Study/ Follow-up

14 day titration period and 56 day maintenance period. No follow up reported.
Number who were seizure free; adverse events

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 360mg 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.

Funding
Wallace Laboratories, Division of Carter-Wallace, Inc and Public health services grant

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?
No power calculation given and n=73 participants in total.

How directly applicable to population of the guideline?
Direct.
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]

2006 367

Number of subjects 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 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.

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.

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.

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.

Intranasal lorazepam (0.1mg [100micrograms]/kg) and intramuscular paraldehyde (0.2mg [200micrograms]/kg).

Comparisons Intranasal lorazepam versus intramuscular paraldehyde.

Length of Study/ Follow-up Not clear.

Outcome measures studies Seizure cessation, incidence of cardio respiratory depression, need for further anticonvulsant/s.

Results 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).

The median time for the presenting seizure to stop after drug administration did not differ between groups.

No significant difference was found between either treatment in terms of seizure recurrence within 24 hours.

No difference was found between either treatment group in terms of clinically important cardiorespiratory events.

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)

**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.

**Does the study answer the question?**

Relevant study.

**Effect due to factor in study?**

Overall well conducted study, with appropriate power calculations.

**How directly applicable to population of the guideline?**

Sub-Saharan population, otherwise direct comparisons.

**Internal Validity**

No risk on selection, performance or detection bias, even though blinding was not done (however one drug is intranasal and the other intramuscular). No risk of attrition bias.

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**Alldredge BK; Gelb AM; Isaacs SM; Corry MD; Allen F; Ulrich S; Gottwald MD; O’Neil N; Neuhaus JM; Segal MR; Lowenstein DH;**

**Reference number** 4792  **Study Type** Randomised Controlled Trial  **RID:** 255

A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus

2001 345  N Engl J Med  pg5 631 637

**Number of subjects**

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:**

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 <60 bpm
2. Systolic blood pressure <100 mm 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.
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 5 mg, Lorazepam 2 mg 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 for four minutes or more after then a 2nd identical injection was given. Intravenous diazepam 5 mg; intravenous lorazepam 2 mg. If seizures continued or recurred after 4 minutes second identical dose given. Maximum diazepam 10 mg, lorazepam 4 mg.

Comparisons
Intravenous Diazepam versus intravenous Lorazepam versus placebo.

Length of Study/ Follow-up
Not reported.

Outcome measures studies
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).

Funding
Supported by a grant from the National Institutes of Health.
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.

### Internal Validity


Selection bias: low risk of bias.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.

### Leppik IE; Derivan AT; Homan RW; Walker J; Ramsay RE; Patrick B;

Reference number 4782 Study Type Randomised Controlled Trial

Double-blind study of lorazepam and diazepam in status epilepticus

1983 249 JAMA

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>N=37 in the Lorazepam group and n=33 in the Diazepam group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion Criteria:</td>
<td>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.</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>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.</td>
</tr>
<tr>
<td>Mean age of the Diazepam group was 56 years and 50 years for the Lorazepam group.</td>
<td></td>
</tr>
<tr>
<td>Recruitment:</td>
<td>Not clear.</td>
</tr>
<tr>
<td>Setting:</td>
<td>USA</td>
</tr>
</tbody>
</table>

**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

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.

Not clear.

Relevant study to the clinical question.

Uncertain. No details on randomisation nor allocation concealment.

Direct population.

Risk of selection bias as there is no clear method of randomisation nor allocation concealment. No risk of performance or attrition bias. Unclear risk of detection bias, as it was not stated how outcomes were measured.

Mehta V; Singhi P; Singhi S;

Reference number 202 Study Type Randomised Controlled Trial RID: 364
Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial

2007 Oct J Child Neurol PGS 1191 1197

Number of subjects 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.

23 December 2011 Page 268 of 364
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 10 microg/kg/min until SE was controlled or a maximum dose of 100 microg/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 studies

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.

Funding

Not reported.

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. No power calculation given sample size was small.

How directly applicable to population of the guideline?

Direct population.

Internal Validity

No risk of selection and attrition bias. Unclear performance and detection bias, as it is an un-blinded study. No further explanation provided as to why the study was not blinded.

Mpimbaza A;Ndeezi G;Staedke S;Rosenthal PJ;Byarugaba J;

Reference number 177  Study Type Randomised Controlled Trial  RID: 359

Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial  
2008 121 Pediatrics  
Jan  

Number of subjects Total n=330. Diazepam group: n= 165; Midazolam group: n= 165;

23 December 2011 Page 269 of 364
Diazepam versus midazolam:

Sex: male: 82 (49.7%) s 84 (50.9%); Age, median (IQR), months: 18 (11.5-36) vs 17 (10.5-30); Clinical features: axillary temperature, mean degrees centigrade: 38.2-/-1.15 vs 38.2+/-1.16; no. of convulsions in 24 hours before treatment, median (IQR): 2 (1-4) vs 3 (1-4); Classification of convulsion: Febrile: 115 (69.7%) vs 121 (73.3%); Generalised: 134 (81.2) vs 135 (81.8); Focal: 31 (18.8) vs 30 (18.2); Clinical diagnosis included severe malaria (highest), cerebbral malaria, meningitis, pneumonia, and epilepsy.

Recruitment: Patients presenting at the ACU at Mulago Hospital, Kampala, Uganda who had a seizure that lasted >5 minutes while in the unit were screened for enrollment.

Setting: Pediatric emergency unit, Mulago Hospital, Uganda.

Interventions/Test /Factor being investigated
Rectal diazepam versus buccal midazolam.

For buccal treatment a syringe was placed between the teeth and the cheek and the drug or placebo was administered. For rectal diazepam the drug or placebo was administered via a tube inserted 3 to 4cm into the rectum and flushed with air to ensure complete delivery of the drug.

During seizure oxygen administered by nasal prongs. Peripheral oxygen saturation and bp were recorded on study drug administration and at 5,10,20,40 and 60 minutes after. Random blood sugar level determined with glucometer. Two thick blood films prepared and 1 stained with field stain and the other with Geimsa, both were read by professionals in that field.

Both drugs administered at ~0.5mg/kg (2.5mg for 3-11 months of age; 5mg for ages 1-4 years; 7.5mg for ages 5-9 years; and 10mg for ages 10-12 years.

Comparisons Buccal midazolam versus rectal diazepam and 2 matched placebos.

Length of Study / Follow-up
Peripheral oxygen saturation and bp were recorded on study drug administration and at 5,10,20,40 and 60 minutes after. 24 hours after study drug administration or until cessation of study due to loss of follow-up or death.

Outcome measures studies Primary: cessation of visible seizure activity within 10 minutes, without recurrence within the hour. Secondary: proportion with cessation of convulsions within 10 minutes; proportion of seizure recurrence in subsequent hour and within 24 hours.

Results Diazepam versus midazolam:

Cessation of seizures within 10 minutes: 114 (69.1%) vs 125 (75.8%). RR: 0.91; 95% CI 0.80-1.04, p=0.175.

Median time to cessation fo seizures: 4.4 minutes, IQR (interquartile range): 2.72-6.58 vs 4.8, IQR 3.02-6.52, p=0.518.

Seizures recurred within 1 hour: 20/114 (17.5%) vs 10/125 (8%). RR 2.19, 95% CI 1.07-4.50, p=0.026. Time (median) to experience a seizure recurrence in the subsequent hour after initial control: 20 minutes (IQR 11-47.2) vs 25 minutes (IQR 2.75-36.7), p=0.492.

Seizures recurred within 24 hours of treatment: 51 (46.3%) vs 47 (39.1%). The median time to recurrence wazs 1.8 hours (IQR 0.93-3.48) vs 5.11 hours (IQR 1.08-10, p=0.001).

Funding Fogarty International Centre of the National Institutes of Health grant. Financial support from Nuffield Foundation, UK.
The authors concluded that in this study of treatment for prolonged seizures in African children, patients who received buccal midazolam were more likely than those who received rectal diazepam to have successful control of seizures. Buccal midazolam was as safe as rectal diazepam.

90% power required n=176 in each arm, whereas only N=165 were randomised in each arm.

Selection bias: low risk of bias.
Performance bias: unknown/unclear risk of bias - single blinded - study team were aware of the treatment code to which a patient was assigned.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.

Continuous midazolam versus diazepam infusion for refractory convulsive status epilepticus

Singhi S; Murthy A; Singhi P; Jayashree M;

Reference number 4784 Study Type Randomised Controlled Trial

2002 J Child Neurol pgs 106 110

Number of subjects 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 studies

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.

Funding

Not reported.

Does the study answer the question?

Relevant study

Effect due to factor in study?

Uncertain. No power calculation and there was a very low sample size and the study was not blinded.

How directly applicable to population of the guideline?

Direct population

Internal Validity

No risk of selection bias. Unclear risk of performance bias, as the study is open-label.
No risk of attrition bias. Unclear risk of detection bias, as it is an open label study.
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

**Reference number**: 220

**Study Type**: Randomised Controlled Trial

**Length of Study/ Follow-up**: 7 days.

**Outcome measures studies**: 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.

**Number of subjects**
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.
Intravenous VPA 20mg/kg as loading dose at rate of 40mg/min. Intravenous PHT at 20mg/kg (max rate of 50mg/min) after dilution with normal saline. Previously diazepam was given in doses of 0.2mg/kg at 2mg/min up to a maximum of 20mg before labelling as refractory to diazepam.

**Comparisons**
Intravenous sodium valproate versus intravenous phenytoin.
Not reported. 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. Treated with both drugs: 4/7 (57%) vs 2/5 (40%).< 18 years of age responding to treatment: 20/22 vs 12/16.

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%).

Funding

Not reported.

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.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Selection bias: high risk of bias: authors say randomised but no details given about randomisation except that they were randomly divided into groups A and B after matching for age and sex. No allocation concealment.
Performance bias: high risk of bias: no mention of blinding.
Attrition bias: low risk of bias.
Detection bias: unclear/unknown risk of bias: no reporting of blinding.

Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus

1995 Aug
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. Arm 1 = diazepam 0.3 - 0.4 mg/kg IV/rectal. Arm 2 = lorazepam 0.05 - 0.1 mg/kg IV/rectal.

Comparisons
IV Diazepam versus IV lorazepam.
Appears to be up to 24 hours.

Cessation of seizures.
Requirement for ventilatory support.
ICU admission.
Adverse effects.

Mean time for initial seizure to stop (sec)
(IV)
DIA: 26
LOR: 29

Additional drugs required to terminate presenting seizures
(IV)
DIA: 5/34
LOR: 1/27

Seizure stopped:
(IV)
DIA: 22/34
LOR: 19/27

(rectal)
DIA: 6/19
LOR: 6/6

Not reported.

Relevant study to the clinical question.

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. No power calculation.

Direct Population.

Risk of selection, performance and detection bias. Quasi-randomised as patients were assigned to drugs on odd and even dates. Unblinded study. Low risk of attrition bias.

Baysun S; Aydin OF; Atmaca E; Gurer YK;

A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures

2005 Nov
Clin Pediatr (Phila) pg 771-776

Number of subjects
Total n= 43. Midazolam n=23; Diazepam n=20.

Inclusion/Exclusion Criteria:
Inclusion criteria:
Aged 2 months to 12 years.
All patients who were seen at ER room of hospital included in study.

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.

Nasal oxygen given to all patients. ECG closely monitored and IV access established.
BP and oxygen saturation monitored.

Midazolam (dormicum 15mg midazolam/dmL ampul) given on even days by squirting around buccal mucosa. Diazepam (desitin rectal tube 10mg) given on odd days.

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.

Buccal midazolam versus rectal diazepam.

\[
\begin{array}{|l|}
\hline
\text{Comparisons} \\
\hline
\text{Midazolam versus diazepam:} \\
\text{\% of those whose seizure was stopped (in the first 10 minutes): 18 (78\%) vs 17 (85\%).} \\
\text{Time to cessation of seizure:} \\
\text{Midazolam:} \\
3 \text{ minutes: 12 (67\%);} \\
3 \text{ to 5 minutes: 3 (17\%);} \\
5 \text{ to 10 minutes: 3 (17\%);} \\
\text{Diazepam:} \\
3 \text{ minutes: 10 (59\%);} \\
3 \text{ to 5 minutes: 4 (23.5\%);} \\
5 \text{ to 10 minutes: 3 (18\%);} \\
\text{Anticonvulsant effect: midazolam was found to be as effective as diazepam (p>0.05).} \\
\text{Response periods of the 2 drugs showed no significant difference (p>0.05).} \\
\text{Non-responders (5) crossed over to diazepam:} \\
2 \text{ responded in 1 to 3 minutes;} \\
1 \text{ responded in 3 to 5 minutes;} \\
1 \text{ responded in 5 to 10 minutes;} \\
1 \text{ did not respond.} \\
\text{Non-responders (3) crossed over to midazolam:} \\
1 \text{ responded in 3 to 5 minutes;} \\
1 \text{ responded in 5 to 10 minutes;} \\
1 \text{ did not respond.} \\
\text{The need for a second drug for seizures not stopped iwht first was equal in the 2 groups, the difference was not statistically significant (p<0.05).} \\
\text{The 2 nonresponders for both drugs had midazolam infusion in 1 and phenytoin infusion in the other.} \\
\text{Not reported.} \\
\text{The authors concluded that buccal midazolam is safe and as effective as rectal diazepam for treating seizures.} \\
\text{No. No power calculation and no allocation concealment and quasi-randomised.} \\
\end{array}
\]
Internal Validity

Quasi randomised study - odds and even days randomisation.

Selection bias - high risk of bias - no allocation concealment and randomisation was by odd and even days.
Performance bias - high risk of bias - no mention of blinding; Different routes of administration.
Attrition bias - low risk of bias.
Detection bias - unknown/unclear - no mention of blinding.

How directly applicable to population of the guideline?
Direct.

Cereghino JJ; Mitchell WG; Murphy J; Kriel RL; Rosenfeld WE; Tревathan Е;

Reference number 4776
Study Type Randomised Controlled Trial
Treatment type Treating repetitive seizures with a rectal diazepam formulation: a randomized study. The North American Diastat Study Group
1998 pg 51
1274 1282

Number of subjects
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.

Inclusion/Exclusion Criteria:
Inclusion criteria:
Outpatients or institutionalised patients aged 2 years or older with documented history of Acute repetitive seizures (ARS);
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;
At least 2 episodes of ARS had to have occurred within 1 year and one episode within 6 months of study entry;
Maximal weight 111kg.
Postmenarcheal women had to used a standard form of birth control, or abstinence, if capable of becoming pregnant.
Normal results on rectal examination and a negative result for blood in stool at study entry.
Availability of a caregiver to administer drug accurately and to monitor the patient during treatment and to complete the data collection forms.
Written consent from parent or legal guardian.

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 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
ARS - various definitions of ARS given.
Diastat versus placebo:
Sex: male: 31 (55%) vs 26 (45%) female: 25 (45%) vs 32 (55%).
Age group (years):
Athena. One of authors has been a paid consultant to provide expert testimony to the FDA Advisory Board for Diastat. They are familiar with those who received placebo. Caregivers could administer treatment safely and effectively in a no medical setting.

**Interventions/Test**

Single administration of Diastat (diazepam gel) versus matching placebo.

**Recruitment:**

Not reported.

**Setting:**

29 centres in North America.

**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.

5 mg or 10 mg of diazepam or placebo for children; 10, 15, or 20mg diazepam or placebo for adults. Given in 3 and 5mL syringes which were prefilled and packaged identically and supplied with a rectal tip and water-soluble lubricant. Dosage based on patient age and weight and rounded up so no-one treated with less than 90% or more than 1890% of target dose.

**Comparisons**

Diazepam versus placebo.

**Length of Study/ Follow-up**

Patients exited the study after treatment of one ARS episode.

**Outcome measures studies**

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).

**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.

**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.
Internal Validity

Multicentre, randomised, parallel, double-blind, placebo-controlled study. Randomisation was in blocks by study site and patient age group - randomisation codes were generated by a statistician and then given to the clinical pharmacist (who was the only unblinded staff member). Patients were randomised after screening as they were enrolled by the clinical pharmacist, who dispensed the study medications as prescribed by the investigator.

Selection bias: unclear risk of bias: there was details of randomisation but no mention of allocation concealment methods.

Performance bias: unknown/unclear risk of bias: the authors stated that the study was double-blind. However they do not give details of blinding except that the control group were placebo-matched and the clinical pharmacist who enrolled the patients and who dispensed the appropriate medication were unblinded. The placebo group had significantly more patients using carbamazepine (27% diastat patients vs 50% placebo patients) or lorazepam (2% diastat vs 17% placebo than the diastat group. The diastat patients had significantly more patients using clonazepam (20% diastat versus 5% placebo) or phenobarbital (23% diastat patients versus 9% placebo patients). They thought it was unlikely to have an impact on the study as all patients were refractory and continued to have seizures despite the fact most received polytherapy at optimal doses of each AED.

Attrition bias: unclear/unknown risk of bias: there was no ITT; 27% dropped out from the study after randomisation. 20 diastat and 24 placebo did not receive the study medication. Of those not treated none were the result of an adverse event, change in medical condition or death.

Detection bias: low risk of bias.

Patient Characteristics

- 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.

How directly applicable to population of the guideline?

Direct.

Reference number 74

A prospective, randomized study comparing intramuscular midazolam with intravenous diazepam for the treatment of seizures in children.[see comment]

1997 Apr

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.


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.
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.

IM midazolam versus IV diazepam.

Not reported.

The authors concluded that IM midazolam is an effective anticonvulsant for children with motor seizures. It may be particularly useful in physicians' offices, in the prehospital setting and for children with difficult IV access.

Internal Validity

There were different modes of administration. No ITT analysis.

Selection bias: high risk of bias - no allocation concealment method mentioned.

Randomisation method mentioned - patients randomly selected by computer to receive midazolam or diazepam but no other details.

Performance bias: high risk of bias - no mention of blinding.

Attrition bias: high risk of bias - no ITT analysis. 4 dropped out from diazepam arm. Not large sample.

Detection bias: unknown/unclear risk of bias - no blinding mentioned.

Setting:

ED of children and general hospitals (3), USA.

Interventions/Test / Factor being investigated

Intramuscular midazolam versus intravenous diazepam.

Length of Study/ Follow-up

Not reported.

Outcome measures studies

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 unsuccessful 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.

Funding

Not reported.

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.

How directly applicable to population of the guideline?

Direct.
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.
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 o, 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 8vs 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.
Caregivers and patients returned to the clinic 72 hours after treatment review the recorded data. 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.

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.

The authors conclude that rectal diazepam gel, administered at home by trained care givers, 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.

How directly applicable to population of the guideline?
ARS not status epilepticus.

Internal Validity
Prospective, randomised, double-blind, placebo-controlled, parallel-group design.
All patients who received at least one dose of study medication were included in the analysis.
Selection bias: high risk of bias; block randomisation. No details of allocation concealment. Baseline differences in race.
Performance bias: low risk of bias.
Attrition bias: unknown/unclear risk of bias.
Detection bias: low risk of bias.

Fallah R; Gofrani M;

Reference number 608 Study Type Randomised Controlled Trial RID: 754
Comparison of intravenous lidocaine and midazolam infusion for refractory convulsive status epilepticus in children
2007 5 PGS 287 290

Number of subjects
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 of 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;

Patients admitted in the ICU of children's hospital.

Mofid children's hospital, Iran.

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 recurrent. Followed by phenytoin (15-20mg/kg) infused intravenously over 20 minutes. If seizures recurrent, 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.

IV lidocaine vs IV midazolam as second line treatment.

Midazolam group: given every 15 minutes until seizures controlled or max dose reached. If effective infused up to 24 hours; Lidocaine group: if not stopped within 15 minutes it was increased every 15 minutes until controlled. Then infused up to 12 hours.

Cessation of seizures; safety of drugs;

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.

The authors concluded that lidocaine can be used in refractory status epilepticus treatment especially when respiratory care and intubation facilities are not present.

No. No power calculation. Poor methodology.

Direct.

Selection bias: high risk of bias - says selected on systematic randomisation but no details and no mention of allocation concealment.
Performance bias: high risk of bias - no blinding.
Attrition bias: low risk of bias.
Detection bias: unknown/unclear risk of bias - no blinding.
Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: prospective randomized study

Total n=45. diazepam group n=22; midazolam group: n=23.

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;

Nasal oxygen given to all patients. Electrocardiogram closely monitored and IV access established. Biochemical tests and arterial blood gas measurements evaluated.

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.

Heart rate, respiratory rate and bp were monitored after 5 and 10 minutes.

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.

Rectal diazepam versus intranasal midazolam.

% of those whose seizure stopped within 10 minutes: diazepam 13/22 (60%) vs midazolam 20/23 (87%);

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%).
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.

**Internal Validity**

**Selection bias:** high risk of bias - rectal diazepam was given on the odd days of the month and midazolam was given on the even days of the month; no allocation concealment.

**Attrition bias:** high risk of bias - no mention of blinding.

**Detection bias:** low risk of bias.

**Funding**

Not reported.

**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.

**How directly applicable to population of the guideline?**

Direct.

**Selection bias:** high risk of bias - rectal diazepam was given on the odd days of the month and midazolam was given on the even days of the month; no allocation concealment.

**Performance bias:** high risk of bias - no mention of blinding; different routes of administration.

**Attrition bias:** high risk of bias - no mention of blinding.

**Detection bias:** high risk of bias - no mention of blinding.

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**Mahmoudian T; Zadeh MM;**

**Reference number** 696  
**Study Type** Randomised Controlled Trial  
**RID:** 461

Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children

2004 Apr  

**Number of subjects** 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**

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. IV diazepam 0.2mg/kg; midazolam solution 5mg/ml intranasally.
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 10 minutes.
Outcome measures studies 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.

Funding Not reported.

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.

How directly applicable to population of the guideline? Direct.

Internal Validity
Brief communication. Quasi-randomised: odds and evens randomisation.
Selection bias: unclear/unknown risk: odds and evens randomisation but allocation concealment by opaque envelopes.
Performance bias: low risk of bias.
Attrition bias: low risk of bias.
Detection bias: low risk of bias.
All patients had generalized tonic-clonic seizures. Sixteen patients had a mean ± SD age of 3.83 ± 3.79 years and received Midazolam. Another 16 patients with a mean ± age of 5.08±4.82 were treated with Propofol.

### Effect due to factor in study?
No details on randomisation nor allocation concealment. Unblinded study. Risk of bias in this study. No power calculation and very small sample size.

### How directly applicable to population of the guideline?
Direct Population.

### Internal Validity
Risk of selection, performance and detection bias as no details on randomisation, allocation concealment and no blinding. No further explanation provided as to why the study was not blinded. No risk of attrition bias.

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References:

**Mahvelati F; Tonekaboni H; Javadzade M; Ghofrani M;**

Reference number 1372  
Study Type Randomised Controlled Trial  
RID: 571  
The efficacy of propofol and midazolam in treatment of refractory status epilepticus in children  
2007 32  
pgs 74 79

**Recruitment:**  
Patients being treated at an Intensive Care Unit.

**Setting:**  
Iran. ICU

**Interventions/Test / Factor being investigated**  
Propofol versus Midazolam. 0.3mg/kg Diazepam, 20mg/kg Phenytoin and 10mg/kg Phenobarbital intravenously.

**Comparisons**  
IV Propofol versus IV Midazolam.

**Length of Study/ Follow-up**  
Appears to be up to 48 hours.

**Outcome measures studies**  
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.

**Funding**  
Not reported.

**Does the study answer the question?**  
Relevant to the clinical question.

**Number of subjects**  
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 ± SD age of 3.83 ± 3.79 years and received Midazolam. Another 16 patients with a mean ± age of 5.08±4.82 were treated with Propofol.

**Reference number**  
1372

**Number of subjects**  
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 ± SD age of 3.83 ± 3.79 years and received Midazolam. Another 16 patients with a mean ± 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. 0.3mg/kg Diazepam, 20mg/kg Phenytoin and 10mg/kg Phenobarbital intravenously.

**Comparisons**  
IV Propofol versus IV Midazolam.

**Length of Study/ Follow-up**  
Appears to be up to 48 hours.

**Outcome measures studies**  
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.

**Funding**  
Not reported.

**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. No power calculation and very small sample size.

**How directly applicable to population of the guideline?**  
Direct Population.

**Internal Validity**  
Risk of selection, performance and detection bias as no details on randomisation, allocation concealment and no blinding. No further explanation provided as to why the study was not blinded. No risk of attrition bias.

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**McIntyre J; Robertson S; Norris E; Appleton R; Whitehouse WP; Phillips B;Martland T; Berry K; Collier J; Smith S; Choonara I;**

Reference number 4591  
Study Type Randomised Controlled Trial  
RID: 57

23 December 2011  
Page 287 of 364
Most children were aged between 1 and 4 years (109 [62%] and 135 [62%], respectively). 14 infants (6%) were 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.

Buccal midazolam compared to rectal diazepam as the first line treatment of children aged 6 months to 15 years presenting to an emergency department with active generalised tonic-clonic seizures including established convulsive status epilepticus. 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. Buccal midazolam (approximately 0.5mg/kg) compared to rectal diazepam (0.5mg/kg). Determined by the child's age and was designed to give about 0.5 mg/kg (2.5mg for children aged 6-12 months; 5 mg for 1-4 years, 7.5mg for 5-9 years, and 10 years and older).

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.

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).

By SEARCH, Derbyshire Children's Research Fund, and Alder Hey Children's Hospital Research Fund.
Relevant study to the clinical question.

Internal Validity

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. Power calculation: 107 episodes required in each group and 109 and 110 episodes occurred in the groups.

Risk of selection bias, as no detail on allocation concealment. Unclear risk of performance and detection bias, as it is an 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. No risk of attrition bias.

Does the study answer the 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. Power calculation: 107 episodes required in each group and 109 and 110 episodes occurred in the groups.

How directly applicable to population of the guideline?

Direct Population.

Risk of selection bias, as no detail on allocation concealment. Unclear risk of performance and detection bias, as it is an 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. No risk of attrition bias.

**Misra UK; Kalita J; Patel R;**

Reference number 4655 Study Type Randomised Controlled Trial RID: 125

Sodium valproate vs phenytoin in status epilepticus: a pilot study

2006 67 pgs 340 342

Number of subjects 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 PHR 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 Phenyltoin. Subsequent failure was treated by diazepam or lorazepam. VPA 30mg/kg in 100ml saline infused over 15 minutes. PHT group 18mg/kg in 100ml saline infused immediately at a rate of 50mg/minute.

Comparisons IV VPA vs IV PHT.

Length of Study/ Follow-up

Up to 24 hours.

Outcome measures studies

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).

Funding
Not reported.

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. Power calculated at 80% but this was not reached and so the power was 71%.

How directly applicable to population of the guideline?
Direct population.

Internal Validity
Risk of selection, performance bias and detection, as no detail on allocation concealment and blinding. No risk of attrition bias. No ITT analysis reported.

Scott RC; Besag FM; Neville BG;

Reference number 4778
Study Type Randomised Controlled Trial

Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial
1999 353

Number of subjects 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.

Midazolam 2mL (10mg) and rectal diazepam (10mg)

Comparisons
buccal administration of liquid midazolam and rectal administration of liquid diazepam

Length of Study/ Follow-up
Emergency care

Outcome measures studies
Termination of seizures, Time to response, Seizure duration, Oxygen saturation and blood pressure.
Results

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).

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).

Time from administration to end of seizure did not differ significantly between the two treatments.

The median time from arrival of the nurse to administration of medication was 2 min.

Funding

Not reported.

Does the study answer the question?

Relevant study to the clinical question.

Effect due to factor in study?


How directly applicable to population of the guideline?

Direct.

Internal Validity

No risk of selection bias. Unclear risk of attrition bias, as main outcome is episode counts and not the number of participants having the episode. Unclear risk of performance and detection bias, as no blinding is mentioned in study.

Shaner DM; McCurdy SA; Herring MO; Gabor AJ;

Reference number 484

Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin

1988 38

February

Number of subjects

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. Two 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

Diazepam and phenytoin versus phenobarbital:

Mean age +/- SD (*years): 43.8 +/- 16.5 versus 55.9 +/- 19.4.

History of previous seizures (n): 14 vs 11.


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.

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).

Recruitment:

Presenting to the ER with status epilepticus.

Setting:

USA?

Interventions/Test /Factor being investigated

Diazepam and phenytoin versus phenobarbital as initial therapy.

Diazepam infused at 2mg/min IV. Drug administration was ended when convulsions stopped or after 20mg administered. Phenytoin was administered at the same time at 40mg/min. Loading dose of 18mg/kg phenytoin given if serum phenytoin levels unknown or 0-4mg/l. 75% of the calculated loading dose was administered at pretreatment levels between 5 and 9mg/l. 50% of the calculated loading dose if initial levels were 10-15mg/l or if known to be taking phenytoin regularly as an outpatient and 25% of calculated loading dose if initial levels were 16-20mg/l. If convulsions stopped after 20mg dose then a continuous IV infusion of diazepam was delivered at 40ml/hr (8mg/hr) was started. General anaesthesia was considered if seizure activity continued. Phenobarbital was infused at 100mg/min until dose of 10mg/kg administered. If continued to convulse after 10 minutes phenytoin infusion was started as in the diazepam and phenytoin protocol. Simultaneously additional IV phenobarbital was administered at a rate of 50mg/min.

Comparisons

IV Diazepam and IV phenytoin versus IV phenobarbital as initial therapy.

Length of Study/ Follow-up

Not reported.

Outcome measures studies

Response latency; cumulative convulsion time; adverse events; death.

Results

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).

The median response latency was shorter for the phenobarbital group compared to the diazepam group (5.5 vs 15 minutes, p<0.10).

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.

Funding

Not reported.
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.

This does not point out that some of the patients who were on phenobarbital (5) were then put on phenytoin.

No power calculation and small sample.

Selection bias: Unclear/unknown risk of bias - envelope used for allocation concealment but not mentioned if opaque.

Performance bias: High risk of bias - no blinding.

Attrition bias: Low risk of bias; there was no ITT analysis even though 5 of the PHB patients were treated with Phenytoin.

Detection bias: Unknown/unclear risk of bias - no blinding.

Sreenath TG; Gupta P; Sharma KK; Krishnamurthy S;

Reference number 582

Study Type Randomised Controlled Trial

Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: A randomized controlled trial

2010 14

Number of subjects 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.
Lorazepam was given intravenously in 0.1mg/kg and diazepam in 0.2/kg. If iv access not possible, the drug was given rectally in the same dose.

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 studies
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.

Funding

None

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.

How directly applicable to population of the guideline?

Direct.

Internal Validity

The main performance bias affecting the internal validity of the study was that it was unblinded study. Low risk of detection and attrition bias.

Talukdar B; Chakrabarty B;

Reference number 53

Study Type: Randomised Controlled Trial

Efficacy of buccal midazolam compared to intravenous diazepam in controlling convulsions in children: a randomized controlled trial

2009 Nov

Page 744-749

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 studies:

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.

Funding

None.

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.

Internal Validity

The study was unblinded and this would impact on the validity of the study and would bias the results. No clear information on randomization and no allocation concealment.

Treuiman DM; Meyers PD; Walton NY; Collins JF; Colling C; Rowan AJ; Handforth A; Faught E; Calabrese VP; Uthman BM; Ramsay RE; Mamdani MB;

Reference number 4783

A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group


ClinicalTrials.gov ID: 271

Number of subjects

Total n=570.
Lorazepam n=146.
Phenobarbital n=133.
Diazepam and phenytoin n=146.
Phenytoin n=145.

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.

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.
- Toxic effects of therapeutic or recreational drug: 6.3 vs 5.2.
- Alcohol withdrawal: 6.1 vs 0.7.

Recruitment:
Not reported.

Setting:
16 Veterans medical centers & 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:
<table>
<thead>
<tr>
<th>Tubex</th>
<th>Lorazepam</th>
<th>Phenobarbital</th>
<th>Diazepam &amp; Phenytoin</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial A</td>
<td>Dummy</td>
<td>Dummy</td>
<td>Dummy</td>
<td>Dummy</td>
</tr>
<tr>
<td>Vial B</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Diazepam</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Vial C</td>
<td>Dummy</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Vial D</td>
<td>Dummy</td>
<td>Dummy</td>
<td>Phenytoin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Vial E</td>
<td>Dummy</td>
<td>Dummy</td>
<td>Phenytoin</td>
<td>Dummy</td>
</tr>
</tbody>
</table>

Active drug in second treatment box:
| Phenytoin | Phenytoin | Lorazepam | Lorazepam |

Active drug in third treatment box:
| Phenobarbital | Lorazepam | Phenobarbital |

Comparisons
Lorazepam versus phenobarbital versus phenytoin versus diazepam.

Length of Study/ Follow-up
30 days after treatment.

Outcome measures studies
Rate of successful initial treatment.

Results
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.

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].

23 December 2011
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.

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.

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.

No power calculation but large sample size.

Selection bias: unclear/high risk of bias - authors state that randomly assigned but no details given except that separate randomisation schemes were used at each site for each type of status epilepticus. No mention of allocation concealment.
Performance bias: Low risk of bias - double-blinded.
Attrition bias: low risk of bias - mainly due to misclassification and not greatly different between groups.
Detection bias: Low risk of bias - double-blinded.

Funding

Internal Validity
Comparing the effect of intravenous midazolam with rectal sodium valproate in controlling of children with refractory status epilepticus

**Number of subjects**
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 Phenobarbital (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 studies**
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.

**Funding**
Not reported.

**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 inadequate randomisation methods (odd, even method), no allocation concealment, nor blinding. Main outcome not clearly reported in the study. Baseline characteristics between groups not clear. No power calculation given and very small sample size.

**How directly applicable to population of the guideline?**
Direct population.
Internal Validity

Risk of selection, performance and detection bias. Unadequate randomisation methods (odd, even method), no allocation concealment, nor blinding. Unclear risk of attrition bias, as main outcome not clearly reported, and baseline characteristics between groups not clear

Question: Which AEDs are clinically effective and cost-effective for people with Non-Convulsive status epilepticus?
Holsti M; Dudley N; Schunk J; Adelgais K; Greenberg R; Olsen C; Healy A; Firth S; Filloux F;

Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy

Reference number: 5297
Study Type: Randomised Controlled Trial
RID: 879

Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy

2010 164
Aug

Number of subjects: 358
N allocated to IN-MAD group (no. received IN-MAD): 179 (50)
N allocated to RD group (no. received RD): 179 (42)

Inclusion/Exclusion Criteria:
Inclusion criteria:
- Known seizure disorder of any type
- < 18 years old
- Prescribed a rescue antiepileptic for home use by their neurologist.

Exclusion criteria:
- Not prescribed a home rescue medication by their neurologist
- ≥ 18 years of age
- Prescribed lorazepam as home rescue medication

Patient Characteristics
Group 1 (IN-MAD)
Age median (IQR): 5.6 (2.5-0.7)
Male: 24 (48%)
Taking seizure medications: 41 (82%)
Caretakers who have previously given RD: 21 (42%)
Overall satisfaction with RD on enrolment median on a scale of 0-10 points (IQR): 6 (4-9)
Who missed dose(s) of daily seizure medications within 24h of seizure: 6 (12%)
Dose mg/kg, mean (SD): 0.20 (0.04)

Group 2 (RD)
Age median (IQR): 6.9 (3.8-10.8)
Male: 22 (52%)
Taking seizure medications: 32 (76%)
Caretakers who have previously given RD: 13 (31%)
Overall satisfaction with RD on enrolment median on a scale of 0-10 points (IQR): 8 (6-9)
Who missed dose(s) of daily seizure medications within 24h of seizure: 0 (0%)
Dose mg/kg, mean (SD): 0.41 (0.13)

Recruitment: Paediatric neurology clinic- identification of potential patients by research assistant.
Setting: Patients' homes

Interventions/Test Factor being investigated
IN-MAD (intranasal midazolam) 0.2mg/kg (maximum 10 mg), Rectal diazepam (RD) 0.3 to 0.5 mg/kg (maximum 20 kg)

Comparisons
IN-MAD (intranasal midazolam) v Rectal diazepam (RD)

Length of Study/ Follow-up not stated.
Outcome measures studied
1 total seizure time after med administration 2 total seizure time, time to medication administration, resp complications, emergency medical service support, emergency department visits, hospitalisations + caretakers’ ease of admin. + satisfaction with the medication.

Results
Time to seizure cessation from medication administration
Group 1 (IN-MAD): 3 minutes (median), IQR 1.0-10.0
Group 2 (RD): 4.3 minutes (median), IQR 2.0-14.5
Difference: 1.3 minutes
95% CI: 0.0-3.5
p value: 0.09

Total seizure time
Group 1: 10.5 minutes (median), IQR 7.0-18.0
Group 2: 12.5 minutes (median), IQR 7.0-30.0
Difference: 2.0 minutes
95% CI: -1.0 to 5.7
p value: 0.25

Time to rescue medication administration
Group 1: 5.0 minutes (median), IQR 4.0-7.0
Group 2: 5.0 minutes, IQR 4.0-8.0
Difference: 0.0 minutes
95% CI: -1.0 to 1.0
p value: 0.57

Ease of administration with study medication (scale where 0= not at all satisfied and 10= very satisfied)
Group 1: 10 (median), IQR 9-10
Group 2: 9 (median, IQR 7-10)
OR: 1
95% CI: 0.1-10
p value: 0.02

Overall satisfaction with study medication (scale where 0= not at all satisfied and 10= very satisfied)
Prehospital: called 911
Group 1: 21 (42%)
Group 2: 16 (38%)
OR: 1.2
95% CI: 0.5-3.0
p value: not sig

Prehospital: seizure when EMS arrived
Group 1: 8 (16%)
Group 2: 8 (19%)
OR: 0.8
95% CI: 0.2-2.8
p value: not sig

Prehospital: seizure treated by EMS
Group 1: 2 (4%)
Group 2: 4 (10%)
OR: 0.4
95% CI: 0.0-3.0
p value: not sig

Prehospital: transport by ambulance
Group 1: 10 (20%)
Group 2: 12 (29%)
OR: 0.6
95% CI: 0.2-1.8
p value: not sig

ED visit
Group 1: 21 (42%)
Group 2: 17 (40%)
OR: 1.1
95% CI: 0.4-2.7
p value: not sig

Seizure in the ED
Group 1: 5 (10%)
Group 2: 4 (10%)
OR: 1.1
95% CI: 0.2-5.7
p value: not sig

Seizure treated in ED
Group 1: 5 (10%)
Group 2: 5 (12%)
OR: 0.8
95% CI: 0.2-3.9
p value: not sig

Intubation in ED
Group 1: 1 (2%)
Group 2: 0 (0%)
OR: 0.8
95% CI: 0.0-infinity
No significant differences were found between the 2 groups in terms of the outcome measures. Caretakers were more satisfied with IN-MAD and report that it was easier to give than RD.

Funding

Primary Children’s Medical Centre Foundation, Salt Lake City, Utah

Does the study answer the question?

No significant differences were found between the 2 groups in terms of the outcome measures. Caretakers were more satisfied with IN-MAD and report that it was easier to give than RD.

Effect due to factor in study?

90% power calculated at n=60 in each group. Only n=50 and n=42 analysed.

How directly applicable to population of the guideline?

See GRADE

Internal Validity

• Times were recorded by parents- recall bias
• Not blinded
• Possible selection bias
• Caretakers may have had more experience with a study medication or preference toward one treatment which could have affected administration of study medication and recorded times.
• Parent who received the training may not have been the one giving treatment.
• Differences in caretakers assessment of when a seizure stopped.
• Researchers had full access to medical records at one of the participating institutions.
• 6/8 of withdrawals were in the RD group.
• Randomisation: blocks of 6 using a computer programme by a statistician
• Allocation concealment: sequence was inside a numbered folder and concealed until intervention was assigned.
• Blinding: not double blind- ‘attending physicians, research assistants and patients/caretakers were blinded to the rescue drug to be prescribed until after written consent was obtained’

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 risk of selective outcome reporting.

Adab N; Tudur SC; Vinten J; Williamson P; Winterbottom J;

Reference number 5217  
Study Type Systematic Review  
Common antiepileptic drugs in pregnancy in women with epilepsy  
2004  
pgs CD004 848

Number of subjects cohort

Inclusion/Exclusion Criteria:

Patient Characteristics

Recruitment:
Setting:

Interventions/Test Factor being investigated

Comparisons

Length of Study/ Follow-up  
Outcome measures studies

Results

Funding

Does the study answer the question? not reported.

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; uncertain due to studies limitations.
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?

How directly applicable to population of the guideline?

Internal Validity

The Newcastle-Ottawa Scale (NOS) was adapted to assess quality of non randomized studies; ascertainment of the cohort and control groups (method of recruitment, clinical setting and proportion of eligible mothers or children recruited), basis for the diagnosis of epilepsy, basis for the diagnosis of epilepsy, ascertainment of exposure, comparability of the cohort to the control group and attention to potential confounding factors, standard and valid criteria for assessment of outcomes, blinding of assessors to exposure and completeness of follow up. No meta-analysis was performed due to study’s limited quality and great degree of heterogeneity. Therefore, only a qualitative description of the results is given.
No sources of funding were used for this study.

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 McCarthey scale, the mean FSIQ of children exposed to carbamazepine was not statistically different from the unexposed control group.

The combinability of data across studies was tested by tests of heterogeneity. However, the quality of studies was not taken into consideration in the meta-analysis of studies.
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

Outcome measures studies
1) proportion of children with congenital anomalies 2) proportion of children with neonatal conditions 3) proportion of neonatal deaths 4) developmental impairment

Results
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. 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 hypoplast left heart syndrome, 2/61 had cranial nerve palsy. Hypoplasia of nails affected 11/61 (18%) of children of epileptic mothers.
2) neonatal conditions were diagnosed in 26/61 children in the study group (43%) and 6/62 (10%) in control group.
3) 2/61 neonatal deaths among children of epileptic mothers.
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.

Funding
North Western Regional Health Authority.

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 good methodology, however no estimation of statistical power was performed so uncertain about the effect of the exposure on the outcomes measures.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Low risk of selection bias; the design of the study balanced for potential confounders between the two groups. Low risk of performance and detection bias. Low risk of attrition bias.

Gaily E; Kantola-Sorsa E; Granstrom ML;
The children were examined at 66+3 months of age.

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 studies
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
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).
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.
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 (-8, -2), P=0.06).
4) Any AED exposure in utero 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 -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.

Funding
Not reported.

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.
Leavitt AM; Yerby MS; Robinson N; Sells CJ; Erickson DM;

Reference number 4936  Study Type Cohort  RID: 844

Epilepsy in pregnancy: developmental outcome of offspring at 12 months

1992 42  pgs 141 143

Number of subjects  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 studies
1) minor anomalies 2) mental development 3) psychomotor development

Results
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.

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).

3) There was no statistically significant difference between the two groups on the Psychomotor Development Index.

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).

Not reported.

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.

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.

Unclear the risk of selection bias due to absence of allocation of treatments. Low risk of attrition bias although no information were given for the drop outs per arm. Low risk of detection and performance bias.

**Meador K; Reynolds MW; Crean S; Fahrbach K; Probst C;**

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Study Type</th>
<th>Systematic Review</th>
<th>RID:</th>
<th>862</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. [Review] [99 refs]</strong></td>
<td>2008 81</td>
<td>Epilepsy Res</td>
<td>PGS</td>
<td>1 13</td>
</tr>
</tbody>
</table>

**Number of subjects**

Population cross sectional studies

**Inclusion/Exclusion Criteria:**

**Patient Characteristics**

**Recruitment:**

Setting:

Interventions/Test Factor being investigated:

Comparisons

Length of Study/ Follow-up

Outcome measures studies

Results

Funding Shire Development Inc.
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 or more other AEDs 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 or more other AEDs was valproate with 25% (95% c.i. 5.97, 44.03).

**Internal Validity**

Although test for heterogeneity was significant, still results of studies were metaanalyzed. Poor reporting of the description of the studies.

Rovet JF; Cole S; Nulman I; Scolnik D; Altmann D; Koren G;

**Reference number** | 4959  
**Study Type** | Cohort  
**Effects of maternal epilepsy on children's neurodevelopment** |  
**1995 1**  
**Reference number** | 4959  
**Study Type** | Cohort  
**Effects of maternal epilepsy on children's neurodevelopment** |  
**1995 1**  
**Number of subjects** | 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 studies between 7 and 85 months of age (mean=29.8 months, sd=16.1 months)  
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### Results

<table>
<thead>
<tr>
<th>Outcome measures studies</th>
<th>PHT (n=16)</th>
<th>CBZ (n=24)</th>
<th>Difference in means (95%ci) (by Cochrane Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Index, T scores (Verbal, Perceptual, Quantitative, Memory, Motor)</td>
<td>108.2 (17.8) MDI</td>
<td>114.2 (17.8)</td>
<td>-6 (-17.26, 5.26) P=0.3</td>
</tr>
<tr>
<td>Cogn -0.75 (3.4)</td>
<td>106.0 (12.1)</td>
<td>-1.2 (-9.84, 7.44) P=0.8</td>
<td></td>
</tr>
<tr>
<td>Lang -3.13 (3.3)</td>
<td>-1.96 (3.0)</td>
<td>0.21 (-1.92, 2.34) P=0.8</td>
<td></td>
</tr>
<tr>
<td>Mo 0.38 (4.1)</td>
<td>-0.29 (4.1)</td>
<td>0.67 (-1.92, 3.26) P=0.6</td>
<td></td>
</tr>
<tr>
<td>Reynell scores (comprehension, expressive)</td>
<td>99.3 (28) PHT</td>
<td>93.5 (11.2) CBZ</td>
<td>5.80 (-12.31, 23.91) p=0.5</td>
</tr>
<tr>
<td>Verbal 50.3 (15.9)</td>
<td>46.0 (5.7)</td>
<td>4.30 (-5.68, 14.28) P=0.4</td>
<td></td>
</tr>
<tr>
<td>Perceptual 48.8 (14.6)</td>
<td>46.0 (7.1)</td>
<td>2.80 (-7.29, 12.89) P=0.6</td>
<td></td>
</tr>
<tr>
<td>Quantitat 45.9 (15.1)</td>
<td>45.8 (5.0)</td>
<td>0.10 (-9.21, 9.41) P=1.0</td>
<td></td>
</tr>
<tr>
<td>Memory 47.7 (14.5)</td>
<td>39.3 (3.8)</td>
<td>8.4 (-0.16, 16.96) P=0.05</td>
<td></td>
</tr>
<tr>
<td>Mortor 46.3 (13.7)</td>
<td>38.5 (7.9)</td>
<td>7.8 (-2.37, 17.97) P=0.13</td>
<td></td>
</tr>
</tbody>
</table>

### Funding

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%.

### How directly applicable to population of the guideline?

Direct.

### Internal Validity

Low risk of selection bias as both groups were matched for many confounding factors. Unclear the risk of attrition bias as no information given. Low risk of detection and performance bias.

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**Vanoverloop D; Schnell RR; Harvey EA; Holmes LB**

**Reference number** 4935

**Study Type** Cohort

**Cohort**

**RID:** 857

**Number of subjects**

N study group (exposed to phenytoin)=20 and n controls (unexposed)=98.

**Inclusion/Exclusion Criteria:**


**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

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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 studies**
1) intelligence (and two subtypes; verbal and performance intelligence) 2) visual motor integration 3) psycholinguistic abilities (two subtypes; grammatic closure and auditory association)

**Results**
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, -.012, P=0.05). 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<0.0001). 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).

**Funding**
In part by NIH Grant no 10910 and the Easter Seal Research Fund.

**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 auditory 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.

**How directly applicable to population of the guideline?**
Direct.

**Internal Validity**
Unclear the risk of attrition bias. Low risk of performance and deteciton bias. No exploration of confounding factors in analysis.
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).

Patient Characteristics

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.

Results

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 score (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)

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-Wellcome company and the Research Foundation of Pediatric Research of the Freemasons.

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.
How directly applicable to population of the guideline? Direct.

Internal Validity

Unclear the risk of selection bias. Low risk of detection and performance bias.
Barqawi R;

Reference number 448  Study Type Cohort  RID: 419

Evaluation of antiepileptic drugs in pregnancy in a Jordanian army hospital

FundingDoes the study answer the question? Effect due to factor in study? How directly applicable to population of the guideline?

Evaluation of antiepileptic drugs in pregnancy in a Jordanian army hospital

2005 Jul 11 EAST MEDITERRANEAN HEALTH J pgs 601-605

Patient Characteristics

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.

Comparison are made between participants and their children on carbamazepine, on carbamazepine and phenytoin and on no medication.

Inclusion/Exclusion Criteria:

Inclusion criteria: pregnant women aged 25-35 years, multiparous, with known past history of epilepsy for the last 5 years and no obvious cause of the disease, attending regularly the internal medicine clinic at King Husein Medical Centre, Amman, Jordan.

They were recruited from the medicine clinic at King Husein Medical Centre, Amman, Jordan. See inclusion criteria.

Number of subjects

N=50, Group A (carbamazepine)=16, Group B (carbamazepine and phenytoin)=16, group C (no medication)=18.

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.

How directly applicable to population of the guideline?

Direct.

Results

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.

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%).

Not mentioned.
Internal Validity

Unclear risk of selection bias as no information is given for the two groups in relation to other prognostic factors. Unclear also the risk of detection bias as no information are given for the measurement of outcome measures. Unclear risk of performance bias.

Gaily E; Kantola-Sorsa E; Granstrom ML;

Reference number 4940  
Study Type Cohort  
RID: 846

Specific cognitive dysfunction in children with epileptic mothers

1990 May  
DEV MED CHILD NEUROL  
pgs 403 414

Number of subjects
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 1979, 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 studies  
mental deficiency, borderline intelligence (defined as both scores for WIPPSI and LIPS<85, and at least one<70), proprotion 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.

Funding  
Rinnekoti Research Foundation, Espoo, Finland, the Foundation of Paediatric Research and Orion Foundation.

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?  
Uncertainty due to absence of information the methodological rigorous of the study couldn't be assessed. Uncertain about the statistical power of the study to detect a significant difference if it existed.

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Internal Validity

Unclear risk of selection and attrition bias. No information given regarding the drop outs. Low risk of performance bias.

Hanson JW;Myrianthopoulos NC;Harvey MA;Smith DW;

Risks to the offspring of women treated with hydantoin anticonvulsants, with emphasis on the fetal hydantoin syndrome

1976 Oct J Pediatr 89

Number of subjects
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 studies
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.

Funding
Not reported.

Does the study answer the question?
The mental performance score was significantly lower in the exposed group compared to placebo.
Internal Validity

Unclear risk of selection bias. No information on drop outs so unclear risk of attrition bias. No information on blindness.

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.

How directly applicable to population of the guideline?

Direct.

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 studies

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
Internal Validity

Because of the selective drop out of the study, the full matched pair design of the initial study could not be maintained, so unclear risk of attrition bias. Unclear also risk of performance bias as no blinding is reported.

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

2002 11
Dec

Number of subjects

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.
Epilepsy.

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 studies:
1) number of miscarriages 2) dysmorphic features 3) developmental delay 4) structural anomalies

Results:
1) 10/69 pregnancies were lost (miscarriages)
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.
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.
4) monotherapy with carbamazepine: no significant association with adverse outcome and CBZ dose in any assessment area.
5) monotherapy with phenytoin and lamotrigine: adverse features were absent or mild.
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.

Funding:
No funding.

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.

How directly applicable to population of the guideline?
Not clear.

Internal Validity:
This is an observational study in all but four cases the pregnancies were assessed prospectively. There was no control group of mothers with no history of epilepsy but within the population of women with epilepsy comparisons were made between different treatment groups (sodium valproate monotherapy, carbamazepine monotherapy and polytherapy).

Ornoy A; Cohen E;

Reference number 4930
Study Type Cohort
RID: 835

Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy

1996 75
Dec

Number of subjects 47 children whose mothers were treated on carbamazepine during pregnancy (Group A) and 47 control children (Group B).

23 December 2011
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
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
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 palate. 3/47 in Group B had major anomalies (unilateral stenosis, hypoplasia and a solitary cyst of the kidney)
2) in Group A 6/47 children had typical facial dysmorphic features as described in carbamazepine syndrome (uplifting palpebral fissure, epicanthic folds, micrognathia, broad nasal bridge, high arched palate or cleft palate. 0/47 children in Group B had dysmorphic features.
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.
4) All children with facial dysmorphic features (carbamazepine syndrome) had a development quotient or intelligence quotient below 90.

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.

How directly applicable to population of the guideline?
Unclear.

Internal Validity
Low risk of selection bias. Control children were matched by birth weight, gestational age, and parental socioeconomic status. Both groups were comparable also in relation to age at examination, weight and head circumference. Unclear performance risk as the paediatricians were not blinded.
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.

exposure to anticonvulsant during pregnancy. 2 comparisons were made; 1) between phenobarbitone in utero and general population, 2) between phenytoin and phenobarbitone exposure in utero.

Comparisons

All results were adjusted for ethnic group, SES and hospital.

1) comparison on the mental development between phenobarbitone exposure in utero (n= 35) compared to the general population (n=27,832) at 8 moths: 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).

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).

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).

Funding


No statistically significant differences were found on either the mental or 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?

Unable to assess study's methodology due to absence of information.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Unable to assess study's methodology due to absence of information.

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**van der Pol MC; Hadders-Algra M; Huisjes HJ; Touwen BC;**

<table>
<thead>
<tr>
<th>Reference number</th>
<th>Study Type</th>
<th>Cohort</th>
<th>RID</th>
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<td>4938</td>
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Antiepileptic medication in pregnancy: late effects on the children's central nervous system development

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<th>Year</th>
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<tr>
<td>1991</td>
<td>164</td>
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**Number of subjects**

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 studies**

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.

Not reported.

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.

How directly applicable to population of the guideline? Direct.

Low risk of attrition bias. Unlear risk of selection bias.
and 39.5 for the control infants.

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). 9 months follow up.

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 hypospadia 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 phenytoine group (N=21) was 346 (307-385) and for controls 344 (318-378) (mean difference -7.13,11.34).

Funding

Research Grant 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.

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 selection and attrition bias. The study used a control group of children with non epileptic mothers.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Prospective cohort study. Unclear risk of selection bias as controls were selected based on the place of birth. They had non epileptic mothers. However they were matched for gestational age and mode of delivery and the majority of them for sex. The two groups were comparable at baseline characteristics. Low risk of performance bias. Unclear risk of attrition bias as the information from drop outs were inconsistent. Low risk of detection bias as the methods used to determine outcomes were valid and reliable and the investigators were kept blinded to major prognostic factors, such as gestational age and mode of delivery and during the assessment of child's psychomotor development.

Question: Which AEDs are the most tolerable for older people

23 December 2011 Page 325 of 364
Grading: 1+  Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias

Brodie MJ; Overstall PW; Giorgi L;

Reference number 4722  Study Type Randomised Controlled Trial  RID: 838

Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group 1999 37  Epilepsy Res  pgs 81 87

Number of subjects 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

<table>
<thead>
<tr>
<th></th>
<th>LTG</th>
<th>CBZ</th>
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<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td>65-94</td>
<td>66-88</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>54/46</td>
<td>58/42</td>
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<tr>
<td>Wt (kg)</td>
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<td>68</td>
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<tr>
<td>Ht (cm)</td>
<td>164</td>
<td>164</td>
</tr>
<tr>
<td>Baseline seizures (mean)</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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 studies 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).

Funding Glaxo Wellcome
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? No power calculation, sample size was n=77 and n=76 but very high drop-out in carbamazepine arm and high drop-out in lamotrigine arm.
How directly applicable to population of the guideline? See GRADE
Internal Validity

Use of seizure diary may be inaccurate. Low risk of performance and selection bias. High risk of attrition bias, especially in CBZ group where 58% dropped out.

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] 2005 Jun 14 64 pgs

Reference number 534

Study Type Randomised Controlled Trial

Number of subjects 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 comedations 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%) vs 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 (46.5%) 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 51/196 (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 49/196 (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 Comparisons Length of Study/ Follow-up Outcome measures studies

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.

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? Uncertain. Good methodology. For a power of 90% the original proposed sample size was 720 patients based on being able to detect a 15% difference among the treatment groups on the primary outcome measures of retention at 12 months assuming an estimate of 65% retention for the standard drug. The number randomised was 593. There was a very high drop-out.

How directly applicable to population of the guideline? Direct.

23 December 2011 Page 329 of 364
Selection bias - low risk of bias. Randomisation separately for each site using varying block sizes. Nurse co-ordinator/site investigator phoned data co-ordinating centre where staff member assigned a nonconsecutive, site-specific patient number from a computer generated randomisation list. The patient number corresponded to a patient drug kit in the site's pharmacy.

Performance bias - low risk of bias.

Attrition bias - High risk of bias - High dropout especially in CBZ group, differences between CBZ and GBP drop-out (p=0.008) and between CBZ and LTG dropout (p<0.0001) were significant. High drop-out who voluntarily withdrew in all arms; high drop-out for all other reasons in all arms. Did not use an ITT analysis.

Double-blind, double-dummy study. Should be noted that majority of participants were men.

Detection bias - low risk of bias.

Changed age of enrolment from >/=65 years to >/=60 years.
Craig I; Tallis R;

Reference number: 4635

Study Type: Randomised Controlled Trial

Impact of valproate and phenytoin on cognitive function in elderly patients: results of a single-blind randomized comparative study

1994  35

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);
- Seizure type: generalised 8 vs 8; partial with generalisation 6 vs 5; complex partial 6 vs 5.

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 <150x10^9/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 tranquillisers) or drugs known to affect plasma PHT or VPA levels when the regimen was likely to change during the trial period.

Recruitment:
- Referred by GPs or consultants in geriatric medicine.

Setting:
- Salford or adjacent districts.

Interventions/Test /Factor being investigated

Phenytoin versus sodium valproate. PHT 100mg twice daily; VPA 200mg twice daily;
- After 2 and 4 weeks increased by 25mg PHT or 200mg VPA; Max 300mg PHT or 1000mg VPA;
- Mean steady state total daily doses at 6 weeks 247mg (175-275mg) PHT; 688mg (400-1000mg VPA).

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 studies

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 form 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 form letter cancellation time, which appeared to be better in PHT group. Significant of this is doubtful as observed only once. Other tests unchanged.
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.

Unclear - no allocation concealment or power calculation, and only 38 participants assessed and no ITT.

Selection bias: unclear risk of bias - no mention of allocation concealment. Randomisation method is mentioned. Performance bias: unclear bias - Single-blinded - the main investigator was blinded; the prescription was disclosed to the GP and the consultant; 4 patients inadvertently told the investigator their medication; blinding maintained until at least 3 months. No details given of how blinded medication but both received doses twice daily. Attrition bias: high risk of bias - It did not state the amount randomised initially to each arm and which arm the withdrawals withdrew from up to the first assessment at 6 weeks. Patients stratified for age, sex and seizure type; baseline test for significant differences in baseline scores found no significant differences. Protocol used for dosing and assessment - tests given in same setting and at same time of day.

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

Reference number 4723     Study Type Randomised Controlled Trial
A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy
2001    46    Epilepsy Res

Number of subjects 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

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

Sanofi UK; Parke Davis;
A comparison of monotherapy with lamotrigine or carbamazepine. Total daily dose: Lamotrigine 25mg once daily (od) weeks 1-2; 50mg od weeks 3-4; 100mg od week 5; 100 or 150mg od week 6; maintenance phase 100-700mg od. Carbamazepine: 100-1500mg/day.

Comparisons
Lamotrigine vs. carbamazepine.

Length of Study/ Follow-up
6 weeks dose escalation; 17 weeks maintenance.

Outcome measures
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.

Funding
Unknown

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?
No power calculation given.

How directly applicable to population of the guideline?
See GRADE

Compliance may also be an issue.

Internal Validity
Subset of elderly patients (aged 65 years or above).

Selection bias: high risk of bias - no allocation concealment; randomisation as 2:1 ratio with stratification by age and country;
Performance bias: high risk of bias - open study;
Attrition bias: high risk of bias - high withdrawal from the CBZ compared to the LTG group and low sample to begin with who were elderly.
Detection bias: low risk of bias.

Saetre E; Abdelnoor M; Amlie JP; Tossebro M; Perucca E; Tauboll E; Anfinsen OG; Isojarvi J; Gjerstad L;

Reference number 5089

Study Type Randomised Controlled Trial

Cardiac function and antiepileptic drug treatment in the elderly: a comparison between lamotrigine and sustained-release carbamazepine

2009 50
Aug

Number of subjects
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.
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.

Participants were recruited at Norwegian centers.

Comparison of efficacy between lamotrigine and carbamazepine in the elderly. Target dose at the end of titration period: LTG was 100 mg/day and for CBZ was 400 mg/day.

Between lamotrigine and carbamazepine.

There was a 4 week dose escalation and a 36 week maintenance phase.

1) withdrawal due to adverse events

ITT analysis: LTG 15/54 and CBZ 9/54

GlaxoSmithKline, Eastern Norway Regional Health Authority AND Ulleval University Hospital.

Yes. Although more participants in LTG withdrew due to adverse events compared to those in carbamazepine, this difference was not significant.

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.

Direct.

Unclear risk of selection bias as study was double blinded and the two groups were comparable but no allocation concealment was performed. High risk of performance bias as study was unblinded. and allocation concealment. High risk of attrition bias.

Reference number 611

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

2010 17

N=167 (CBZ 83 and LTG 84)

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.
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.
Target maintenance dose were 100 and 400 mg/day for LTG and CBZ respectively.

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 studies
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)

Funding
Eastern Norway Regional Health Authority and Ulleval University Hospital.

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. The power calculation was 190 patients for 80% power, which was not reached. High drop outs.

How directly applicable to population of the guideline?
Direct.

Internal Validity
Unclear risk of selection bias as no details of allocation concealment or randomisation method. High/unclear risk of attrition bias as high drop-out. Low risk performance and detection bias.

Saetre E;Perucca E;Isojarvi J;Gjerstad L;Study Group;.

Reference number 231 Study Type Randomised Controlled Trial RID: 377
An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly
2007 Jul
48

Number of subjects
Total randomised n=186. Lamotrigine n=94; Carbamazepine n=92.

Page 335 of 364
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 or five elimination half-lives in the period immediately preceding study entry; severe psychiatric disease or severe intellectual impairment; acute or chronic hepatic failure; significant unpaced AV defect; alcohol or substance abuse; 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 (68-71);
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 (tegretol 100 and 200mg divisible tablets).

Comparisons

Lamotrigine vs carbamazepine.

Length of Study/ Follow-up

4 week dose escalation phase; 36-week maintenance phase.

Those completing the study could continue on an open label basis. Those who withdrew from treatment had a 4-week taper down.

Outcome measures studies

Seizure freedom; Time to withdrawal; no. withdrawn; adverse events;

Results

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).

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).

See below for tolerability.

Funding

GlaxoSmithKline Inc.

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.

How directly applicable to population of the guideline?

Direct. Newly diagnosed epilepsy in the elderly.

Internal Validity

Multi-centre (29 centres) study from 5 countries. States it was double-blind and double-dummy.
Selection bias: unclear/high risk of bias - states randomisation but no details given; does not mention allocation concealment; they do state that there was a modest predominance of males over females in the CBZ group, but they were well balanced in demographic and clinical characteristics.
Performance bias: low risk of bias - double-blinding was well-covered;
Attrition bias: low risk of bias - similar % drop-in each arm.
Detection bias: low risk of bias - binding upheld in trial; various types of outcome
measures used.

Carbamazepine was given as sustained-release divisible tablets and lamotrigine by chewable dispersible tablets together with double-dummy placebo of the alternative treatment. Active and placebo were encapsulated and packaged in a double-blind, double-dummy presentation.

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;

Reference number 367 Study Type Randomised Controlled Trial

A randomized, double-blind, placebo-controlled trial of topiramate in adults with epilepsy and intellectual disability: impact on seizures, severity, and quality of life

2005 7 pg 472 480

Number of subjects
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 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

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%), asthenia (10.8%)
placebo group; somnolence (10.8%), abnormal gait (5.4%), weight loss (8.1%), anorexia (2.7%), infection (16.2%), hostility (8.1%), asthenia (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.

Funding

Janssen-Cilag Ltd.

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.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Study was underpowered: powered at 120 but only 88 entered study.
37 topiramate and 37 placebo were randomised but only demographic details of 35 placebo.
Selection bias: high/unknown risk - no details of randomisation method or allocation concealment.
Performance bias: low risk of bias.
Attrition bias: high risk - 23% and 21% dropped out in each group.
Detection bias: low 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

2001 10

Number of subjects

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.

Maximum dose for gabapentin was 3600 mg (taken in three divided doses) and 400 mg lamotrigine (in three divided doses). For patients taking concurrent sodium valproate the lamotrigine dose was 200 mg.

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 studies

> 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.
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Grading: 2- Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that

Losche G; Steinhausen HC; Koch S; Helge H;

Reference number 4932 Study Type Cohort RID: 858

The psychological development of children of epileptic parents. II. The differential impact of intrauterine exposure to anticonvulsant drugs and further influential factors

1994 83 Pgs 961 966

Number of subjects 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 pregnancy. 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

Comparisons 1) any monotherapy exposure in utero compared to the general population 2) any polytherapy exposure in utero compared to monotherapy exposure.

Length of Study/ Follow-up up to preschool years.

Outcome measures studies 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 Cochrane 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 Cochrane 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 Cochrane 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 Cochrane 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 Cochrane 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)

23 December 2011 Page 343 of 364
(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 Mcg 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).

Funding

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.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Unclear the risk of attrition bias as no information on drop outs are given.

Steinhausen HC;Losche G;Koch S;Helge H;

Reference number 4933
Study Type Cohort
The psychological development of children of epileptic parents. I. Study design and comparative findings

1994 83
Sep

Number of subjects
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.
Exposure to anticonvulsant during pregnancy, born to epileptic mother (without treatment during pregnancy), having epileptic fathers.

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.

**Results**

1) any AED exposure in utero compared to the general population: at 15 months children exposed to AED scored significantly less in Bayley 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 AEDs 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).

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 -2.5 (-5.91, 0.91), P=0.15).

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 Bayley 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 the 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).

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 unexposed groups to AEDs 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 unexposed groups respectively (mean difference by Cochrane 4 (-0.34, 8.34),
German Reseach Council.

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.

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.

Direct.

Unclear risk of attrition bias as no information on drop outs are given.

Question: What is the clinical effectiveness and cost-effectiveness of a ketogenic diet?
The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial.
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%).
HAS, Smiths Charity, Scientific Hospital Supplies, and the Milk Development Council. The findings support the use of ketogenic diet in children with intractable epilepsy.

Internal Validity

Low risk of selection bias. Unknown risk of performance bias, as no blinding was performed. However, authors did raise the issue of not being feasible to blind the study. Low risk of attrition bias. Unknown risk of detection bias, again due to the study not being blinded.

No clear comment on ITT analysis being undertaken.

Funding

HAS, Smiths Charity, Scientific Hospital Supplies, and the Milk Development Council.

The findings support the use of ketogenic diet in children with intractable epilepsy.

Study is not blinded, however a good quality study. For a 90% power the sample size was n=47 in each group was required, the number randomised was n=72 and n=73.

Direct population.

Effect due to factor in study?

How directly applicable to population of the guideline?

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%).

Funding

Does the study answer the question?

Hunger 6 (19%).

Taste problems 11 (34%).

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abdominal pain 4 (17%).

Constipation 9 (39%).

Lack of energy 3 (13%).

Hunger 4 (17%).

Taste problems 5 (22%).
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;

Reference number: 4832  
Study Type: Randomised Controlled Trial  
RID: 727

A blinded, crossover study of the efficacy of the ketogenic diet.[see comment]

Number of subjects: 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 pattern of 2.5 Hz spike and slow wave discharges, and an average of at least 15 tonic-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 studies: >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 an 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).

Funding: Supported by the NIH and by the Paediatric Clinical Research Unit.

23 December 2011  Page 350 of 364
Internal Validity

Low risk of selection bias. Unknown risk of performance bias, as no details were given on blinding. Unknown risk of attrition bias and unknown risk of detection bias as there is no comment on ITT analysis being undertaken. Lack of statistical data in results.

Patient Characteristics

Intractable epilepsy.

Recruitment:

Recruited from epilepsy clinics at Great Ormond street Hospital for Children NHS Trust and from pediatric neurologists and pediatricians around the UK.

Setting:

UK

Interventions/Test /Factor being investigated

Classical or MCT diet. Nonfasting initiation protocol used. Classical diets started at a 2:1 ratio and increased gradually to a 4:1 ratio as tolerated over 1-2 weeks. MCT diets commenced on a full prescription for carbohydrate (generally 15% energy), protein (usually 10% energy) and long-chain fatty acids (usually 30% energy). MCT fat was increased incrementally over 7-10 day period as tolerated to an initial level on average 40-45% of total dietary energy. Diets supplemented with vitamins and minerals.

Classical versus MCT diet.

Length of Study/ Follow-up

Followed up at 3, 6 and 12 months.
Efficacy - change in seizure activity.

Classical diet group (n=73) vs MCT diet group (n=72):
3 months:
greater than 90% seizure reduction: 5/73 (6.8%) vs 2/72 (2.7%) p value 0.442
greater than 50% seizure reduction: 18/73 (24.7%) vs 21/72 (29.2%) p value 0.578

6 months:
greater than 90% seizure reduction: 6/73 (8.2%) vs 4/72 (5.6%) p value 0.745
greater than 50% seizure reduction: 18/73 (24.7%) vs 14/72 (19.4%) p value 0.549

12 months:
greater than 90% seizure reduction: 7/73 (9.6%) vs 7/72 (9.7%) p value 1.000
greater than 50% seizure reduction: 13/73 (17.8%) vs 16/72 (22.2%) p value 0.539

Funding

HAS, smiths charity, SHS international, and the milk development council. UCL Institute of Child Health received funding as a National Institute for Health and Research Specialist Biomedical Research Centre.

Does the study answer the question?

Yes

Effect due to factor in study?

Uncertain. No blinding. For a power of 90% a sample size of n=47 in each group was required. The sample size randomised was N=73 and n=72. There was a high drop-out.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Selection bias: low risk of bias
Performance bias: unclear/high risk of bias - no blinding of ketogenic diet team or parents or caregivers.
Attrition bias: unclear/high risk of bias - high drop-out in both arms.
Detection bias: unclear/high risk of bias - no blinding.
At 12 months 22/73 and 25/72 remained for analysis.

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

Reference number 157  
Study Type Randomised Controlled Trial  
RID: 354

2008 70  
Feb 19  

Page 353 of 364 23 December 2011
(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 HRQol (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).

UCB Pharma SA.

**Funding**
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. For 90% power a randomised sample size of 58 patients in each group was required. The numbers randomised were: n=62 and n=60.

**How directly applicable to population of the guideline?**
Direct population and intervention.

**Internal Validity**
Low risk of selection bias; low risk of performance bias; low risk of attrition bias; unclear risk of detection bias as no clear method to measure outcomes was reported and the funding of the study was by pharmaceutical industry.
Berkovic SF; Knowlton RC; Leroy RF; Schiemann J; Falter U; Levetiracetam N;

Reference number 200

Study Type Randomised Controlled Trial

RID: 363

Placebo-controlled study of levetiracetam in idiopathic generalized epilepsy. [See comment]

2007 Oct 30

Levetiracetam group: 80 patients.
Placebo group: 84 patients.

Inclusion criteria:
- Aged 4 to 65 years (weight >/=20kg);
- Confirmed electroclinical diagnosis consistent with idiopathic generalised epilepsy;
- Experiencing GTC seizures despite treatment with one or two AEDs.
- Had to have experienced >/=3GTC seizures during the 8-week combined baseline period, with >/=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 >/=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
Patients had a 4 week historical baseline period and a 4 week prospective single-blind placebo baseline period before randomisation to double blind period.

Levetiracetam dose 3000mg/day for adults and 60mg/kg/day for paediatric patients and adolescents aged <16 years and weighing <50kg.

4 week double-blind titration period followed by a 20 week evaluation period.

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.

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 studies
% 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
Responder rates:
ITT analysis: Levetiracetam n=80 and placebo n=84.
% of patients demonstrating >=50% reduction in GTC seizure frequency per week between the combined baseline and treatment:57/80 in Levetiracetam vs 38/84 in placebo.

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.

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.

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.

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).

Funding Not reported.

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. Sample size of 77 randomised patients in each treatment group calculated to have 80% power, the sample size was n=80 and n=84.

How directly applicable to population of the guideline? Direct.
Internal Validity

Randomisation using a computerised central randomisation system. The blind treatment identity was kept at a central randomisation center.

Selection bias: unclear risk of bias - Mention that patient demographics and characteristics were similar across the two treatment groups but that the mean age was slightly higher in the placebo group.

Performance bias: unclear risk of bias - No standardisation for syndrome diagnosis between different recruiting centres.

Attrition bias: unclear risk of bias - 12.5% Levetiracetam and 16.7% placebo dropped out.

Glauser TA;Cnaan A;Shinnar S;Hirtz DG;Dlugos D;Masur D;Clark PO;Capparelli EV;Adamson PC;

Reference number 4968 Study Type Randomised Controlled Trial

Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy

2010 Mar 4 N ENGL J MED pgs 790 799

Number of subjects 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: 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. febrile 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 16 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. ethosuximide (Zarontin) (250 mg capsules or 250 mg per 5 ml of syrup), valproic acid (Depakote) (25 mg capsules or 125 mg dose of sprinkles) and lamotrigine (Lamictal) (5 mg and 25 mg chewable tablets or 25 mg tablets). The maximum dose for lamotrigine used was 600mg/day (recommended max dose by BNF is 500mg/day).

Comparisons 1)Ethosuximide versus Lamotrigine 2)Valproid acid versus Ethosuximide 3)Valproid acid versus Lamotrigine

Length of Study/ Follow-up Outcome measures studies 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.

1) experience of adverse events (>10%) 2)attentional dysfunction (for children 4 years or older).
Results

1) Experience of adverse events: fatigue (ethosuximide 15/156 (10%), lamotrigine 13/149 (9%), valproic acid 18/148 (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 21/154 (12%), valproic acid 20/148 (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%)).

2) Attentional dysfunction: Secondary analysis in a subgroup of 104 participants in lamotrigine group and 106 in valproic acid group. CPT confidence index = 0.60 (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.

Funding

National Institutes of Health (NS045911, 5 U10 HD037249, 1 UL1 RR026314 and P30 HD26979).

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.

How directly applicable to population of the guideline?

Direct.

Internal Validity

Low risk of selection, attrition, performance and detection bias. A well conducted double blind randomized clinical trial with good randomization procedure and allocation concealment.
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%).

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
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.

Comparisons
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
not 1:1:1.

Drug was randomised but drug, dosage and preparation were those used typically by the
clinician.

Length of Study/ Follow-up
Guidelines for initial maintenance doses and rates of titration: children aged <16 years:
LTG 3-6mg/kg/day; TPM 3-6mg/kg/day; VPA 20-30mg/kg/day. Adults aged over or 16
years:LTG 150mg/dg; TPM 150mg/dg; VPA 1000mg/dg.

Outcomes measures studies
Two arms. Arm A: carbamazepine versus gabapentin versus lamotrigine versus
oxcarbazepine versus topiramate.
Arm B: sodium valproate versus lamotrigine versus topiramate.

Results
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).

Primary clinical outcomes:
Time from randomisation to remission of seizures. Quality of life.

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 (8.6%) in VPA.

HR estimates and 95% CI (IGE only):
- time to first seizure: LTG vs VPA: 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)

Incidence 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 disturbances, tremor, vomiting, word finding difficulty, alopecia, accidental injury, dizziness/vomiting, 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 (2.00)
VPA: TPM -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: TPM 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: TPM 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: TPM 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: TPM 1.22 (0.48 to 3.08) TPM 1.24 (0.48 to 3.23)

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Two year GQoL scores:

LTG: \begin{align*}
\text{TPM} & : 1.24 (0.66 \text{ to } 2.34) \\
\text{VPA} & : 1.17 (0.64 \text{ to } 2.16)
\end{align*}

TPM: LTG: 0.81 (0.43 \text{ to } 1.53)

VPA: LTG: 0.85 (0.46 \text{ to } 1.57)

Analysis of generalised epilepsy (data not published yet):

\begin{align*}
\text{HRs (95\% CI) for relative treatment effects:} \\
\text{Time to 12-month remission} & \quad \text{Time to treatment failure} \quad \text{Time to 1st seizure} \\
\text{LTG: VPA Absence} & : 0.74 (0.43 \text{, 1.26}) \quad 1.66 (0.75 \text{, 3.66}) \quad 1.63 (0.98 \text{, 2.72}) \\
\text{LTG: VPA TC on waking} & : 0.88 (0.44 \text{, 1.74}) \quad 1.14 (0.39 \text{, 3.35}) \quad 2.27 (0.95 \text{, 5.46}) \\
\text{LTG: VPA Other} & : 0.62 (0.39 \text{, 0.99}) \quad 1.71 (0.92 \text{, 3.18}) \quad 1.39 (0.88 \text{, 2.23}) \\
\text{TPM: VPA Absence} & : 1.02 (0.61 \text{, 1.72}) \quad 4.10 (1.89 \text{, 8.91}) \quad 1.098 (0.66 \text{, 1.81}) \\
\text{TPM: VPA TC on waking} & : 0.81 (0.41 \text{, 1.57}) \quad 2.44 (0.84 \text{, 7.07}) \quad 1.71 (0.71 \text{, 4.10}) \\
\text{TPM: VPA Other} & : 0.67 (0.43 \text{, 1.05}) \quad 1.23 (0.68 \text{, 2.24}) \quad 1.15 (0.72 \text{, 1.83})
\end{align*}

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.

Effect due to factor in study?

Yes. Unblinded study but large pragmatic trial.

Internal Validity

Randomisation by telephone using minimisation (stratified by centre, sex and drug history (newly diagnosed and untreated, treated with ineffective monotherapy, relapse after remission of epilepsy)) and a list of random allocations was prepared to break ties.

Funding

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

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 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.

How directly applicable to population of the guideline?

The population had a lot of unclassified seizure type so not all of the population had idiopathic generalised epilepsy.

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.

Selection bias: low risk of bias.

Performance bias: unknown risk of bias - no blinding of treatment allocation.

Attrition bias: low risk of bias.

Detection bias: unknown risk of bias - no blinding of investigators.
Levisohn PM; Holland KD;

**Reference number** 252  **Study Type** Randomised Controlled Trial  **RID:** 383

**Number of subjects**
- 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 or as an adjunct to another AED (not topiramate or valproate) that was then withdrawn, as clinically indicated, to achieve topiramate or valproate monotherapy;
  - Females of child-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 times the upper limit of the normal range;
  - Co-therapy with a carbonic anhydrase inhibitor or barbiturate AED;
  - Use of an experimental medication or device within 30 days of study entry.

**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%);
  - PTCS 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.
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 80mg/kg/day). Topiramate was provided in 25 or 100mg TOPAMAX tablets; valproate was provided as 125, 250 or 500mg depakote tablets.

Topiramate versus valproate.

Topiramate versus sodium valproate.

26 weeks in total: 14 week titration phase followed by a 12-week maintenance phase

Reduction in seizures; evaluations of improvement; toxicity and neurotoxicity scores.

Topiramate vs valproate seizure reduction from baseline:

ITT:

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%);

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%);

Study completers:

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%);

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%).

Not reported.

Author concludes that topiramate may be an effective, well-tolerated alternative to valproate which warrants validation by a double-blind trial.

There is no power calculation and the numbers are small with variations in the groups.

Direct.

Unblinded trial. Pilot study with unequal number of patients in the two groups. 14/19 (74%) of the sample had myoclonic seizures, 12/19 (63%) had primary generalized tonic clonic seizures and 2/19 (11%) had absence seizures.

Selection bias: Unknown/unclear risk of bias - the topiramate group had a higher proportion of females as well as patients with PGTCS and fewer patients receiving AED therapy at study entry.

Performance bias: high risk of bias - there was no blinding. Contrary to protocol, 2 patients received valproate at suboptimal dosages for the study - one was randomised to topiramate and the other to valproate; there was more than double the amount of participants in the topiramate group.

Attrition bias: low risk of bias.
Detection bias: unclear/unknown risk of bias - no blinding of assessors.