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Appendices only

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Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation

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Appendix 1

List of peer reviewers

Professor David Chadwick (Professor of Neurology), University of Liverpool, Walton Centre for Neurology and Surgery, Rice Lane, Liverpool L9 1AE, UK

Professor John Duncan (Professor of Neurology, Consultant Neurologist and Medical Director of National Society for Epilepsy), UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Dr John Geddes (Honorary consultant psychiatrist, Professor of Epidemiological Psychiatry, Director of the Centre for Evidence-Based Mental Health and Editor of *Evidence-Based Mental Health*), Centre for Evidence-Based Mental Health, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK

Professor Alison Kitson (Director of the RCN Institute), RCN Institute, 20 Cavendish Square, London W1M 0AB, UK

Dr Tony Marson (Senior Lecturer and Coordinating Editor of the Cochrane Epilepsy Group), Department of Neurological Science, Clinical Science Centre for Research and Education, Lower Lane
Liverpool L9 7LJ, UK

Professor Ley Sander (Professor of Epilepsy, University College London), UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK

Dr Sally Stearns (Associate Professor), Department of Health Policy and Administration, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7411, USA

Conflicts of interest of peer reviewers

Professor David Chadwick: President of British Branch of International League against Epilepsy and Mersey Regional Epilepsy Association. Professor Chadwick's department (Department of Neurological Science) has received research funding and funding for posts from all companies whose drugs are being appraised in this review.

Professor John Duncan: Has been on advisory panels for the following pharmaceutical companies during the past 10 years: GlaxoSmithKline, Parke Davis, Novartis, MarionMerrell Dow, Sanofi, Esai and UCB. Professor Duncan and the Department of Clinical and Experimental Epilepsy at UCL have received educational grants and sponsorship to attend and organise epilepsy meetings and symposia.

Dr John Geddes: No competing interests stated.

Professor Alison Kitson: No competing interests stated.

Dr Tony Marson: Has received fees for speaking at meetings by Johnson & Johnson, and has also received sponsorship from Janssen-Cilag, Sanofi and Glaxo Wellcome to attend conferences. Has also undertaken consultancy work for GlaxoSmithKline.

Professor Ley Sander: A Council member of the British Branch of the International League Against Epilepsy, a member of the Management Committee of the International League Against Epilepsy, and over the last 10 years has been a member of Advisory Panels for all companies whose drugs are being reviewed. The Department of Clinical and Experimental Epilepsy has received research funding from all companies whose drugs are being reviewed.

Dr Sally Stearns: No competing interests stated.

Appendix 2

Search strategies

Clinical effectiveness search strategies

Internal CRD administration databases

The Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database

Searched: 20 March 2002

The DARE and HTA Databases were searched via the NHS CRD's internal administration databases. This provides more detailed and more up-to-date versions of the databases than those on the Cochrane Library or the Internet and includes additional records to those in the public databases. The same search strategy was used for both databases:

1. s labileno or lamictal or lamotrigine or lamicitin
2. s dichlorophenyltrazinediyldiamine
3. s ltg or bw(W)430c or bw(W)430(W)c or bw(W)430c78
4. s gabapentin or neurontin or neurotonin or gbp
5. s goe(W)3450 or go(W)3450 or ci(W)945
6. s 1(W)aminomethyl(W)cyclohexaneacetic (W)acid
7. s levetiracetam or etiracetam or keppra or lev or lvt
8. s 1(W)1(W)carbamoylpropyl(W)2 (W)pyrrolidinone
9. s alpha(W)ethyl(W)2(W)oxo(W)1 (W)pyrrolidineacetamide
10. s lo(W)59 or ucb(W)6474 or ucb(W)I059 or ucb(W)I(W)059
11. s oxcarbazepine or gp(W)47680 or trileptal or oxocarbazepine or oxc
12. s tiagabine or gabitril or nnc(W)05(W)0328 or nnc(W)328
13. s no(w)05(W)0328 or no(W)05(W)0329 or no(W)328 or no(W)329
14. s tiabex or tgb or topiramate or epitomax
15. s mcn(W)4853 or rwj(W)17021 or rwj(W)17021-000
16. s topamax or topimax or tpm
17. s vigabatrin or 3(W)amino(W)5(W)carboxyhexene
18. s 4(W)amino(W)4(W)ethenylbutyric(W)acid
19. s 4(W)amino(W)4(W)vinylbutyric(W)acid
20. s 4(W)amino(W)4(W)vinylbutanoic(W)acid
21. s 4(W)vinyl(W)4(W)aminobutyric(W)acid
22. s 4(W)vinylaminobutyric(W)acid or 4(W)amino(W)5(W)hexenoic(W)acid
23. s 4(W)aminohex(W)5(W)enoic(W)acid or 4(W)vinylaminobutyric(W)acid
24. s 4(W)vinylgaba or gamma(W)vinyl(W)4(W)aminobutyric(W)acid
25. s gamma(W)vinyl(W)gaba or gamma(W)vinylgaba
26. s gamma(W)vinyl(W)gamma(W)aminobutyric (W)acid or mdl(W)71754
27. s n(W)vinyl(W)4(W)aminobutyric(W)acid or n(W)vinyl(W)gaba
28. s n(W)vinyl(W)gamma(W)aminobutyric(W)acid
29. s rmi(W)71754 or rmi(W)71890
30. s sabril or sabrilex or gvg or vgb
31. s 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. s epilep$ or seizure$ or convulsion$
33. s 31 and 32

Internet resources

Science Citation Index (SCI) (1981 onwards)

Searched: 4 April 2002 on Web of Science

This search was conducted by the Information Officer at Aggressive Research Intelligence Facility (ARIF), Birmingham, and the search strategy was similar to that used for the ISTP.

Index to Scientific and Technical Proceedings (ISTP) (1990 onwards)

Searched: 4 April 2002 on Web of Science

The search strategy was limited to the drug terms and epilepsy:

labileno or lamictal or lamotrigine or lamicitin or dichlorophenyltrazinediyldiamine or ltg or gabapentin or neurontin or neurotonin or gbp or goe or aminomethyl cyclohexaneacetic acid or levetiracetam or etiracetam or keppra or lev or lvt or carbamoylpropyl or pyrrolidineacetamide or ucb or oxcarbazepine or trileptal or oxocarbazepine or oxc or tiagabine or gabitril or nnc or tiabex or tgb or topiramate or tpm or epitomax or mcn or rwj or topamax or topimax or vigabatrin or carboxyhexene or ethenybutyric acid or vinylbutyric acid or vinylbutanoic acid or aminobutyric acid or vinylaminobutyric acid or

hexenoic acid or enoic acid or vinylgaba or gamma vinyl or gamma vinylgaba or vinyl gaba or mdl or rmi or sabril or sabrilex or gvg

and

epilep* or seizure* or convulsion*

Other Internet resources
Searched: 4 April 2002 on individual websites
Those Internet sites that contained only a few references were simply browsed for relevant papers. Other Internet sites were searched using a search engine/search form. The search interfaces allowed only very simple searching and in most instances a series of keywords were entered and the results scanned for relevant material. Most web interfaces do not offer date restriction and none of the searches were limited by date. There was some duplication between the results and these were removed before all potentially relevant records were entered into an Endnote Library. The search terms used were as follows (not all the terms used retrieved records):

labileno
lamictal
lamotrigine
lamicitin
dichlorophenyltrazinediyldiamine
ltg
bw 430c
bw 430 c
bw 430c78
gabapentin
neurontin
neurotonin
gbp
goe 3450
go 3450
ci 945
1 aminomethyl cyclohexaneacetic acid
levetiracetam
etiracetam
keppra
lev
lvt
1 1 carbamoylpropyl 2 pyrrolidinone
alpha ethyl 2 oxo 1 pyrrolidineacetamide
lo 59
ucb 6474
ucb I059
ucb I 059
oxcarbazepine
gp 47680
trileptal
oxocarbazepine
oxc
tiagabine
gabitril
nnc 05 0328
nnc 328
no 05 0328
no 05 0329
no 328
no 329
tiabex
tgb
topiramate
epitomax
mcn 4853
rwj 17021
rwj 17021-000
topamax
topimax
tpm
vigabatrin
3 amino 5 carboxyhexene
4 amino 4 ethenylbutyric acid
4 amino 4 vinylbutyric acid
4 amino 4 vinylbutanoic acid
4 vinyl 4 aminobutyric acid
4 vinylaminobutyric acid
4 amino 5 hexenoic acid
4 aminohex 5 enoic acid
4 vinylaminobutyric acid
4 vinylgaba
gamma vinyl 4 aminobutyric acid
gamma vinyl gaba
gamma vinylgaba
gamma vinyl gamma aminobutyric acid
mdl 71754
n vinyl 4 aminobutyric acid
n vinyl gaba
n vinyl gamma aminobutyric acid
rmi 71754
rmi 71890
sabril
sabrilex
gvg
vgb

CD-ROM resources

The Cochrane Library (2002, Issue 1)
Searched: 2 April 2002 on CD-ROM
The Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Controlled Trials Register (CCTR) were searched via the Cochrane Library CD-ROM. The numerical drug identities are excluded from the search strategy since all numbers are ignored by the Cochrane Library software and drug terms which include numbers have been simplified where possible.

1. Labileno

2. Lamictal
3. Lamotrigine
4. Lamicitin
5. Dichlorophenyltrazinediyldiamine
6. Ltg
7. Gabapentin
8. Neurontin
9. Neurotonin
10. Gbp
11. Goe
12. aminomethyl cyclohexaneacetic acid
13. levetiracetam
14. etiracetam
15. keppra
16. lev
17. lvt
18. carbamoylpropyl
19. pyrrolidineacetamide
20. ucb
21. oxcarbazepine
22. trileptal
23. oxocarbazepine
24. oxc
25. tiagabine
26. gabitril
27. nnc
28. tiabex
29. tgb
30. topiramate
31. tpm
32. epitomax
33. mcn
34. rwj
35. topamax
36. topimax
37. vigabatrin
38. carboxyhexene
39. ethenybutyric acid
40. vinylbutyric acid
41. vinylbutanoic acid
42. aminobutyric acid
43. vinylaminobutyric acid
44. hexenoic acid
45. enoic acid
46. vinylgaba
47. gamma vinyl
48. gamma vinylgaba
49. vinyl gaba
50. mdl
51. rmi
52. sabril
53. sabrilex
54. gvg
55. #1 or #2 or #3 or #4 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
56. epilepsy*:me
57. seizures*:me
58. epilep*
59. seizure*
60. convulsion*
61. #56 or #57 or #58 or #59 or #60
62. #55 and #61

National Research Register (NRR) (2002, Issue 1)
Searched: 2 April 2002 on CD-ROM
The National Research Register (NRR) was searched using the CD-ROM interface. Since this database can be searched in the same way as the Cochrane Library the same search strategy was used.

EMBASE (1980–February 2002)
Searched: 27 March 2002 on SilverPlatter
EMBASE was searched for systematic reviews and RCTs in turn.

Search strategy for systematic reviews
The drug terms were combined with 'epilepsy' and then a filter for systematic reviews was applied.

1. labileno
2. lamictal
3. lamotrigine
4. lamicitin
5. dichlorophenyltrazinediyldiamine
6. ltg
7. bw 430c
8. bw 430 c
9. bw 430c78
10. gabapentin
11. neurontin
12. neurotonin
13. gbp
14. goe 3450
15. go 3450
16. ci 945
17. 1 aminomethyl cyclohexaneacetic acid
18. etiracetam
19. keppra
20. lev or lvt
21. 1 1 carbamoylpropyl 2 pyrrolidinone
22. alpha ethyl 2 oxo 1 pyrrolidineacetamide
23. lo 59
24. ucb 6474
25. ucb I059
26. ucb I 059
27. oxcarbazepine
28. gp 47680

29. trileptal
30. oxocarbazepine
31. tiagabine
32. gabitril
33. nnc 05 0328
34. nnc 328
35. no 05 0328
36. no 05 0329
37. no 328
38. no 329
39. tiabex
40. topiramate
41. epitomax
42. mcn 4853
43. rwj 17021
44. rwj 17021-000
45. topamax
46. topimax
47. vigabatrin
48. 3 amino 5 carboxyhexene
49. 4 amino 4 ethenylbutyric acid
50. 4 amino 5 hexenoic acid
51. 4 aminohex 5 enoic acid
52. 4 vinylaminobutyric acid
53. 4 vinylgaba
54. gamma vinyl 4 aminobutyric acid
55. gamma vinyl gaba
56. gamma vinylgaba
57. gamma vinyl gamma aminobutyric acid
58. mdl 71754
59. n vinyl 4 aminobutyric acid
60. n vinyl gaba
61. n vinyl gamma aminobutyric acid
62. rmi 71754
63. rmi 71890
64. sabril
65. sabrilex
66. gvg or oxc
67. tpm or tgb
68. levetiracetam
69. 84057-84-1 in rn
70. 60142-96-3 in rn
71. 33996-58-6 in rn
72. 28721-07-5 in rn
73. 115103-54-3 in rn
74. 97240-79-4 in rn
75. 60643-86-9 in rn
76. "lamotrigine"/ all subheadings
77. "gabapentin"/ all subheadings
78. "etiracetam"/ all subheadings
79. "oxcarbazepine"/ all subheadings
80. "tiagabine"/ all subheadings
81. "topiramate"/ all subheadings
82. "vigabatrin"/ all subheadings
83. 4 amino 4 vinylbutyric
84. 4 vinyl 4 aminobutyric
85. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
86. #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73
87. #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84
88. #85 or #86 or #87
89. explode "seizure-epilepsy-and-convulsion"/ all subheadings
90. epilep* in ti ab
91. seizure* in ti ab
92. convuls* in ti ab
93. #89 or #90 or #91 or #92
94. #88 and #93
95. "meta-analysis"/ all subheadings
96. metaanalys* in ti,ab
97. meta-analys* in ti, ab
98. meta analys* in ti, ab
99. cochrane in ti,ab
100. (review* or overview*) in ti
101. review in dt
102. synthes* near3 ((literature* or research* or studies or data) in ti,ab)
103. (pooled analys*) in ti,ab
104. (data near2 pool*) and studies
105. (medline or medlars or embase or cinahl or scisearch or psychinfo or psycinfo or psychlit or psyclit) in ti,ab
106. ((hand or manual or database* or computer*) near2 search*) in ti,ab
107. ((electronic or bibliographic*) near2 (database* or data base*)) in ti,ab
108. (review* or overview*) near10 ((systematic* or methodologic* or quantitativ* or research* or literature* or studies or trial* or effective*) in ab)
109. #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108
110. (retrospective* near2 review*) in ti,ab
111. (case* near2 review*)in ti,ab
112. (record* near2 review*) in ti,ab
113. (patient* near2 review*)in ti,ab
114. (patient* near2 chart*)in ti,ab
115. (peer near2 review*) in ti,ab
116. (chart* near2 review*) in ti,ab
117. (case* near2 report*) in ti,ab
118. (rat or rats or mouse or mice or hamster or

hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep) in ti,ab
119. #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118
120. #119 not (#119 and #109)
121. #109 not #120
122. editorial in dt
123. letter in dt
124. #122 or #123
125. #121 not #124
126. explode "animal"/ all subheadings
127. explode "human"/ all subheadings
128. #126 not (#126 and #127)
129. explode "nonhuman"/ all subheadings
130. explode "human"/ all subheadings
131. #129 not (#129 and #130)
132. #128 or #131
133. #125 not #132
134. #94 and #133

Search strategy for RCTs

The search strategy used to find references to trials of the drugs for use in epilepsy was as follows:

1. labileno
2. lamictal
3. lamotrigine
4. lamicitin
5. dichlorophenyltrazinediyldiamine
6. ltg or lvt
7. bw 430c
8. bw 430 c
9. bw 430c78
10. gabapentin
11. neurontin
12. neurotonin
13. gbp
14. goe 3450
15. go 3450
16. ci 945
17. 1 aminomethyl cyclohexaneacetic acid
18. etiracetam
19. keppra
20. lev
21. 1 1 carbamoylpropyl 2 pyrrolidinone
22. alpha ethyl 2 oxo 1 pyrrolidineacetamide
23. lo 59
24. ucb 6474
25. ucb I059
26. ucb I 059
27. oxcarbazepine
28. gp 47680
29. trileptal
30. oxocarbazepine
31. tiagabine
32. gabitril
33. nnc 05 0328
34. nnc 328
35. no 05 0328
36. no 05 0329
37. no 328
38. no 329
39. tiabex
40. topiramate
41. epitomax
42. mcn 4853
43. rwj 17021
44. rwj 17021-000
45. topamax
46. topimax
47. vigabatrin
48. 3 amino 5 carboxyhexene
49. 4 amino 4 ethenylbutyric acid
50. 4 amino 5 hexenoic acid
51. 4 aminohex 5 enoic acid
52. 4 vinylaminobutyric acid
53. 4 vinylgaba
54. gamma vinyl 4 aminobutyric acid
55. gamma vinyl gaba
56. gamma vinylgaba
57. gamma vinyl gamma aminobutyric acid
58. mdl 71754
59. n vinyl 4 aminobutyric acid
60. n vinyl gaba
61. n vinyl gamma aminobutyric acid
62. rmi 71754
63. rmi 71890
64. sabril
65. sabrilex
66. gvg or oxc
67. tpm or tgb
68. levetiracetam
69. 84057-84-1 in rn
70. 60142-96-3 in rn
71. 33996-58-6 in rn
72. 28721-07-5 in rn
73. 115103-54-3 in rn
74. 97240-79-4 in rn
75. 60643-86-9 in rn
76. "lamotrigine"/ all subheadings
77. "gabapentin"/ all subheadings
78. "etiracetam"/ all subheadings
79. "oxcarbazepine"/ all subheadings
80. "tiagabine"/ all subheadings
81. "topiramate"/ all subheadings
82. "vigabatrin"/ all subheadings
83. 4 amino 4 vinylbutyric
84. 4 vinyl 4 aminobutyric
85. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30

or #31 or #32 or #33 or #34 or #35 or #36 or #37
86. #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73
87. #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84
88. #85 or #86 or #87
89. explode "seizure-epilepsy-and-convulsion"/ all subheadings
90. epilep* in ti ab
91. seizure* in ti ab
92. convuls* in ti ab
93. #89 or #90 or #91 or #92
94. #88 and #93
95. explode "controlled-study"/ all subheadings
96. "randomization"/ all subheadings
97. "double-blind-procedure"/ all subheadings
98. "single-blind-procedure"/ all subheadings
99. "placebo"/ all subheadings
100. (singl* or doubl* or trebl* or tripl*) near5 (blind* or mask*)
101. placebo*
102. matched communities or matched schools or matched populations
103. control* near (trial* or stud* or evaluation* or experiment*)
104. comparison group* or control group*
105. matched pairs
106. outcome study or outcome studies
107. quasiexperimental or quasi experimental or pseudo experimental
108. explode "clinical-trial"/ all subheadings
109. (clinical trial*) in ti ab
110. random* in ti ab
111. #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110
112. explode "animal"/ all subheadings
113. explode "animal-experiment"/ all subheadings
114. explode "human"/ all subheadings
115. "human-experiment"/ all subheadings
116. #112 or #113
117. #114 or #115
118. #116 not (#116 and #117)
119. #111 not #118
120. #94 and #119

MEDLINE (1966–March 2002)

Searched: 26 March 2002 on SilverPlatter

MEDLINE was searched separately for systematic reviews and RCTs.

Search strategy for systematic reviews

The drug terms were combined with epilepsy terms and then a systematic review filter was added:

1. labileno
2. lamictal
3. lamotrigine
4. lamicitin
5. dichlorophenyltrazinediyldiamine
6. ltg
7. bw 430c
8. bw 430 c
9. bw 430c78
10. gabapentin
11. neurontin
12. neurotonin
13. gbp
14. goe 3450
15. go 3450
16. ci 945
17. 1 aminomethyl cyclohexaneacetic acid
18. levetiracetam
19. etiracetam
20. keppra
21. lev or lvt
22. 1 1 carbamoylpropyl 2 pyrrolidinone
23. alpha ethyl 2 oxo 1 pyrrolidineacetamide
24. lo 59
25. ucb 6474
26. ucb I059
27. ucb I 059
28. oxcarbazepine
29. gp 47680
30. trileptal
31. oxocarbazepine
32. oxc
33. tiagabine
34. gabitril
35. nnc 05 0328
36. nnc 328
37. no 05 0328
38. no 05 0329
39. no 328
40. no 329
41. tiabex
42. tgb
43. topiramate
44. epitomax
45. mcn 4853
46. rwj 17021
47. rwj 17021-000
48. topamax
49. topimax
50. tpm
51. vigabatrin
52. 3 amino 5 carboxyhexene

53. 4 amino 4 ethenylbutyric acid
54. 4 amino 4 vinylbutyric acid
55. 4 amino 4 vinylbutanoic acid
56. 4 amino 4 aminobutyric acid
57. 4 amino 5 hexenoic acid
58. 4 aminohex 5 enoic acid
59. 4 vinylaminobutyric acid
60. 4 vinylgaba
61. gamma vinyl 4 aminobutyric acid
62. gamma vinyl gaba
63. gamma vinylgaba
64. gamma vinyl gamma aminobutyric acid
65. mdl 71754
66. n vinyl 4 aminobutyric acid
67. n vinyl gaba
68. n vinyl gamma aminobutyric acid
69. rmi 71754
70. rmi 71890
71. sabril
72. sabrilex
73. gvg
74. vgb
75. 60643-86-9 in cas
76. 84057-84-1 in cas
77. 60142-96-3 in cas
78. 33996-58-6 in cas
79. 115103-54-3 in cas
80. 28721-07-5 in cas
81. 97240-79-4 in cas
82. "Vigabatrin"/ all subheadings
83. explode "Epilepsy"/ all subheadings
84. epilep* in ti ab
85. seizure* in ti ab
86. convuls* in ti ab
87. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
88. #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
89. #70 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82
90. #83 or #84 or #85 or #86
91. #87 or #88 or #89
92. #90 and #91
93. meta in ab
94. synthesis in ab
95. literature in ab
96. randomized in mesh
97. published in ab
98. meta-analysis in pt
99. extraction in ab
100. trials in mesh
101. controlled in mesh
102. medline in ab
103. selection in ab
104. sources in ab
105. trials in ab
106. review in ab
107. review in pt
108. articles in ab
109. reviewed in ab
110. english in ab
111. language in ab
112. comment in pt
113. letter in pt
114. editorial in pt
115. animal in tg
116. human in tg
117. #115 not (#115 and #116)
118. #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111
119. #118 not (#112 or #113 or #114 or #117)
120. #92 and #119

Search Strategy for RCTs

The drug terms were combined with epilepsy terms and then an RCT filter was added

1. labileno
2. lamictal
3. lamotrigine
4. lamicitin
5. dichlorophenyltrazinediyldiamine
6. ltg
7. bw 430c
8. bw 430 c
9. bw 430c78
10. gabapentin
11. neurontin
12. neurotonin
13. gbp
14. goe 3450
15. go 3450
16. ci 945
17. 1 aminomethyl cyclohexaneacetic acid
18. levetiracetam
19. etiracetam
20. keppra
21. lev or lvt
22. 1 1 carbamoylpropyl 2 pyrrolidinone
23. alpha ethyl 2 oxo 1 pyrrolidineacetamide
24. lo 59
25. ucb 6474

26. ucb I059
27. ucb I 059
28. oxcarbazepine
29. gp 47680
30. trileptal
31. oxocarbazepine
32. oxc
33. tiagabine
34. gabitril
35. nnc 05 0328
36. nnc 328
37. no 05 0328
38. no 05 0329
39. no 328
40. no 329
41. tiabex
42. tgb
43. topiramate
44. epitomax
45. mcn 4853
46. rwj 17021
47. rwj 17021-000
48. topamax
49. topimax
50. tpm
51. vigabatrin
52. 3 amino 5 carboxyhexene
53. 4 amino 4 ethenylbutyric acid
54. 4 amino 4 vinylbutyric acid
55. 4 amino 4 vinylbutanoic acid
56. 4 amino 4 aminobutyric acid
57. 4 amino 5 hexenoic acid
58. 4 aminohex 5 enoic acid
59. 4 vinylaminobutyric acid
60. 4 vinylgaba
61. gamma vinyl 4 aminobutyric acid
62. gamma vinyl gaba
63. gamma vinylgaba
64. gamma vinyl gamma aminobutyric acid
65. mdl 71754
66. n vinyl 4 aminobutyric acid
67. n vinyl gaba
68. n vinyl gamma aminobutyric acid
69. rmi 71754
70. rmi 71890
71. sabril
72. sabrilex
73. gvg
74. vgb
75. 60643-86-9 in cas
76. 84057-84-1 in cas
77. 60142-96-3 in cas
78. 33996-58-6 in cas
79. 115103-54-3 in cas
80. 28721-07-5 in cas
81. 97240-79-4 in cas
82. "Vigabatrin"/ all subheadings
83. explode "Epilepsy"/ all subheadings
84. epilep* in ti ab
85. seizure* in ti ab
86. convuls* in ti ab
87. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
88. #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
89. #70 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82
90. #83 or #84 or #85 or #86
91. #87 or #88 or #89
92. #90 and #91
93. PT = "RANDOMIZED-CONTROLLED-TRIAL"
94. PT = "CONTROLLED-CLINICAL-TRIAL"
95. "Randomized-Controlled-Trials"/ all subheadings
96. "double-blind-method"/ all subheadings
97. "single-blind-method"/ all subheadings
98. PT = "CLINICAL-TRIAL"
99. explode "Clinical-Trials"/ all subheadings
100. (clin* near trial*) in ti,ab
101. (singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
102. "Placebos"/ all subheadings
103. placebo* in ti,ab
104. random* in ti,ab
105. "Research-Design"/ all subheadings
106. "Random-Allocation"
107. (control* near (trial* or stud*)) in ti,ab,mesh
108. crossover in ti,ab,mesh
109. explode "Evaluation-Studies"/ all subheadings
110. tg=comparative-study
111. #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110
112. editorial in pt
113. comment in pt
114. letter in pt
115. TG = "ANIMAL"
116. TG = "HUMAN"
117. #115 not (#115 and #116)
118. #111 not (#112 or #113 or #114 or #117)
119. #92 and #118

PREMEDLINE (up to 22 March 2002)
Searched: 26 March 2002 on SilverPlatter

1. labileno
2. lamictal
3. lamotrigine
4. lamicitin
5. dichlorophenyltrazinediyldiamine
6. ltg
7. bw 430c
8. bw 430 c
9. bw 430c78
10. gabapentin
11. neurontin
12. neurotonin
13. gbp
14. goe 3450
15. go 3450
16. ci 945
17. 1 aminomethyl cyclohexaneacetic acid
18. levetiracetam
19. etiracetam
20. keppra
21. lev or lvt
22. 1 1 carbamoylpropyl 2 pyrrolidinone
23. alpha ethyl 2 oxo 1 pyrrolidineacetamide
24. lo 59
25. ucb 6474
26. ucb I059
27. ucb I 059
28. oxcarbazepine
29. gp 47680
30. trileptal
31. oxocarbazepine
32. oxc
33. tiagabine
34. gabitril
35. nnc 05 0328
36. nnc 328
37. no 05 0328
38. no 05 0329
39. no 328
40. no 329
41. tiabex
42. tgb
43. topiramate
44. epitomax
45. mcn 4853
46. rwj 17021
47. rwj 17021-000
48. topamax
49. topimax
50. tpm
51. vigabatrin
52. 3 amino 5 carboxyhexene
53. 4 amino 4 ethenylbutyric acid
54. 4 amino 4 vinylbutyric acid
55. 4 amino 4 vinylbutanoic acid
56. 4 vinyl 4 aminobutyric acid
57. 4 vinylaminobutyric acid
58. 4 amino 5 hexenoic acid
59. 4 aminohex 5 enoic acid
60. 4 vinylaminobutyric acid
61. 4 vinylgaba
62. gamma vinyl 4 aminobutyric acid
63. gamma vinyl gaba
64. gamma vinylgaba
65. gamma vinyl gamma aminobutyric acid
66. mdl 71754
67. n vinyl 4 aminobutyric acid
68. n vinyl gaba
69. n vinyl gamma aminobutyric acid
70. rmi 71754
71. rmi 71890
72. sabril
73. sabrilex
74. gvg or vgb
75. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74
76. epilep* or seizure* or convulsion*
77. #75 and #79

PsycINFO (1967–weekly July 2002, week 3)
Searched: 3 September 2002 on WebSPIRS
The search strategy aimed to retrieve all non-animal papers that linked any of the drugs with epilepsy. A total of 354 records were retrieved which were then scanned for the relevant study design.

4 #3 not (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep)
3 #1 and #2
2 epilep* or seizure* or convuls*
1 (labileno or lamictal or lamotrigine or lamicitin or dichlorophenyltraz* or ltg or bw 430* or gabapentin or neurontin or neurotonin or gbp or goe 3450 or go 3450 or ci 945 or aminomethyl cyclohexaneacetic acid* or etiracetam or keppra or lev or lvt or pyrrolidinone or pyrrolidinacetamide or lo 59) or ((ucb or oxcarbazepine or gp 47680 or

trieptal or oxocarbazepine or tiagabine or gabitril or nnc or no 05 032* or no 32* or tiabex or topiramate or epitomax or mcn or rwj or topamax or topimax or vigabatrin or amino* or vinyl* or mdl or rmi or sabril* or gvg or oxc or tpm or tgb or levetiracetam))

Online resources

Conference Papers Index (CPI) (1973–present)
Searched: 8 April 2002 on DIALOG
The drug terms and epilepsy terms were searched. There was no need to limit the search any further owing to the small number of retrieved records that could easily be scanned.

1. s labileno
2. s lamictal
3. s lamotrigine
4. s lamicitin
5. s dichlorophenyltrazinediyldiamine
6. s ltg
7. s bw(W)430c
8. s bw(W)430(W)c
9. s bw(W)430c78
10. s gabapentin
11. s neurontin
12. s neurotonin
13. s gbp
14. s goe(W)3450
15. s go(W)3450
16. s ci(W)945
17. s 1(W)aminomethyl(W)cyclohexaneacetic (W)acid
18. s levetiracetam
19. s etiracetam
20. s keppra
21. s lev or lvt
22. s 1(W)1(W)carbamoylpropyl(W)2 (W)pyrrolidinone
23. s alpha(W)ethyl(W)2(W)oxo(W)1 (W)pyrrolidineacetamide
24. s lo(W)59
25. s ucb(W)6474
26. s ucb(W)I059
27. s ucb(W)I(W)059
28. s oxcarbazepine
29. s gp(W)47680
30. s trileptal
31. s oxocarbazepine
32. s oxc
33. s tiagabine
34. s gabitril
35. s nnc(W)05(W)0328
36. s nnc(W)328
37. s no(w)05(W)0328
38. s no(W)05(W)0329
39. s no(W)328
40. s no(W)329
41. s tiabex
42. s tgb
43. s topiramate
44. s epitomax
45. s mcn(W)4853
46. s rwj(W)17021
47. s rwj(W)17021-000
48. s topamax
49. s topimax
50. s tpm
51. s vigabatrin
52. s 3(W)amino(W)5(W)carboxyhexene
53. s 4(W)amino(W)4(W)ethenylbutyric(W)acid
54. s 4(W)amino(W)4(W)vinylbutyric(W)acid
55. s 4(W)amino(W)4(W)vinylbutanoic(W)acid
56. s 4(W)vinyl(W)4(W)aminobutyric(W)acid
57. s 4(W)vinylaminobutyric(W)acid
58. s 4(W)amino(W)5(W)hexenoic(W)acid
59. s 4(W)aminohex(W)5(W)enoic(W)acid
60. s 4(W)vinylaminobutyric(W)acid
61. s 4(W)vinylgaba
62. s gamma(W)vinyl(W)4(W)aminobutyric(W)acid
63. s gamma(W)vinyl(W)gaba
64. s gamma(W)vinylgaba
65. s gamma(W)vinyl(W)gamma(W)aminobutyric (W)acid
66. s mdl(W)71754
67. s n(W)vinyl(W)4(W)aminobutyric(W)acid
68. s n(W)vinyl(W)gaba
69. s n(W)vinyl(W)gamma(W)aminobutyric(W)acid
70. s rmi(W)71754
71. s rmi(W)71890
72. s sabril
73. s sabrilex
74. s gvg or vgb
75. s s1:s74
76. s epilep$
77. s seizure$
78. s convulsion$
79. s s76:s78
80. s s75 and s79

All the search results from the CD-ROMs, Internet sources and online databases were downloaded into an Endnote file and duplicate references were then deleted.

Cost-effectiveness search strategies

EMBASE (1980–February 2002)
Searched: 27 March 2002 on SilverPlatter
1. "cost-benefit-analysis"/ all subheadings
2. "cost-effectiveness-analysis"/ all subheadings
3. "cost-minimization-analysis"/ all subheadings

4. "cost-utility-analysis"/ all subheadings
5. "economic-evaluation"/ all subheadings
6. cost effect* in ti,ab
7. cost benefit* in ti,ab
8. economic evaluation* in ti,ab
9. technology assessment* in ti,ab
10. pharmacoeconomic* in ti,ab
11. cost util* in ti,ab
12. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13. labileno
14. lamictal
15. lamotrigine
16. lamicitin
17. dichlorophenyltrazinediyldiamine
18. ltg
19. bw 430c
20. bw 430 c
21. bw 430c78
22. gabapentin
23. neurontin
24. neurotonin
25. gbp
26. goe 3450
27. go 3450
28. ci 945
29. 1 aminomethyl cyclohexaneacetic acid
30. etiracetam
31. keppra
32. lev or lvt
33. 1 1 carbamoylpropyl 2 pyrrolidinone
34. alpha ethyl 2 oxo 1 pyrrolidineacetamide
35. lo 59
36. ucb 6474
37. ucb I059
38. ucb I 059
39. oxcarbazepine
40. gp 47680
41. trileptal
42. oxocarbazepine
43. tiagabine
44. gabitril
45. nnc 05 0328
46. nnc 328
47. no 05 0328
48. no 05 0329
49. no 328
50. no 329
51. tiabex
52. topiramate
53. epitomax
54. mcn 4853
55. rwj 17021
56. rwj 17021-000
57. topamax
58. topimax
59. vigabatrin
60. 3 amino 5 carboxyhexene
61. 4 amino 4 ethenylbutyric acid
62. 4 amino 5 hexenoic acid
63. 4 aminohex 5 enoic acid
64. 4 vinylaminobutyric acid
65. 4 vinylgaba
66. gamma vinyl 4 aminobutyric acid
67. gamma vinyl gaba
68. gamma vinylgaba
69. gamma vinyl gamma aminobutyric acid
70. mdl 71754
71. n vinyl 4 aminobutyric acid
72. n vinyl gaba
73. n vinyl gamma aminobutyric acid
74. rmi 71754
75. rmi 71890
76. sabril
77. sabrilex
78. gvg or oxc
79. tpm or tgb
80. levetiracetam
81. 84057-84-1 in rn
82. 60142-96-3 in rn
83. 33996-58-6 in rn
84. 28721-07-5 in rn
85. 115103-54-3 in rn
86. 97240-79-4 in rn
87. 60643-86-9 in rn
88. "lamotrigine"/ all subheadings
89. "gabapentin"/ all subheadings
90. "etiracetam"/ all subheadings
91. "oxcarbazepine"/ all subheadings
92. "tiagabine"/ all subheadings
93. "topiramate"/ all subheadings
94. "vigabatrin"/ all subheadings
95. 4 amino 4 vinylbutyric
96. 4 vinyl 4 aminobutyric
97. #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49
98. #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85
99. #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96
100. #97 or #98 or #99
101. explode "seizure-epilepsy-and-convulsion"/ all subheadings
102. epilep* in ti ab

103. seizure* in ti ab
104. convuls* in ti ab
105. #101 or #102 or #103 or #104
106. #100 and #105
107. #12 and #106
108. "decision-support-system"/ all subheadings
109. markov in ti ab
110. decision analysis in ti ab
111. explode "mathematical-model"/ all subheadings
112. "theoretical-model"/ all subheadings
113. "population-model"/ all subheadings
114. #108 or #109 or #110 or #111 or #112 or #113
115. #114 and #106
*116. #115 and #107

MEDLINE (1966–March 2002)

Searched: 27 March 2002 on SilverPlatter

1. labileno
2. lamictal
3. lamotrigine
4. lamicitin
5. dichlorophenyltrazinediyldiamine
6. ltg
7. bw 430c
8. bw 430 c
9. bw 430c78
10. gabapentin
11. neurontin
12. neurotonin
13. gbp
14. goe 3450
15. go 3450
16. ci 945
17. 1 aminomethyl cyclohexaneacetic acid
18. levetiracetam
19. etiracetam
20. keppra
21. lev or lvt
22. 1 1 carbamoylpropyl 2 pyrrolidinone
23. alpha ethyl 2 oxo 1 pyrrolidineacetamide
24. lo 59
25. ucb 6474
26. ucb I059
27. ucb I 059
28. oxcarbazepine
29. gp 47680
30. trileptal
31. oxocarbazepine
32. oxc
33. tiagabine
34. gabitril
35. nnc 05 0328
36. nnc 328
37. no 05 0328
38. no 05 0329
39. no 328
40. no 329
41. tiabex
42. tgb
43. topiramate
44. epitomax
45. mcn 4853
46. rwj 17021
47. rwj 17021-000
48. topamax
49. topimax
50. tpm
51. vigabatrin
52. 3 amino 5 carboxyhexene
53. 4 amino 4 ethenylbutyric acid
54. 4 amino 4 vinylbutyric acid
55. 4 amino 4 vinylbutanoic acid
56. 4 amino 4 aminobutyric acid
57. 4 amino 5 hexenoic acid
58. 4 aminohex 5 enoic acid
59. 4 vinylaminobutyric acid
60. 4 vinylgaba
61. gamma vinyl 4 aminobutyric acid
62. gamma vinyl gaba
63. gamma vinylgaba
64. gamma vinyl gamma aminobutyric acid
65. mdl 71754
66. n vinyl 4 aminobutyric acid
67. n vinyl gaba
68. n vinyl gamma aminobutyric acid
69. rmi 71754
70. rmi 71890
71. sabril
72. sabrilex
73. gvg
74. vgb
75. 60643-86-9 in cas
76. 84057-84-1 in cas
77. 60142-96-3 in cas
78. 33996-58-6 in cas
79. 115103-54-3 in cas
80. 28721-07-5 in cas
81. 97240-79-4 in cas
82. "Vigabatrin"/ all subheadings
83. explode "Epilepsy"/ all subheadings
84. epilep* in ti ab
85. seizure* in ti ab
86. convuls* in ti ab
87. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
88. #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or

#48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
89. #70 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82
90. #83 or #84 or #85 or #86
91. #87 or #88 or #89
92. #90 and #91
93. "Economics"/ all subheadings
94. explode "Costs-and-Cost-Analysis"/ all subheadings
95. economic value of life in mesh
96. "Economics-Dental"/ all subheadings
97. explode "Economics-Hospital"/ all subheadings
98. "Economics-Medical"/ all subheadings
99. "Economics-Nursing"/ all subheadings
100. "Economics-Pharmaceutical"/ all subheadings
101. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$) in ti ab
102. (expenditure$ not energy) in ti ab
103. (value near1 money) in ti ab
104. budget* in ti ab
105. #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104
106. letter in pt
107. editorial in pt
108. #106 or #107
109. #105 not #108
110. animal in tg
111. human in tg
112. #110 not (#110 and #111)
113. (metabolic near cost) in ti ab mesh
114. ((energy or oxygen) near cost) in ti ab mesh
115. #109 not (#112 or #113 or #114)
116. #92 and #115
117. explode "Decision-Support-Techniques"/ all subheadings
118. markov in ti ab mesh
119. explode "Models-Economic"/ all subheadings
120. decision analysis in ti ab mesh
121. "Cost-Benefit-Analysis"/ all subheadings
122. #117 or #118 or #119 or #120 or #121
123. #92 and #122
124. #123 and #116

Health Economic Evaluation Database (HEED) (March 2002)

Searched: 28 March 2002 on CD-ROM

The HEED database was searched for economic evaluations using the drug terms in combination with epilepsy terms:

labileno or lamictal or lamotrigine or lamicitin or dichlorophenyltrazinediyldiamine or ltg or gabapentin or neurontin or neurotonin or gbp or goe or aminomethyl cyclohexaneacetic acid or levetiracetam or etiracetam or keppra or lev or lvt or carbamoylpropyl or pyrrolidineacetamide or ucb or oxcarbazepine or trileptal or oxocarbazepine or oxc or tiagabine or gabitril or nnc or tiabex or tgb or topiramate or tpm or epitomax or mcn or rwj or topamax or topimax or vigabatrin or carboxyhexene or ethenybutyric acid or vinylbutyric acid or vinylbutanoic acid or aminobutyric acid or vinylaminobutyric acid or hexenoic acid or enoic acid or vinylgaba or gamma vinyl or gamma vinylgaba or vinyl gaba or mdl or rmi or sabril or sabrilex or gvg

AND

epilep* or seizure* or convulsion*

NHS Economic Evaluation Database (NHS EED)

Searched 20 March 2002

The NHS Economic Evaluation Database (NHS EED) was searched via the NHS CRD's internal administration databases. This provides a more up-to-date version of the database than the Cochrane Library or the Internet and includes additional records to those in the public database. The search strategy used was as follows:

1. s labileno or lamictal or lamotrigine or lamicitin
2. s dichlorophenyltrazinediyldiamine
3. s ltg or bw(W)430c or bw(W)430(W)c or bw(W)430c78
4. s gabapentin or neurontin or neurotonin or gbp
5. s goe(W)3450 or go(W)3450 or ci(W)945
6. s 1(W)aminomethyl(W)cyclohexaneacetic (W)acid
7. s levetiracetam or etiracetam or keppra or lev or lvt
8. s 1(W)1(W)carbamoylpropyl(W)2 (W)pyrrolidinone
9. s alpha(W)ethyl(W)2(W)oxo(W)1 (W)pyrrolidineacetamide
10. s lo(W)59 or ucb(W)6474 or ucb(W)I059 or ucb(W)I(W)059
11. s oxcarbazepine or gp(W)47680 or trileptal or oxocarbazepine or oxc
12. s tiagabine or gabitril or nnc(W)05(W)0328 or nnc(W)328
13. s no(w)05(W)0328 or no(W)05(W)0329 or no(W)328 or no(W)329
14. s tiabex or tgb or topiramate or epitomax
15. s mcn(W)4853 or rwj(W)17021 or rwj(W)17021-000

16. s topamax or topimax or tpm
17. s vigabatrin or 3(W)amino(W)5(W)carboxyhexene
18. s 4(W)amino(W)4(W)ethenylbutyric(W)acid
19. s 4(W)amino(W)4(W)vinylbutyric(W)acid
20. s 4(W)amino(W)4(W)vinylbutanoic(W)acid
21. s 4(W)vinyl(W)4(W)aminobutyric(W)acid
22. s 4(W)vinylaminobutyric(W)acid or 4(W)amino(W)5(W)hexenoic(W)acid
23. s 4(W)aminohex(W)5(W)enoic(W)acid or 4(W)vinylaminobutyric(W)acid
24. s 4(W)vinylgaba or gamma(W)vinyl(W)4(W)aminobutyric(W)acid
25. s gamma(W)vinyl(W)gaba or gamma(W)vinylgaba
26. s gamma(W)vinyl(W)gamma(W)aminobutyric (W)acid or mdl(W)71754
27. s n(W)vinyl(W)4(W)aminobutyric(W)acid or n(W)vinyl(W)gaba
28. s n(W)vinyl(W)gamma(W)aminobutyric(W)acid
29. s rmi(W)71754 or rmi(W)71890
30. s sabril or sabrilex or gvg or vgb
31. s 1 or 2 or 3 or 4.or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. s epilep$ or seizure$ or convulsion$
33. s 31 and 32

Adverse effects searches

Internet resources and databases

Searched: 9 October 2002

The Internet sources and databases were searched using the drug terms alone:

labileno or lamicital or lamotrigine or lamicitin or dichlorophenyltrazinediydiamine or ltg or lvt or bw or gabapentin or neurontin or neurotonin or gbp or goe or cyclohexanacetic acid or etiracetam or keppra or lev or pyrrolidinone or pyrrolidineacetamide or lo or ucb or oxcarbazepine or trileptal or oxocarbazepine or tiagabine or gabitril or nnc or tiabex or topiramate or epitomax or mcn or rwj or topamax or topimax or vigabatrin or amino$ or vinyl$ or mdl or rmi or sabril$ or gvg

CD-ROM resources

MEDLINE (1996 to August, Week 4, 2002)

Searched: 10 September 2002 on OVID BioMed

1. exp Vigabatrin/ae, po, to [Adverse Effects, Poisoning, Toxicity]
2. labileno.mp.
3. lamictal.mp.
4. lamotrigine.mp.
5. lamicitin.mp.
6. dichlorophenyltrazinediyldiamine.mp.
7. ltg.mp.
8. bw 430c.mp.
9. bw 430c78.mp.
10. bw 430 c.mp.
11. gabapentin.mp.
12. neurontin.mp.
13. neurotonin.mp.
14. gbp.mp.
15. goe 3450.mp.
16. go 3450.mp.
17. ci 945.mp.
18. aminomethyl cyclohexaneacetic acid.mp.
19. levetiracetam.mp.
20. etiracetam.mp.
21. keppra.mp.
22. lev.mp.
23. lvt.mp.
24. alpha ethyl 2 oxo 1 pyrrolidineacetamide.mp.
25. 1 1 carbamoylpropyl 2 pyrrolidinone.mp.
26. lo 59.mp.
27. ucb 6474.mp.
28. ucb I059.mp.
29. "ucb I 059".mp.
30. oxcarbazepine.mp.
31. gp 47680.mp.
32. trileptal.mp.
33. oxocarbazepine.mp.
34. oxc.mp.
35. tiagabine.mp.
36. gabitril.mp.
37. "nnc 05 0328".mp.
38. nnc 328.mp.
39. "no 05 0328".mp.
40. "no 05 0329".mp.
41. tiabex.mp.
42. tgb.mp.
43. topiramate.mp.
44. epitomax.mp.
45. mcn 4853.mp.
46. rwj 17021$.mp.
47. topamax.mp.
48. topimax.mp.
49. tpm.mp.
50. vigabatrin.mp.
51. 3 amino 5 carboxyhexene.mp.
52. 4 amino 4 ethenylbutyric acid.mp.
53. 4 amino 4 vinylbutyric acid.mp.
54. 4 amino 4 vinylbutanoic acid.mp.
55. 4 vinyl 4 aminobutyric acid.mp.
56. 4 vinylaminobutyric acid.mp.
57. 4 amino 5 hexenoic acid.mp.
58. 4 aminohex 5 enoic acid.mp.
59. 4 vinylaminobutyric acid.mp.
60. 4 vinylgaba.mp.

61. gamma vinyl 4 aminobutyric acid.mp.
62. gamma vinyl gaba.mp.
63. gamma vinylgaba.mp.
64. gamma vinyl gamma aminobutyric acid.mp.
65. mdl 71754.mp.
66. n vinyl 4 aminobutyric acid.mp.
67. n vinyl gaba.mp.
68. n vinyl gamma aminobutyric acid.mp.
69. rmi 71754.mp.
70. rmi 71890.mp.
71. sabril.mp.
72. sabrilex.mp.
73. gvg.mp.
74. vgb.mp.
75. or/2-74
76. (safe or safety).ti,ab.
77. side effect$.ti,ab.
78. (undesirable effect$ or treatment emergent).ti,ab.
79. tolerability.ti,ab.
80. toxicity.ti,ab.
81. adrs.ti,ab.
82. (adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
83. or/76-82
84. exp Death, Sudden/
85. exp Fetal Death/
86. exp Embryo Loss/
87. Brain Death/
88. ((sudden adj2 death) or sudep).ti,ab.
89. encephalopathy.mp.
90. exp Liver Diseases/ci [Chemically Induced]
91. exp Kidney Diseases/ci [Chemically Induced]
92. exp Disseminated Intravascular Coagulation/ci [Chemically Induced]
93. intramyelinic edema.mp.
94. exp Multiple Organ Failure/ci [Chemically Induced]
95. exp Stevens-Johnson Syndrome/ci [Chemically Induced]
96. exp Heart Block/ci [Chemically Induced]
97. Epidermal Necrolysis, Toxic/ci [Chemically Induced]
98. exp Coma/ci [Chemically Induced]
99. exp Paresis/ci [Chemically Induced]
100. permanently disabl$.ti,ab.
101. life threatening.ti,ab.
102. Tourette Syndrome/ci [Chemically Induced]
103. (congenital adj (malformation$ or defect$ or abnormalit$ or impairment$)).ti,ab.
104. exp Abnormalities, Drug-Induced/
105. exp Vision Disorders/ci [Chemically Induced]
106. exp Glaucoma/ci [Chemically Induced]
107. exp Optic Neuritis/ci [Chemically Induced]
108. exp Retinal Diseases/ci [Chemically Induced]
109. Overdose/dt [Drug Therapy]
110. (still birth$ or stillbirth$ or abortion$ or miscarriage$).ti,ab.
111. exp Drug Toxicity/
112. (83 or 111) and 75
113. or/84-110
114. 113 and 75
115. 1 or 114 or 112

EMBASE (1980 to week 36, 2002)

Searched: 10 September 2002 on OVID BioMed

1. labileno.mp.
2. lamictal.mp.
3. lamotrigine.mp.
4. lamicitin.mp.
5. dichlorophenyltrazinediyldiamine.mp.
6. ltg.mp.
7. bw 430c.mp.
8. bw 430c78.mp.
9. bw 430 c.mp.
10. gabapentin.mp.
11. neurontin.mp.
12. neurotonin.mp.
13. gbp.mp.
14. goe 3450.mp.
15. go 3450.mp.
16. ci 945.mp.
17. aminomethyl cyclohexaneacetic acid.mp.
18. levetiracetam.mp.
19. etiracetam.mp.
20. keppra.mp.
21. lev.mp.
22. lvt.mp.
23. alpha ethyl 2 oxo 1 pyrrolidineacetamide.mp.
24. 1 1 carbamoylpropyl 2 pyrrolidinone.mp.
25. lo 59.mp.
26. ucb 6474.mp.
27. ucb I059.mp.
28. "ucb I 059".mp.
29. oxcarbazepine.mp.
30. gp 47680.mp.
31. trileptal.mp.
32. oxocarbazepine.mp.
33. oxc.mp.
34. tiagabine.mp.
35. gabitril.mp.
36. "nnc 05 0328".mp.
37. nnc 328.mp.
38. "no 05 0328".mp.
39. "no 05 0329".mp.
40. tiabex.mp.
41. tgb.mp.
42. topiramate.mp.
43. epitomax.mp.
44. mcn 4853.mp.
45. rwj 17021$.mp.
46. topamax.mp.

47. topimax.mp.
48. tpm.mp.
49. vigabatrin.mp.
50. 3 amino 5 carboxyhexene.mp.
51. 4 amino 4 ethenylbutyric acid.mp.
52. 4 amino 4 vinylbutyric acid.mp.
53. 4 amino 4 vinylbutanoic acid.mp.
54. 4 vinyl 4 aminobutyric acid.mp.
55. 4 vinylaminobutyric acid.mp.
56. 4 amino 5 hexenoic acid.mp.
57. 4 aminohex 5 enoic acid.mp.
58. 4 vinylaminobutyric acid.mp.
59. 4 vinylgaba.mp.
60. gamma vinyl 4 aminobutyric acid.mp.
61. gamma vinyl gaba.mp.
62. gamma vinylgaba.mp.
63. gamma vinyl gamma aminobutyric acid.mp.
64. mdl 71754.mp.
65. n vinyl 4 aminobutyric acid.mp.
66. n vinyl gaba.mp.
67. n vinyl gamma aminobutyric acid.mp.
68. rmi 71754.mp.
69. rmi 71890.mp.
70. sabril.mp.
71. sabrilex.mp.
72. gvg.mp.
73. vgb.mp.
74. 84057-84-1.rn.
75. 60142-96-3.rn.
76. 33996-58-6.rn.
77. 28721-07-5.rn.
78. 115103-54-3.rn.
79. 97240-79-4.rn.
80. 60643-86-9.rn.
81. or/1-80
82. (safe or safety).ti,ab.
83. side effect$.ti,ab.
84. (undesirable effect$ or treatment emergent).ti,ab.
85. tolerability.ti,ab.
86. toxicity.ti,ab.
87. adrs.ti,ab.
88. (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).ti,ab.
89. (or/82-86) or 87 or 88
90. exp LAMOTRIGINE/ae, to [Adverse Drug Reaction, Drug Toxicity]
91. exp GABAPENTIN/ae, to [Adverse Drug Reaction, Drug Toxicity]
92. exp ETIRACETAM/ae, to [Adverse Drug Reaction, Drug Toxicity]
93. exp OXCARBAZEPINE/ae, to [Adverse Drug Reaction, Drug Toxicity]
94. exp TIAGABINE/ae, to [Adverse Drug Reaction, Drug Toxicity]
95. exp TOPIRAMATE/ae, to [Adverse Drug Reaction, Drug Toxicity]
96. exp VIGABATRIN/ae, to [Adverse Drug Reaction, Drug Toxicity]
97. or/90-96
98. exp Death, Sudden/
99. exp Fetus Death/ or embryo death/
100. (still birth$ or stillbirth$ or abortion$ or miscarriage$).ti,ab.
101. exp adverse drug reaction/ or exp side effect/
102. exp Death, Sudden/
103. Brain Death/
104. ((sudden adj2 death) or sudep).ti,ab.
105. encephalopathy.mp.
106. intramyelinic edema.mp.
107. exp Multiple Organ Failure/si [side effect]
108. Epidermal Necrolysis, Toxic/si [side effect]
109. exp Coma/si [side effect]
110. permanently disabl$.ti,ab.
111. life threatening.ti,ab.
112. Tourette Syndrome/si [side effect]
113. (congenital adj (malformation$ or defect$ or abnormalit$ or impairment$)).ti,ab.
114. Spontaneous Abortion/si [Side Effect]
115. exp Drug Overdose/si [Side Effect]
116. exp Congenital Disorder/si [Side Effect]
117. exp Liver Disease/si [Side Effect]
118. exp Paralysis/si [Side Effect]
119. Epidermolysis/si [Side Effect]
120. Stevens Johnson Syndrome/si [Side Effect]
121. Toxic Epidermal Necrolysis/si [Side Effect]
122. Multiple Organ Failure/si [Side Effect]
123. exp Edema/si [Side Effect]
124. Disseminated Intravascular Clotting/si [Side Effect]
125. exp Kidney Disease/si [Side Effect]
126. exp Brain Disease/si [Side Effect]
127. exp Heart Block/si [Side Effect]
128. exp Glaucoma/si [Side Effect]
129. exp Optic Neuropathy/si [Side Effect]
130. exp Retina Disease/si [Side Effect]
131. exp Visual Impairment/si [Side Effect]
132. exp Amblyopia/si [Side Effect]
133. Visual Field Defect/si [Side Effect]
134. or/98-100
135. or/102-134
136. 134 or 135
137. 136 and 81
138. (89 or 101) and 81
139. 97 or 137 or 138

Appendix 3

Details of studies excluded from this review referenced by industry submissions or other review bibliographies

Drug	Author, year, trial ID	Study description	Decision to exclude
GBP	Bergey, 1997[289]	An 8-day, randomised, double-blind, dose-controlled, parallel-group, multicentre study comparing dosages of 300 and 3600 mg/day gabapentin in 82 hospitalised patients	Not an included comparison for this review
LTG	Betts, 1991[290]	LTG assessed in four completed randomised, double-blind, placebo-controlled crossover trials and an interim analysis of 27 12-month open studies	Not RCT; not systematic review
	GlaxoSmithKline, 1987[291]	Open-label 1-week trial of LTG as adjunctive therapy in patients with refractory epilepsy	Uncontrolled study; not an included study design
	Critchley, 2000[292], 1998[293]	Open-label, follow-up study of LTG	Not an included study design
	Akyol, 1998[294]	LTG versus VPA as monotherapy in patients with newly diagnosed epilepsy	GlaxoSmithKline cannot verify that this was a randomised trial
	Duchowny, 1999[295]	Add-on therapy for partial seizures in children	Not an included study population
	Fakhoury, 2001[296]	QoL in patients switched to monotherapy with LTG or VPA	Publication unavailable
	Mouzichouk, 1995[297]	Improvement in well-being	Not an included study design
	Bisgaard, 1994[298]	Add-on AED in 210 patients with resistant epilepsy	Not an included study design
	Marciani, 1998[299]	Add-on therapy in focal epilepsy: EEG and neuropsychological evaluation	Not an included outcome
LEV	French, 2001[300]	Safety review of 3347 patients or volunteers	Not RCT; not systematic review
	Krakow, 2001[301]	1422 patients in Europe and USA followed up for long-term retention rates	Excluded open-label extension studies
	Betts, 2002[302]	Double-blind, placebo-controlled trial	Excluded dose comparison study
	Mohanraj, 2002[303]	Prospective observational study	Excluded open-label observational study
	Morrell, 2002[304]	K.E.E.P.E.R. follow-up trial from Ben-Menachem, 2000[144] Study N138	Excluded extension study
	Ben-Menachem, 2002[478]	One-year follow-up study	Excluded extension study

continued

Drug	Author, year, trial ID	Study description	Decision to exclude
OXC	Sachdeo, 2001[305] Protocol 026	Multicentre, randomised, double-blind, parallel group trial to evaluate high-dose (2400 mg/day) compared with low-dose (300 mg/day) in refractory adults and adolescents	Not an included comparison for this review
	Beydoun, 2000[306] Protocol 028	Multicentre, randomised, double-blind, parallel group trial to evaluate high-dose (2400 mg/day) compared with low-dose (300 mg/day) in refractory adults, adolescents and children	Not an included comparison for this review
	Schachter, 2001[203]	One-year open-label extension phase of presurgical study 004 (Schachter, 1999[78])	Excluded open-label extension studies
	Beydoun, 2001[307]	One-year open-label extension phase of protocol 028 (Beydoun[306])	Excluded open-label extension studies
	Van Parys, 1994[308]	10-year open-label trial in The Netherlands	Excluded open-label extension studies
	Friis, 1993[309]	10-year open-label trial in Denmark	Excluded open-label extension studies
	Nielsen, 1988[310]	Cross-sectional study	Not an included study design
	Jensen, 1985[311]		
	Novartis, 1999[312] Protocol 011	Double-blind, placebo-controlled, parallel group study in children with refractory partial seizures	Not an included group of participants
	Guerreiro, 1997[313] Protocol OT/F04	Double-blind, PHT comparison, parallel group study in children and adolescents with newly diagnosed partial or generalised seizures	Not an included group of participants
TGB	Ben-Menachem, 1997[314]	Meta-analysis of 3 RCTs	Does not meet criteria for systematic review
	Ben-Menachem, 1995[315]	Five add-on, placebo-controlled trials and six non-comparative, open-label, long-term multicentre trials have been or are being conducted in Australia, Europe and the USA	Does not meet criteria for systematic review
	Biraben, 2001[316]	A multicentre, open-label, randomised, parallel group of two dosing regimens, t.d.s. and b.d., of TGB as an adjunctive therapy for the treatment of refractory patients with partial seizures	Not an included comparison for this review
	Arroyo, 2001[317]	An open assessment of TGB in a population of patients with drug-resistant partial seizures (Spain)	Not an included comparison for this review
	Cramer, 2001[318]	Choices available for patients whose partial seizures are poorly controlled include seven new AEDs or vagal nerve stimulation as add-on therapy	Not an included comparison or study design for this review
	Kazibutowska, 2000[319]	Study of 45 patients with refractory partial seizures, randomised to either GBP, TGB or TPM	Study data unobtainable
	Kazibutowska, 2001[320]	Study of 47 patients with refractory partial seizures, allowed to choose either TGB or TPM	Not an included study design
TPM	Baker, 2002[321]	Non-comparative, open-label trial to assess seizure severity and health-related QoL in Canada	Not an RCT
	Biton, 2001[322]	To evaluate two titration rates for TPM initiated as adjunctive therapy in adults with POSs, with or without secondary generalisation, in a multicentre, double-blind trial	Not an included comparison for this review

continued

Drug	Author, year, trial ID	Study description	Decision to exclude
	Abou-Khalil, 2000[213]	Adult patients with refractory partial and/or generalised seizures were treated with open-label TPM at dosages of 100–1600 mg/day	Not an included study design or comparison for this review
	Stephen, 2000[323]	Prospective observational study of TPM in patients with refractory epilepsy. No comparator	Not an included study design or comparison for this review
	Montouris, 2000[210]	Adults and children with refractory GTC seizures of non-focal origin were treated with open-label TPM after completing double-blind placebo-controlled trials	Not an included study design or comparison for this review
	Janssen-Cilag, Appendix F, EPMN104[218]	Dose comparison of 25 or 50 mg/day depending on body weight compared with 200 or 500 mg/day depending on body weight	Not an included study design or comparison for this review
	Arroyo, 2002[324]	TPM monotherapy in newly diagnosed epilepsy; dose–response study EPMN106	Not an included study design or comparison for this review
	Peeters, 2002[325]	Add-on therapy in refractory POSs: pooled analysis of RCTs in adults	Not systematic review
VGB	Penry, 1993[326]	RCT; multicentre dose–response study in adults with partial epilepsy	Full report included as Dean, 1999[154]

Appendix 4

Details of QoL measures used in RCTs

QoL measure	Details
Affect Balance Scale	Considers positive aspects of mental health
ABNC	A measure of patient-based subjective complaints in relation to drug treatment. Score is the number of complaints ranging from 0 to 72
Behaviour Checklist	This behaviour adjective checklist was based on a scale devised by Brooks and McKinley, 1983,[481] and was completed by a family member
BDI	A measure of psychological status, on which scores range from 0 to 63, with higher scores reflecting more severe symptomatology
CDRS	A measure of psychological status, on which scores range from 0 to 80, with higher scores reflecting greater symptom severity
General Health Questionnaire-28	A measure of psychological status, where investigators are able to examine a profile of scores rather than a single score making. This version of the GHQ contains 28 items that, through factor analysis, have been divided into four subscales: A, somatic symptoms; B, anxiety/insomnia; C, social dysfunction; D, severe depression. This 'scaled' version of the GHQ has been developed on the basis of the results of principal components analysis. The first set of seven items can be found in subscale A, the second set in subscale B, the third in subscale C and the fourth set in sub-scale D
Goodrich Inventory	Relatives of participants at the end of the study completed the inventory in order to assess behavioural disturbances possibly arising after the completion of treatment. The inventory contains items about thinking, behaviour, physical condition and feeling
Hospital Anxiety and Depression Scale	This scale incorporates 14 statements each with 4 responses representing intensity. Seven statements measure depression and 7-measure anxiety
Key Carer-rated Visual Analogue Scales	This is a scale devised by Parke Davis used to assess carer outcome
Liverpool AEP	A 19-item patient-rated instrument, which assesses patient-perceived severity of adverse events
LSI	A patient-completed inventory concerning work, family, daily activities, sexuality, social relations, leisure and economic situation
Mastery Scale	This scale assesses mastery, which is an important aspect of an individual's capacity to cope with stress
Mood Adjective Checklist	This provides subjective ratings of depression, anxiety, fatigue, activity and aggression
Mood Rating Scale	Participants completed 100-mm visual analogue scales for 15 dimensions. (One study used 18[57] and the other did not specify the number of dimensions.[153]). An average is taken of all the dimensions to provide a single score
Nottingham Health Profile	This measure of general health has 6 subscales: energy, pain, emotional reaction, sleep, social isolation and physical disability
Patient acceptability	How much patients think the drug has helped control their epilepsy. The five categories are: not at all helpful, not very much help, a little bit of help, very much helped, extremely good, not known
POMS	A measure of psychological status, on which scores range from –32 to 200, with higher scores reflecting greater mood disturbance. Ratings are scored for six mood states: tension–anxiety, depression–dejection, anger–hostility, fatigue–inertia, confusion–bewilderment, and vigour–activity. A single score for mood disturbance is also given
QOLIE-31	This is a self-administered 31-item questionnaire, which is derived from the QOLIE-89. It comprises seven subscales: seizure worry, overall QoL, emotional well-being, energy–fatigue, cognitive functioning, medication effects, social function and health status. Raw scores are converted to 0–100 points, with higher values reflecting better QoL

continued

QoL measure	Details
QOLIE-89	This self-administered questionnaire contains 89 questions that assess 17 dimensions: overall QoL, health perceptions, physical function, physical role limitations, pain, work/driving/social function, energy/fatigue, emotional well-being, attention/concentration, health discouragement, seizure worry, memory, language, medication effects, social support and social isolation. The questionnaire also contains three single items: change in health, sexual relations and overall health. Total QOLIE-89 scores range from 0 to 100. Higher scores reflect better QoL
Rosenberg Self-esteem Scale	This is a measure of self-esteem, which is an important aspect of an individual's capacity to cope with stress
SEALS	This provides subjective ratings on five subscales: worry, temper, cognition, dysphoria, and tiredness. Scoring is as follows: 0 = never, 1 = occasionally, 2 = sometimes, 3 = many times
Social Problems Questionnaire	Was used to determine patient satisfaction with a range of pertinent social issues
Staff/family assessment	An assessment of the individual's behaviour was made by staff or family on a rating scale adapted from Brooks and McKinley, 1983[481]
WPSI	A 132-item inventory of psychosocial adjustment providing indicators of functioning in 7 areas: family background, emotional adjustment, interpersonal adjustment, vocational adjustment, financial status, adjustment to seizures, medicine and medical management, along with an overall score and three validity scales
Zung Depression Scale	A personal inventory with 20 items about mood and feelings where the patient rates each statement as 'rarely', 'sometimes', 'often' and 'very often'

ABNC, Aldenkamp–Baker Neurotoxicity Scale; BDI, Beck Depression Inventory; Liverpool AEP, Adverse Experience Profile; CDRS, Cornell Dysthymia Rating Scale-Self-Report; LSI, Life Satisfaction Index; POMS, Profile of Moods States; QOLIE, Quality of Life in Epilepsy Inventory; SEALS, Side Effect and Life Satisfaction Inventory; WPSI, Washington Psychosocial Seizure Inventory.

Appendix 5

Details of cognitive measures used in RCTs

Cognitive measure	Details
Alternating S Task	A measure of flexible psychomotor performance
Auditory and Visual Reaction Time	A computerised test of sustained attention and perceptuomotor speed. Participants were required to press a key as quickly as possible after presentation of auditory and visual stimuli
Backward Digit Span	The maximum number of digits that a participant could recall in reverse order immediately after oral presentation
Backward Visual Span	The maximum number of squares correctly reproduced in reverse order
Bells Test	Participants cross out bells drawn at random among other pictures of the same size
Benton Visual Retention Test	This is a visual recognition task
Binary Choice Reaction Time	A reaction time task including a decision component
Buschke–Fuld Test	The number of trials a participant requires to learn a word list
Controlled Oral Word Association	This is part of the Multilingual Aphasia Examination. The participant is required to say as many words as possible in 1 minute beginning with each of 3 letters
Bilateral Hand Movements	The participant was asked to alternate between a flat hand and a fist as many times as possible in 20 s
Computerised Visual Searching Task (an adaptation of Goldstein's Visual Searching Task)	This provides an indication of the speed of information processing and perceptual mental strategies
Controlled Oral Word Association	This is part of the Multilingual Aphasia Examination. The participant is required to say as many words as possible in 1 minute beginning with each of 3 letters
Corsi's Blocks	Assesses spatial span and spatial learning abilities. The participant touches an increasingly difficult sequence of blocks in the same order as the investigator
Decision Time	The time taken to respond to a light by removing a finger from the base button
Design Learning	This tests immediate recall of a simple geometric design after presentation on 5 separate occasions. Recall of a second drawing was obtained followed by recall of the first drawing
Digit Cancellation Test	A page of random one-digit numbers is presented and the patient cancels with a single stroke as many as possible of two target digits in a 4-minute period
Digit Span Test	This subtest of the WAIS-R measures immediate auditory memory for digits
Digit Symbol Test	A subtest of the WAIS where participants match symbols to numbers 1–9 according to definite rules
Forward Digit Span	The maximum number of digits that a participant can recall following presentation of an oral list
Forward Visual Span	The maximum number of squares correctly reproduced in sequence as shown by the assessor
H Barrage Test	Participants cross out the letter H among other pictures of the same size
Information Processing Tasks A and B (from Adult Memory and Information Processing Battery)	This was used as a measure of mental speed. A rapid repetitive mental activity, it places little load on memory, reasoning or visual perception
Italian Matrix Test	Participants cross out a target number among other numbers

continued

Cognitive measure	Details
Lafayette Grooved Pegboard Test	A measure of manual dexterity, visuomotor coordination and motor speed
Leeds Psychomotor Test	A measure of psychomotor performance. It consists of two parts. The Critical Flicker Fusion Threshold is a measure of sustained attention arousal and integrity of the visual pathways. Choice React Time is a simple measure of reaction time
Letter Cancellation Task	A measure of attention and visual scanning
List Learning	This is a measure of verbal learning including immediate and delayed verbal recall. This tests immediate recall of the same list of words five consecutive times. Recall of a second list of different words is obtained. Recall of the first list was then obtained
Logical Prose Story A (from the Wechsler Memory Scale)	A measure of logical verbal memory
Logical Reasoning Test	Participants were presented with a series of sentences describing the order in which two signs (+ and –) were presented. They were required to identify whether these were true or false as quickly as possible
Modified Finger Tapping Test	A measure of simple psychomotor speed using thumb tapping
Movement Time	The time taken to move a finger from a base button to extinguish the light in a choice reaction time test
National Adult Reading Test	This is a measure of word reading ability, which is used to provide a measure of premorbid intelligence levels
Number Cancellation Test (from the Adult Memory and Information Processing Battery)	This test assesses repetitive mental activity
Paired Associate Learning Test	The number of attempts required by a participant to name three sets of correctly paired words
Reaction Times	Computer software randomly projects a visual stimulus on a screen and the participant has to push a key
Recognition of Words and Figures	Six words and four figures were presented for 1 s per item. After a delay of 2 s the screen shows one of the items between distractors. The participant tries to identify the target item
Rey Auditory–Verbal Learning Test	This tests immediate recall of the same list of words five consecutive times. Recall of a second list of different words is obtained. After 20 minutes delayed recall and recognition of the first test are obtained
Rey Complex Figure Test	This is a measure of new learning, perceptual organisation and visual memory. Participants copy a complex drawing and are then required to reproduce it 30 minutes later
Rivermead Behavioural Memory Test	The 'screen score' of this standardised psychometric battery was used
Semantic Processing Test	The participant classifies 50 statements as true or false. Each statement is obviously true or false
Simple Reaction Time	The participant was required to depress a key as quickly as possible when a white square appeared on the computer screen with dominant and non-dominant hand
Stroop Test	Assesses decision-making and flexibility. Participants are given a card with the colour names printed in incongruous colours of ink. There are a number of tasks related to naming the colours or the words
Symbol Digit Modalities	This test is similar to the Digit Symbol Substitution Test of the WAIS-R except that numbers rather than symbols are written
Tapping Rate	Speed of hand movement between two steel plates with a metal stylus connected to an electronic counter was assessed
Threshold Detection Test	An array of small triangles were presented on a computer screen. When an extra triangle was added, the participant was required to indicate which it was

continued

Cognitive measure	Details
Tolouse Pieron	Participants cross out a target symbol among other symbols of the same size
Tracking Test	The amount of time the participant was able to keep on the track of a moving target presented on a visual display unit using a joystick
Trailmaking Test A	Measure of time taken to join up the numbers from 1 to 25 randomly written on a page
Trailmaking Test B	Measure of time taken to join up alternately and in order numbers and letters randomly written on a page
Verbal Learning Test	Using a list of words presented individually to a participant this test measures single immediate free recall, up to seven further learning trials, delayed recall and delayed recognition
Verbal fluency	The participant is asked to say as many words as possible beginning with the letter D within 60 s, then asked to name as many different animals as possible at the same time
Verbal Recall	This is a measure of delayed and immediate recall of the contents of a short paragraph read by the assessor
Verbal Memory	The subject was presented with a series of visual arrays each consisting of six words. Following a 2-s delay one of the words reappeared together with five distractors. The participant was required to identify the previously shown word
Visual Reproduction (a subtest of the Wechsler Memory Scale)	A measure of immediate and delayed non-verbal recall
Wonderlic Personnel Test	A written test of mental abilities that yields an IQ score closely approximating that of the WAIS Full-scale IQ

IQ, intelligence quotient.

Appendix 6

Details of the types of data extracted from systematic reviews and clinical effectiveness studies

Data were extracted and entered into structured tables in a standardised manner under the following headings:

Systematic reviews

Study details
- Author name
- Year
- Authors' objective
- Source of reference
- Sources used in the literature search
- Number and type of studies included in the review.

Inclusion/exclusion criteria
- Participants
- Intervention
- Study design
- Outcomes.

Methods
- Criteria used to assess the validity of the studies
- Method of data synthesis
- Investigation of heterogeneity.

Results

Conclusions

Additional comments

Randomised controlled trials

Study details
- Author name
- Year
- Country
- Authors' objective
- Outcomes measured
- Setting
- Length of follow-up.

Inclusion/exclusion criteria
- Population
- Inclusion criteria
- Exclusion criteria.

Baseline characteristics
- Mean ± SD age (years):
  intervention
  control
- Gender (% male, % female):
  intervention
  control
- Type of epilepsy (newly diagnosed, refractory):
  intervention
  control
- Other participant characteristics:
  intervention
  control.

Methods
- Method of randomisation
- Method of data collection
- Statistical analysis.

Intervention details
- Intervention:
  drug name
  length, frequency and dose of treatment
  length and frequency of follow-up
  number of participants
- Any additional treatment (with intervention):
  type of treatment/drug name
  length, frequency and dose of treatment
  length and frequency of follow-up
- Comparator:
  drug name
  length, frequency and dose of treatment
  length and frequency of follow-up
  number of participants.

Results (*repeated for all outcomes*)
- Outcome 1:
  description of outcome measure
  intervention follow-up data
  comparator follow-up data.

Withdrawals

- Number recruited or accrued
- Attrition intervention:
  number
  reason for loss
- Attrition control:
  number
  reason for loss.

Additional comments

- Reviewers' comments on, for example, limitations of the study, biases not reported by authors, validity of authors' conclusions and generalisability.

Appendix 7

Quality assessment checklist used to assess the quality of systematic reviews

In order to be included in the review, systematic reviews must achieve a FAIR/GOOD rating on criteria 1 and 2, and a FAIR/GOOD rating on at least two further criteria from the remaining three.

1. Are inclusion/exclusion criteria reported that address the review question? (This criterion is MANDATORY)
   - NA — Inclusion/exclusion criteria are not addressed.
   - POOR — One of the four components is addressed by the inclusion/exclusion criteria.
   - FAIR — At least two components are addressed by the inclusion/exclusion criteria. One or more reviewer(s) applied the criteria to assess the individual studies (or the number of reviewers is not clear).
   - GOOD — Three or four components are addressed by the inclusion/exclusion criteria. In addition, the criteria are applied by more than one reviewer (double-checked).

2. Is there evidence of a substantial effort to search for all the relevant research literature? (This criterion is MANDATORY)
   - NA — Sources searched are not mentioned.
   - POOR — Only one named database searched with minimal description of date and search terms. If in doubt on this criterion, check with another reviewer.
   - FAIR — EITHER one named database searched with search dates and search terms reported, along with follow-up references from retrieved papers and/or handsearching and/or contacting researchers.
     OR more than one named database searched (search dates and search terms may be reported, but may be omitted owing to space restrictions).
   - GOOD — More than one database searched with a description of dates and more detailed information on search terms. In addition, other retrieval methods are reported: handsearching, locating unpublished literature, experts in the field, Internet searches, citation searching.

3. Is the validity of included studies adequately assessed?
   - NA — Validity of individual studies was not assessed or not reported.
   - POOR — Validity of individual studies may be assessed but not systematically.
   - FAIR — Validity of individual studies was assessed systematically by one reviewer (or the number of reviewers is not clear).
   - GOOD — Validity of individual studies was assessed systematically by more than one reviewer.

4. Is sufficient detail of the individual studies presented?
   - NA — Details of individual studies not available.
   - POOR — Some detail of individual studies may be found in the text of the review. Or studies are inadequately presented in tables.
   - FAIR — Details of individual studies are presented in tables but one or more important study characteristics may not be included, or details of individual studies are well described in the review text. Sometimes it may not be possible to present details of all the individual studies because of the large number of trials included but details may be available elsewhere, for example on the website of the journal in which the review was published.
   - GOOD — Details of individual studies are adequately presented in tables and text. The tables include almost, or all, relevant information (e.g. design, participants, sample size, intervention and outcome). There is

enough information to judge whether the authors' summary and conclusions are appropriate.

5. Are the primary studies summarised appropriately?
   - NA — No effort is made to combine or summarise evidence from individual studies.
   - POOR — Evidence is summarised but not synthesised. The methods used to pool data are not adequate. Heterogeneity is not addressed.
   - FAIR — Individual studies are synthesised with appropriate techniques (either by narrative or meta-analysis) but heterogeneity is not assessed.
   - GOOD — Individual studies are synthesised appropriately. Heterogeneity between studies is investigated adequately.

Appendix 8

Quality assessment checklists used to assess the quality of RCTs

1. Were the eligibility criteria for the study specified?
2. Was an *a priori* power calculation for adequate sample population size performed? (This should be appropriate to test the null hypothesis if an equivalence trial is being performed.)
3. Was the number of participants who were randomised stated?
4. Was the method used to assign participants to the treatment groups really random? (Computer-generated random numbers and random number tables were accepted as adequate, whereas inadequate approaches included the use of alternation, case record numbers, birth dates or days of the week.)
5. Was the allocation of treatment concealed? (Adequate methods included centralised or pharmacy-controlled assignment or where the following were used: serially numbered containers, serially numbered opaque envelopes, on-site computer-based systems where assignment is unreadable until after allocation, other robust methods to prevent foreknowledge of the allocation of sequence to clinicians and patients. Inadequate approaches included alternation, case record numbers, days of the week and open random number lists.)
6. Were the outcome assessors blind to the treatment allocation?
7. Were those individuals who administered the intervention blind to the treatment allocation?
8. Were the participants who received the intervention blind to the treatment allocation?
9. Was the success of the blinding procedure assessed?
10. Were details of the baseline comparability of the treatment groups presented?
11. Were adjustments made for differences in the baseline characteristics of the treatment groups?
12. Were appropriate doses of the intervention drugs used?
13. Were appropriate doses of the control drugs used?
14. Were any co-interventions identified that could influence the outcomes for the treatment groups?
15. Was patient compliance with the assigned treatment assessed?
16. Were all patients who were originally considered for the study accounted for at its conclusion?
17. Was a valid ITT analysis included?
18. Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments? (i.e. was less than 20% of the follow-up data classified as missing data?)
19. Were appropriate methods used to account for missing follow-up data in the ITT analysis? (i.e. sensitivity analyses to examine the effect of missing data and different methods of accounting for missing data).

For crossover studies only

1. Did all participants have established epilepsy with a constant and predictable seizure frequency and type?
2. Was the crossover design appropriate?
3. Was an appropriate washout allowed between the different treatments? (i.e. the investigators should justify their choice of washout period. They may monitor blood levels of the treatment drugs or perform statistical analysis to look for treatment period interactions).
4. Was an appropriate analysis using paired data performed?

For equivalence studies only

1. Was the equivalence margin specified before the study?
2. Was the active control treatment previously found to be effective? (Ideally this should involve a systematic review of placebo-controlled trials.)
3. Were the study participants and outcome variables similar to those in the original trials establishing the efficacy of the active control?

4. Was it appropriate to test a null hypothesis? (i.e. the null hypothesis should be appropriate, as should the equivalence margin. This should at least be less than the lower 95% CI for the absolute risk difference between the therapy and placebo in a superiority trial).
5. Were treatments applied in an optimal fashion? (i.e. the drug doses should be appropriate, there should be a good level of treatment compliance, a low loss to follow-up and no other co-interventions should be used which could distort the data).
6. Was the analysis appropriate for an equivalence trial? (The analysis should use two-sided tests of statistical significance and a per protocol analysis. An ITT analysis may or may not be performed.)

All criteria were scored as follows: yes, no, partial, unclear, NS (not stated) or NA (not applicable).

Appendix 9

Details of the information extracted from studies included in the assessment of serious, rare and long-term adverse events

- Author
- Year of study
- Aim of study
- Study design
  - systematic review; RCT; non-randomised controlled trial; uncontrolled trial; cohort (controlled); cohort (uncontrolled); case control; unclear
- Duration of study
- Number of participants at entry
  - total; study group; control group
- Number of participants completing study
  - total; study group; control group
- Number of participants included in analysis
  - total; study group; control group
- Age of participants
- Gender of participants
- Seizure type
  - partial; partial with secondary generalisation; partial and generalised; generalised; tonic–clonic; unclassified; not stated
- List of any co-morbidities
- List of previous and concomitant drugs
- Inclusion criteria
- Exclusion criteria
- Outcome measures used and measurement tools
- Study treatment
  - treatment name
  - monotherapy or adjunctive therapy
  - treatment dose
  - number of withdrawals due to AEs
  - number of deaths due to AEs
  - details of AEs
- Control treatment
  - control name
  - monotherapy or adjunctive therapy
  - control dose
  - number of treatments due to AEs
  - number of deaths due to AEs
  - details of AEs
- Authors' conclusions
- Comments.

Appendix 10

Quality assessment checklists used to assess the quality of studies included in the assessment of serious, rare and long-term adverse events

RCTs, non-randomised controlled trials, uncontrolled trials

Were the eligibility criteria for the study specified?

Was a power calculation performed?[a]

Was the number of randomised participants stated?

Was the method used to assign participants really random?

Was the allocation of treatment concealed?

Were the outcome assessors blind to treatment?[b]

Were the individuals who administered the intervention blind to treatment?

Were participants blind to treatment?

Was success of the blinding procedure assessed?

Were details of baseline comparability of the treatment groups presented?

Were adjustments made for differences in the baseline characteristics?

Were appropriate doses of the intervention drugs used?

Were appropriate doses of the control drugs used?

Were any cointerventions identified that could influence outcomes?[c]

Was participant compliance with the assigned treatment assessed?[d]

Were all participants originally included in the study accounted for at its conclusion?[e]

Were at least 80% of participants originally included in the study also assessed?

Was there a valid ITT analysis (were all participants included in the final analysis according to the group to which they were originally randomised)?[f]

Were appropriate methods used to account for missing follow-up data in the ITT analysis?[g]

Controlled and uncontrolled cohort studies

Was it clear who was studied: source of participants, how participants were selected, eligibility criteria?[h]

Does the control group enable a fair comparison to be made?[i]

Was exposure to AED measured accurately (clear description of how the extent of exposure was ascertained; was anything done to confirm that the control group had not been exposed to the drug)?[j]

Were the groups comparable on important confounding factors?

Was adjustment for the effects of confounding variables adequate?

Was a dose response relationship between the AED and the AE demonstrated?[k]

Was assessment of subjective outcomes blind to drug exposure status?[l]

Was follow-up long enough?[m]

What proportion of the cohort (%) was followed up to the end of the study?[n]

Were reasons for drop-out similar between the exposed and control groups?[o]

Were the basic data adequately described?

Was an appropriate statistical analysis (for AEs) used?[p]

continued

Case–control studies

Was the AE case definition explicit?

Was the AE status of the cases reliably assessed and validated?

Were the controls randomly selected from the same source population as the cases?

Were the interventions and other exposures assessed in the same way for cases and controls?

Was an appropriate statistical analysis used?

Open-label extension and follow-up studies

Was it clear who was studied: source of participants, how participants were selected, eligibility criteria?[q]

Were appropriate doses of the intervention drugs used?

Was follow-up long enough?[r]

[a] RCT/CCT not mentioned = NS; UCT = NA.
[b] CCT open = No, otherwise NS; UCT = NA.
[c] Investigation undertaken, irrespective of results = Yes; reported for some but not all adverse events = Partial; not mentioned = NS.
[d] Not mentioned = NS.
[e] Yes or no according to what was reported; number eligible not reported = NS.
[f] RCT only; CCT or UCT = NA.
[g] RCT only; CCT or UCT = NA.
[h] All 3 = Yes; 1 or 2 = Partial; 0 = NS.
[i] Healthy controls = No.
[j] Full description = Yes; cumulative dose reported = ?; otherwise NS.
[k] Incidence of AE vs dose reported, irrespective of results = Yes; No if that is explicitly reported; otherwise NS.
[l] CC: Yes or NS (Partial depending on what was reported); UCC = NA.
[m] Low end of reported range ≤ 6 months = Partial; whole range ≥ 6 months = Yes; full range unclear = ?
[n] Subtract losses for reasons other than AEs, lack of efficacy, exacerbation of seizures or death from independent cause.
[o] CC: Yes or No as reported, or NS; UCC = NA. No drop out = NA.
[p] CC: statistical comparison = Yes. UCC: statistical comparison pre- vs postexposure = Yes; statistical comparison of those with vs those without the AEs (all exposed) = Yes; No statistics = No.
[q] All 3 = Yes; 1 or 2 = Partial; 0 = NS.
[r] Whole range ≥ 24 months = Yes; high end of range <24 months = No; <24 months to ≥ 24 months = Partial; full range unclear = ? Based on ILAE recommended 24–48 months for long-term open studies.

CCT, controlled clinical trials; UCT, uncontrolled clinical trials.

Appendix 11

Details of the types of data extracted from cost-effectiveness studies

Data were extracted and entered into structured tables in a standardised manner under the following headings:

- author
- date
- type of economic evaluation (CEA, CUA, CBA)
- Currency used (e.g. US$, Australian$, £ Sterling, not stated)
- year to which costs apply
- perspective used (e.g. health service, societal, hospital, third-party payer, patient, unclear)
- study population (describe the population characteristics)
- description of intervention 1
- description of intervention 2
- source of effectiveness data (e.g. single study, review/synthesis of previous studies, expert opinion, not stated)
- source of unit cost data (e.g. literature, data from actual source, not stated)
- link between cost and effectiveness data (e.g. prospective/concurrent, retrospective/disconnected)
- clinical outcomes measured and methods of valuation used
- cost data handled appropriately (i.e. summary of methods used to, e.g. discount, inflate)
- modelling (i.e. summary of models used, type of model, purpose of model, components of model, key input parameters and model outputs)
- outcome measures used in economic evaluations (i.e. summary of outcome measures used in economic evaluations, e.g. ICER, net benefit, CEAC)
- direction of result with appropriate quadrant location
- statistical analysis for patient-level stochastic data (i.e. summary of analyses used)
- appropriateness of statistical analysis
- uncertainty around cost-effectiveness expressed
- appropriateness of method of dealing with uncertainty around cost-effectiveness
- sensitivity analysis (i.e. list summary of analysis)
- appropriateness of sensitivity analysis
- modelling inputs and techniques appropriate
- authors' conclusions
- implications for practice
- comments

Appendix 12

Quality assessment checklists used to assess the quality of economic evaluations

Studies of cost-effectiveness were assessed using the following criteria, which represent an updated version of the checklist developed by Drummond and colleagues:[327]

Study question

1. Costs and effects examined.
2. Alternatives compared.
3. The viewpoint(s)/perspective of the analysis is clearly stated (*e.g. NHS, society*).

Selection of alternatives

4. All relevant alternatives are compared (*including do nothing if applicable*).
5. The alternatives being compared are clearly described (*who did what, to whom, where and how often*).
6. The rationale for choosing the alternative programmes or interventions compared is stated.

Form of evaluation

7. The choice of form of economic evaluation is justified in relation to the questions addressed.
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?

Effectiveness data

9. The source(s) of effectiveness estimates used are stated (*e.g. single study, selection of studies, systematic review, expert opinion*).
10. Effectiveness data from RCT or review of RCTs.
11. Potential biases identified (especially if data not from RCTs).
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies).

Costs

13. All the important and relevant resource use included.
14. All the important and relevant resource use measured accurately (with methodology).
15. Appropriate unit costs estimated (with methodology).
16. Unit costs reported separately from resource use data.
17. Productivity costs treated separately from other costs.
18. The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion.

Benefit measurement and valuation

19. The primary outcome measure(s) for the economic evaluation are clearly stated (*cases detected, life years, QALYs, etc.*)
20. Methods to value health states and other benefits are stated (*e.g. time trade-off*).
21. Details of the individuals from whom valuations were obtained are given (*patients, members of the public, healthcare professionals, etc.*)

Decision modelling

22. Details of any decision model used are given (*e.g. decision tree, Markov model*).
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified.
24. All model outputs described adequately.

Discounting

25. Discount rate used for both costs and benefits.
26. Do discount rates accord with NHS guidance (1.5–2% for benefits; 6% for costs)?

Allowance for uncertainty

Stochastic analysis of patient-level data

27. Details of statistical tests and confidence intervals are given for stochastic data.
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs).
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Stochastic analysis of decision models

30. Are all appropriate input parameters included with uncertainty?
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?
32. Are the probability distributions adequately detailed and appropriate?
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).

Deterministic analysis

34. The approach to sensitivity analysis is given (*e.g. univariate, threshold analysis*).
35. The choice of variables for sensitivity analysis is justified.
36. The ranges over which the variables are varied are stated.

Presentation of results

37. Incremental analysis is reported using appropriate decision rules.
38. Major outcomes are presented in both a disaggregated and an aggregated form.
39. Applicable to the NHS setting.

All items will be graded as either Yes (item adequately addressed), No (item not adequately addressed), (unclear or not enough information), NA (not applicable) or NS (not stated).

Appendix 13

Summary of the quality of studies included in the economic model or reason for exclusion

Monotherapy

Drug	Study	Random	Conceal	Blinding[a]	Comments
LTG	Biton, 2001[116]	Yes	NS	Partial	No baseline comparability data and not clear if epilepsy is newly diagnosed or refractory
	Brodie, 1995[121]	Yes	Yes	Partial	
	Gilliam, 1998[112]	NS	NS	Partial	
	GlaxoSmithKline, 2001[62]	NS	NS	No	
	Kerr, 2001[122]	Yes	NS	No	Includes adults and children, but data are not always presented separately for the two groups. Participants were assigned to LTG vs CBZ or LTG vs VPA randomisation branches according to physician's choice.
	Nieto Barrera, 2001[119]	NS	Yes	No	Open-label trial. Seizure freedom only included patients who had ≥ 18 weeks of data. LTG group had higher baseline seizure rate than CBZ group. Unclear if findings consider this
	Reunanen, 1996[120]	NS	NS	No	CBZ dose lower than usual suggested minimum dose. Time to first seizure excluded participants withdrawing before day 42 (data not provided)
	Steiner, 1999[75]	NS	NS	Partial	
OXC	Aikia, 1992[58]	NS	NS	Partial	Only participants who completed entire 12-month follow-up were included in analysis
	Bill, 1997[124]	Yes	NS	Partial	Analysis only included participants who did not discontinue prior to and who had at least one seizure assessment in maintenance phase
	Christe, 1997[123]	NS	NS	Partial	Analysis only included participants who did not discontinue prior to and who had at least one seizure assessment in maintenance phase
TPM	Privitera, 2002[94]	Yes	NS	Partial	Non-inferiority trial

NS, not stated.

[a] Blinding refers to three categories of individuals: patients, clinicians and study assessors. In many cases one or two categories of individuals were blinded to the treatment assignment, but not all. Such studies were described as partially fulfilling the criterion. See Appendix 18 for more details.

Adjunctive therapy

Drug	Study	Random	Conceal	Blinding[a]	Comments
GBP	UK Gabapentin Study Group, 1990[73]	Yes	NS	NS	Absolute numbers of participants and denominators for outcome data lacking
	US Gabapentin Study Group, 1993[138]	NS	NS	NS	Only patients deemed likely to complete the trial were included so findings may not be applicable to the general population
LTG	Matsuo, 1993[142]	NS	NS	Yes	
	Schacter, 1995[56]	Yes	Yes	Partial	
	Veendrick-Meekes, 2000[137]	NS	NS	Partial	Specifically looks at patients with intellectual disabilities so findings may not be applicable to the general population
LEV	Betts, 2000[139]	Yes	Yes	Partial	4000 mg/day dose exceeded the recommended dose of 3000 mg/day
	Cereghino, 2000[143]	Yes	Yes	Partial	Concomitant AEDs allowed included new AEDs GBP, LTG and TGB – may have affected study findings
	Shorvon, 2000[145]	Yes	?	Partial	
OXC	Barcs, 2000[70]	NS	NS	Partial	Numbers of withdrawals and reasons not clearly stated
TGB	Kälviäinen, 1998[164]	Yes	NS	Partial	VGB allowed as concurrent medication (15 TGB and 14 placebo patients received VGB) – may have affected results
	Sachdeo, 1997[140]	NS	Yes	Partial	Specifically looks at patients with intellectual disabilities, so findings may not be applicable to general population
	Uthman, 1998[163]	Yes	Yes	Partial	
TPM	Barrett, 1997[76]	Yes	Yes	Partial	Baseline differences in seizure rate (higher rates in TPM group). Unclear if findings consider this
	Biton, 1999[79]	Yes	Yes	Partial	Concomitant medications included new AEDs (GBP and LTG)
	Faught, 1996[67]	Yes	Yes	Partial	
	Guberman, 2002[150]	Yes	Yes	Yes	Concomitant medications included new AEDs (VGB and LTG)
	Sharief, 1996[148]	NS	NS	Partial	
	Yen, 2000[165]	NS	NS	Partial	No information about baseline comparability

NS, not stated.

[a] Blinding refers to three categories of individuals: patients, clinicians and study assessors. In many cases one or two categories of individuals were blinded to the treatment assignment, but not all. Such studies were described as partially fulfilling the criterion. See Appendix 18 for more details.

Summary of RCTs excluded from the economic evaluation meta-analysis

Drug	Study	Comments
GBP	Leach, 1997[90]	Crossover design
	Wilensky, 1996[69]	Trial outcomes required for meta-analysis not reported
	Anhut, 1994[156]	Trial outcomes required for meta-analysis not reported
	Brodie, 2002[93]	Drug was not licensed as used in the trial
	Chadwick, 1996[74]	Drug was not licensed as used in the trial
	Chadwick, 1998[250]	Drug was not licensed as used in the trial
	Crawford, 2001[131]	Trial outcomes required for meta-analysis not reported
	Lindberger, 2000[132]	Trial outcomes required for meta-analysis not reported
	Lopes-Lima, 1999[46]	Drug was not licensed as used in the trial
	Maton, 1998[128]	Trial outcomes required for meta-analysis not reported
	Sivenius, 1991[157]	Trial outcomes required for meta-analysis not reported
LTG	Banks, 1991[88]	Crossover design
	Beran, 1998[134]	Crossover design
	Binnie, 1989[159]	Crossover design
	Binnie, 1987[50]	Crossover design
	Boas, 1996[136]	Crossover design
	Cordova, 1995[40]	Crossover design
	Jawad, 1989[160]	Crossover design
	Loiseau, 1990[89]	Crossover design
	Messenheimer, 1994[158]	Crossover design
	Sander, 1990[135]	Crossover design
	Schapel, 1993[161]	Crossover design
	Schmidt, 1993[91]	Crossover design
	Smith, 1993[55]	Crossover design
	Stolarek, 1994[162]	Crossover design
	Yaqub, 1995[82]	Crossover design
	Brodie, 1999[117]	Elderly population
	Brodie, 1999[47]	Elderly population
	Bryant-Comstock, 2002[113]	Trial outcomes required for meta-analysis not reported
	Chmielewska, 2001[133]	Trial outcomes required for meta-analysis not reported
	GlaxoSmithKline, 2000[118]	Pseudo-randomisation used
	Martinez, 2002[114]	Pseudo-randomisation used
	Matsuo, 1996[328]	Trial outcomes required for meta-analysis not reported
LEV	Boon, 2002[80]	Crossover design
	Ben-Menachem, 2000[144]	Drug was not licensed as used in the trial
	Cramer, 2000[166]	Concomitant AEDs allowed included new AEDs GBP, LTG and TGB – may have affected study findings
OXC	Houtkooper, 1987[84]	Crossover design
	Dam, 1989[125]	Data for 165/235 participants available, not clear how missing data dealt with
	Loiseau, 1998[72]	[Data have been designated commercial-in-confidence and have been removed]
	Reinikainen, 1987[115]	Trial outcomes required for meta-analysis not reported
	Sachdeo, 1998[111]	Trial outcomes required for meta-analysis not reported
	Schachter, 1999[78]	Trial outcomes required for meta-analysis not reported

continued

TGB	Crawford, 2001[147]	Crossover design
	Richens, 1995[146]	Crossover design
	Sveinbjornsdottir, 1994[39]	Crossover design
	Sommerville, 1998[129]	Study design did not reflect clinical practice
	Aikia, 1999[52]	Drug was not licensed as used in the trial
	Baulac, 2001[329]	Drug was not licensed as used in the trial
	Cramer, 2001[65]	Study design did not reflect clinical practice
	Dodrill, 1997[167]	Study design did not reflect clinical practice
	Dodrill, 2000[57]	Trial outcomes required for meta-analysis not reported
	Schachter, 1995[251]	Drug was not licensed as used in the trial
TPM	Aldenkamp, 2000[130]	Trial outcomes required for meta-analysis not reported
	Ben-Menachem, 1996[151]	Trial outcomes required for meta-analysis not reported
	Korean Topiramate Study Group, 1999[149]	Dose outside range specified in the BNF
	Meador, 2001[44]	Trial outcomes required for meta-analysis not reported
	Privitera, 1996[68]	Dose outside range specified in the BNF
	Rosenfeld, 1996[41]	Dose outside range specified in the BNF
	Tassinari, 1996[42]	Dose outside range specified in the BNF

Appendix 14

Details of RCTs included in the assessment of clinical effectiveness (licensed and unlicensed)

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
GBP	Anhut, 1994[156] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Parke-Davis and Warner-Lambert	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 272 participants recruited	GBP 900 mg/day and 1200 mg/day versus placebo. Follow-up = 12 weeks
	Brodie, 2002[93] Study ID: 945–212 Related publications: Brodie, 2001[330] (abstract)	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Monotherapy, parallel trial, non-inferiority trial, combination of partial/generalised, newly diagnosed, 315 participants recruited	GBP 1800–3600 mg/day versus LTG 100–300 mg/day. Follow-up = 30 weeks
	Chadwick, 1996[74] Study ID: not stated Related publications: Chadwick, 1994[331]	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Adjunctive therapy, parallel trial, superiority trial, generalised onset, refractory, 129 participants recruited	GBP 1200 mg/day versus placebo. Follow-up = 20–24 weeks
	Chadwick, 1998[250] Study ID: Study Group 945–77 Related publications: abstract: Anhut, 1995[333]	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Monotherapy, parallel trial, superiority trial, partial onset, newly diagnosed, 292 participants recruited	GBP 300, 900 mg/day, and 1800 mg/day versus CBZ 600 mg/day. Follow-up = 24 weeks
	Crawford, 2001[131] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Adjunctive therapy, parallel trial, superiority trial, combination of partial/generalised, refractory, 109 participants recruited	GBP 3600 mg/day versus LTG 400 mg/day. Follow-up = 24 weeks
	Leach, 1997[90] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Adjunctive therapy, Crossover trial, superiority trial, partial onset, refractory, 27 participants recruited	GBP/placebo 2400 mg/day versus placebo/GBP. Follow-up = 28 weeks
	Lindberger, 2000[132] Study ID: 945-448-001 Related publications: Lindberger, 1999[460]	Literature search, full paper (final analysis). Sponsorship: Parke-Davis Scandinavia	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 102 participants recruited	GBP 1800–3600 mg/day versus VGB 1000–4000 mg/day. Follow-up = 24 weeks
	Lopes-Lima, 1999[46] Study ID: not stated Related publications: none	Literature search, abstract (final analysis). Sponsorship: not stated	Monotherapy, parallel trial, superiority trial, partial onset, refractory, 64 participants recruited	GBP 1800–2400 mg/day versus VPA 1500 mg/day. Follow-up = 30 weeks
	Maton, 1998[128] Study ID: RR-430-00120 Related publications: National Research Register entry giving very brief study design details[461]	Industry submission, Industry trial report. Sponsorship: Parke-Davis	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 32 participants recruited	GBP 1200, 1800 or 2400 mg/day versus VPA 1000, 1500, or 2000 mg/day. Follow-up = 14–18 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Sivenius, 1991[157] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Warner Lambert/Parke Davis	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 45 participants recruited	GBP 900 and 1200 mg/day versus placebo. Follow-up = 3 months
	UK Gabapentin Study Group, 1990[73] Study ID: not stated Related publications: Patterson, 1988[335] (abstract of preliminary analysis)	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 127 participants recruited	GBP 1200 mg/day versus placebo. Follow-up = 14 weeks
	US Gabapentin Study Group, No.5 1993[138] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Parke-Davis	Adjunctive therapy, parallel trial, superiority trial, combination of partial, refractory, 306 participants recruited	GBP 600, 1200 and 1800 mg/day versus placebo. Follow-up = 12 weeks
	Wilensky, 1996[69] Study ID: 945-36/RR720-03733 Related publications: Trudeau, 1995[336] (abstract)	Industry submission, industry trial report. Sponsorship: Parke-Davis and National Institutes of Health	Combination, crossover trial, equivalence trial, partial onset, refractory, 22 participants recruited	GBP 1200 mg/day and CBZ 1200 mg/day and GBP/CBZ 1200 mg/day each versus the other. Follow-up = 16–28 weeks
LTG	Banks, 1991[88] Study ID: H34-035-C86 Related publications: Schapel, 1993[161] (main report of seizure frequency data); GlaxoSmithKline, 1991[337] (trial report)	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 12 participants recruited	LTG 150 or 300 mg/day versus placebo. Follow-up = 32 weeks
	Beran, 1998[134] Study ID: LAM40057 Related publications: Beran, 1997[338] (abstract of final analysis); GlaxoSmithKline, 1996[432] (GSK trial report)	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, generalised onset, refractory, 26 participants recruited	LTG/placebo 75 mg/day versus placebo/LTG 150 mg/day. Follow-up = 24 weeks
	Binnie, 1987[50] Study ID: H34-007 Related publications: industry trial report[339]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 10 participants recruited	LTG/placebo 100–250 mg/day versus placebo/LTG. Follow-up = 7 days
	Binnie, 1989[159] Study ID: LAM 30029 (H34/C/85/AWP/55/16) (UK-016) Related publications: industry trial report[340]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 34 participants recruited	LTG/placebo 75, 100 or 200 mg/day versus placebo/LTG 75, 100 or 200 mg/day. Follow-up = 44 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Biton, 2001[116] Study ID: SCAA4001 Related publications: Montouris, 1999;[341] Mirza, 1999;[342] Biton, 2000;[343] Edwards, 2001;[344] Sackellares, 2000;[126] GlaxoSmithKline industry trial report[345]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, combination of newly diagnosed/refractory, 141 participants recruited	LTG 200 mg/day versus VPA 20 mg/kg/day. Follow-up = 32 weeks
	Boas, 1996[136] Study ID: LAM30022 Related publications: industry submission,[346] Boas, 1995[347]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 56 participants recruited	LTG/placebo 75–400 mg/day versus placebo/LTG 100–400 mg/day. Follow-up = 11 months
	Brodie, 1999[47] Study ID: LAM30039; H34-049-C87/H34-089-C88 Related publications: GlaxoSmithKline, 1994,[127] industry submission	Literature search, abstract (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 168 participants recruited	LTG 150 mg/day versus CBZ 600 mg/day. Follow-up = 48 weeks
	Brodie, 1995[121] Study ID: LAM30039; H34-049-C87/H34-089-C88 Related publications: Reynolds, 1995[348] letter to the Editor and correction; Richens, 1996[349] (later summary article); GlaxoSmithKline, 1994,[127] industry submission; Brodie, 1999[47] (cognitive); Gillham, 2000[77] (QoL)	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 260 participants recruited	LTG 150 mg/day versus CBZ 600 mg/day. Follow-up = 48 weeks
	Brodie, 1999[117] Study ID: ITR: 105-124-C93 Related publications: Brodie 1998;[350] Park;[351] National Research Register, industry trial report, 1998[352]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 150 participants recruited	LTG 75–500 mg/day versus CBZ 200–2000 mg/day. Follow-up = 24 weeks
	Bryant-Comstock, 2002[113] Study ID: SCAB3001 Related publications: Bryant-Comstock, 1999[363] (abstract); Bryant-Comstock, 1999[335] (abstract); GlaxoSmithKline (Kerr), 2001[122] (effectiveness report)	Industry submission, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy after adjunctive titration, parallel trial, superiority trial, partial onset, refractory, 663 participants recruited	LTG 200–500 mg/day versus VPA not stated. Follow-up = 28 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Chmielewska, 2001[133] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 48 participants recruited	LTG 400 mg/day versus TGB 60 mg/day. Follow-up = 20 weeks
	Cordova, 1995[40] Study ID: not stated Related publications: none	Literature search, abstract (final analysis). Sponsorship: not stated	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 29 participants recruited	LTG/placebo 150 or 300 mg/day versus placebo/LTG. Follow-up = 12 weeks
	Gillham, 2000[77] Study ID: LAM30039; H34-049-C87/H34-089-C88 Related publications: GlaxoSmithKline, 1994,[127] industry submission; Gillham, 1995[354] (abstract)	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 260 participants recruited	LTG 150 mg/day versus CBZ 600 mg/day. Follow-up = 48 weeks
	Gilliam, 1998[112] Study ID: not stated Related publications: letter;[355] industry trial report[356]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, partial onset, refractory, 220 participants recruited	LTG 400–500 mg/day versus VPA 100 mg/day. Follow-up = 12 weeks
	GlaxoSmithKline, 2001[62] Study ID: 105–126 Related publications: National Research Register[357]	Industry submission, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, generalised onset, newly diagnosed, 211 participants recruited	LTG 100–500 mg/day (age >12 years), 2–10 mg/kg/day (paediatrics) versus VPA not stated. Follow-up = 24 weeks
	GlaxoSmithKline, 2000[118] Study ID: 105-405R Related publications: National Research Register entries[358,359]	Industry submission, Industry trial report. Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 713 participants recruited	LTG 200 mg/day versus conventional treatment (CBZ or VPA) according to manufacturer's recommendations. Follow-up = 20 weeks
	Jawad, 1989[160] Study ID: LAM30024 (H34/C/85/AWP/57) (UK-021) Related publications: industry trial report[360]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 24 participants recruited	LTG/placebo 75–400 mg/day versus placebo/LTG 100–300 mg/day. Follow-up = 44 weeks
	Loiseau, 1990[89] Study ID: LAM30009 Related publications: trial report from GlaxoSmithKline[360]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 25 participants recruited	LTG/placebo 150 or 300 mg/day versus placebo/LTG. Follow-up = 28 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Kerr, 2001[122] Study ID: SCAB3001 Related publications: Kerr, 1999[362] (abstract); Bryant-Comstock, 1999[353] (abstract); Bryant-Comstock, 1999[363] (abstract); Bryant-Comstock, 2002[113] (unpublished QoL data)	Literature search, industry trial report. Sponsorship: GlaxoSmithKline	Monotherapy after adjunctive titration, parallel trial, superiority trial, combination of partial/generalised, refractory, 877 participants recruited	LTG 200–500 mg/day and CBZ not stated and LTG 200–500 mg/day versus VPA not stated. Follow-up = 28 weeks
	Martinez, 2002[114] Study ID: SCAA4005 Related publications: Nanry, 2000[364] (abstract of QoL data)	Industry submission, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, refractory, 122 participants recruited	LTG 100–500 mg/day versus conventional therapy (CBZ, PHT or VPA) not stated. Follow-up = 32 weeks
	Matsuo, 1993[142] Study ID: US-05 (P42-05)/GSK16 Related publications: industry trial report[365]	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 216 participants recruited	LTG 500 and 300 mg/day versus placebo. Follow-up = 24 weeks
	Matsuo, 1996[328] Study ID: US14 (P42-14) Related publications: industry submission[366]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 12 participants recruited	LTG max. 700 mg/day versus placebo. Follow-up = 63 days
	Messenheimer, 1994[158] Study ID: P42/06/W7(1) Related publications: industry trial report[367]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 108 participants recruited	LTG/placebo 400 mg/day max. versus placebo/LTG. Follow-up = 43 weeks
	Nieto Barrera, 2001[119] Study ID: 105–136 Related publications: none	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 618 participants recruited	LTG median 200 mg/day versus CBZ median 600 mg/day. Follow-up = 18 weeks
	Reunanen, 1996[120] Study ID: LAM30025 Related publications: Dam, 1996[368] (abstract); Yuen, 1993[369] (internal abstract); Severi, 1994[370] (final paper Italian centre); Severi, 1993[371] (preliminary paper, Italian centre); Severi, 1995[372] (abstract)	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 343 participants recruited	LTG 100 and 200 mg/day versus CBZ 600 mg/day. Follow-up = 26 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Sackellares, 2000[126] Study ID: SCAA4001 Related publications: Biton, 2001;[116] GlaxoSmithKline, industry submission, 2001[345]	Industry submission, full paper (final analysis) unpublished. Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, combination of newly diagnosed/refractory, 141 participants recruited	LTG 200 mg/day versus VPA 20 mg/kg/day. Follow-up = 32 weeks
	Sander, 1990[135] Study ID: H34/C/85/AWP/1(UK–022) Related publications: industry submission, 1989[373]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 26 participants recruited	LTG/placebo 150–300 mg/day versus placebo/LTG. Follow-up = 46 weeks
	Schachter, 1995[56] Study ID: P42–16 Related publications: industry trial report[374]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 446 participants recruited	LTG max. 500 mg/day versus placebo. Follow-up = 28 weeks
	Schapel, 1993[161] Study ID: H34-035-C86 Related publications: GlaxoSmithKline, 1991[337] (full trial report from GlaxoSmithKline); Banks, 1991[88] (cognitive outcomes for 10 patients)	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial, refractory, 41 participants recruited	LTG/placebo 150 or 300 mg/day versus placebo/LTG 150 or 300 mg/day. Follow-up = 12 weeks
	Schmidt, 1993[91] Study ID: H34-18/C/85/WCY/34 (UK-018) Related publications: abstract of final results[375]	Industry submission, Industry trial report. Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 23 participants recruited	LTG/placebo 400 mg/day mean dose versus placebo/LTG. Follow-up = 32 weeks
	Smith, 1993[55] Study ID: H34-086-C88 Related publications: Smith, 1993;[376] Smith, 1992;[377] Industry trial report[378]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 81 participants recruited	LTG/placebo 200 or 400 mg/day versus placebo/LTG. Follow-up = 46 weeks
	Steiner, 1999[75] Study ID: LAM30026 Related publications: abstracts;[379,380] industry trial report[381]	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 181 participants recruited	LTG max. 400 mg/day versus PHT max. 600 mg/day. Follow-up = 48 weeks
	Stolarek 1994[162] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: GlaxoSmithKline	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 22 participants recruited	LTG/placebo 200 mg/day versus placebo/LTG. Follow-up = 36 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Veendrick-Meekes, 2000[137] Study ID: LAM40004 Related publications: none	Industry submission, poster. Sponsorship: GlaxoSmithKline	Adjunctive therapy, parallel trial, superiority trial, combination of partial/generalised, refractory, 68 participants recruited	LTG 100 mg/day for patients on VPA and 200 mg/day for patients on enzyme inducers versus placebo. Follow-up = 16 weeks
	Yaqub, 1995[82] Study ID: not stated Related publications: none	Literature search, abstract (final analysis). Sponsorship: not stated	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 43 participants recruited	LTG/placebo max. 400 mg/day versus placebo/LTG max. 400 mg/day. Follow-up = 20 weeks
LEV	Ben-Menachem, 2000[144] Study ID: not stated Related publications: Ben-Menachem, 1999[382] (abstract); Ben-Menachem, 1999[383] (abstract)	Literature search, full paper (final analysis). Sponsorship: UCB Pharma	Monotherapy, parallel trial, superiority trial, partial onset, refractory, 343 participants recruited. Add-on phase data included, monotherapy phase excluded	LEV 3000 mg/day versus placebo. Follow-up = 42 weeks
	Betts, 2000[139] Study ID: not stated Related publications: Crawford, 1999[384] (abstract only)	Literature search, full paper (final analysis). Sponsorship: UCB Pharma	Adjunctive therapy, parallel trial, superiority trial, combination of partial/generalised, refractory, 136 participants recruited	LEV 2000 and 4000 mg/day versus placebo. Follow-up = 24 weeks
	Boon, 2002[80] Study ID: not stated Related publications: reports data from first phase of crossover study;[145] abstract[385]	Literature search, full paper (final analysis). Sponsorship: UCB Pharma	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 324 participants recruited	LEV 1000 and 2000 mg/day versus placebo. Follow-up = 16 weeks
	Cereghino, 2000[143] Study ID: N132 Related publications: Penovich, 1998;[386] Radtke, 1999;[387] Cramer, 2000,[166] full study of QoL[388]	Literature search, full paper (final analysis). Sponsorship: UCB Pharma	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 385 participants recruited	LEV 1000 and 3000 mg/day versus placebo. Follow-up = 38 weeks
	Cramer, 2000[166] Study ID: N132 Related publications: Cereghino, 2000[143] (effectiveness); abstracts[386,387]	Literature search, full paper (final analysis). Sponsorship: UCB Pharma	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 385 participants recruited	LEV 1000 and 3000 mg/day versus placebo. Follow-up = 38 weeks
	Shorvon, 2000[145] Study ID: not stated Related publications: Boon, 2002[80]	Literature search, full paper (final analysis). Sponsorship: UCB Pharma	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 324 participants recruited	LEV 1000 and 2000 mg/day versus placebo. Follow-up = 16 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
OXC	Aikia, 1992[58] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Ciba-Geigy	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 37 participants recruited	OXC (dose not stated) versus CBZ (dose not stated). Follow-up = 12 months
	Barcs, 2000[70] Study ID: OT/PE1 Related publications: Wroe, 1997[389] (NRR entry)	Literature search, full paper (final analysis). Sponsorship: Novartis Pharmaceuticals	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 694 participants recruited	OXC 600, 1200 and 2400 mg/day versus placebo. Follow-up = 28 weeks
	Bill, 1997[124] Study ID: OT/F02 Related publications: none	Literature search, full paper (final analysis). Sponsorship: Ciba-Geigy and Novartis Pharmaceuticals	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 287 participants recruited	OXC 600–2100 mg/day versus PHT 100–650 mg/day. Follow-up = 56 weeks
	Christe, 1997[123] Study ID: OT/F01 Related publications: none	Literature search, full paper (final analysis). Sponsorship: Ciba-Geigy	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 249 participants recruited	OXC 600–2400 mg/day versus VPA 600–2700 mg/day. Follow-up = 56 weeks
	Dam, 1989[125] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Ciba-Geigy	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 235 participants recruited	OXC 300–1800 mg/day versus CBZ 300–1400 mg/day. Follow-up = 56 weeks
	Houtkooper, 1987[84] Study ID: not stated Related publications: abstract[390]	Literature search, full paper (final analysis). Sponsorship: Ciba Geigy	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 48 participants recruited	OXC 900–3600 mg/day versus CBZ 500–2000 mg/day at steady state. Follow-up = 40 weeks
	Loiseau, 1998[72] Study ID: OT/E25 Related publications: none	Industry submission, Industry trial report. Sponsorship: Novartis Pharmaceuticals UK	[Data have been designated commercial-in-confidence and have been removed]	
	Reinikainen, 1987[115] Study ID: not stated Related publications: Reinikainen, 1984[391] (preliminary paper)	Literature search, full paper (final analysis). Sponsorship: Ciba-Geigy	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, refractory, 40 participants recruited	OXC 600–900 mg/day versus CBZ 400–800 mg/day. Follow-up = 48–50 weeks
	Sachdeo, 1998[111] Study ID: 025 Related publications: Novartis NICE submission, 2002[263]	Industry submission, Industry trial report. Sponsorship: Novartis Pharmaceuticals UK	Monotherapy, parallel trial, superiority trial, partial onset, newly diagnosed, 67 participants recruited	OXC 1200 mg/day versus placebo. Follow-up = 90 days

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Schachter, 1999[78] Study ID: Novartis 004 Related publications: letter[392]	Literature search, full paper (final analysis). Sponsorship: Novartis Pharmaceuticals UK	Monotherapy, parallel trial, superiority trial, partial onset, refractory, 102 participants recruited	OXC 2400 mg/day versus placebo. Follow-up = 10 days
TGB	Aikia, 1999[52] Study ID: not stated Related publications: Aikia, 1999[393]	Literature search, abstract (final analysis). Sponsorship: Sanofi	Monotherapy, parallel trial, superiority trial, partial onset, newly diagnosed, 67 participants recruited	TGB 10–20 mg/day versus CBZ 400–800 mg/day. Follow-up = 6 months
	Baulac, 2001[329] Study ID: TIA126 Related publications: National Research Register entry[394]	Industry submission, industry trial report. Sponsorship: Sanofi-Synthelabo	**[Data have been designated commercial-in-confidence and have been removed]**	
	Cramer, 2001[65] Study ID: M92–825 Related publications: Dodrill, 2000[57] (cognitive); industry trial report M92–825, 1998[129]	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 349 participants recruited	TGB (CBZ baseline) 80 mg/day max. versus PHA (CBZ baseline) max. 600 mg/day and TGB (PHT baseline) max. 80 mg/day versus CBZ (PHT baseline) max. 2000 mg/day. Follow-up = 24 weeks
	Crawford, 2001[147] Study ID: TIA103 Related publications: industry trial report[395]	Literature search, full paper (final analysis). Sponsorship: Novo Nordisk and Abbott Laboratories	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 88 participants recruited	TGB/placebo 16–64 mg/day versus placebo/TGB. Follow-up = 35 weeks
	Dodrill, 1997[167] Study ID: TIA106 Related publications: abstracts;[396,397] Uthman, 1998[163] (effectiveness); trial report 1994[398]	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 322 participants recruited	TGB 16, 32 and 56 mg/day versus placebo. Follow-up = 20 weeks
	Dodrill, 2000[57] Study ID: M92-825/TIA128 Related publications: industry report[129] M92-825; Cramer, 2001[65] (QoL)	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 349 participants recruited	TGB (CBZ baseline) 80 mg/day max. and PHT (CBZ baseline) 600 mg/day max. and TGB (PHT baseline) 80 mg/day max. versus CBZ (PHT baseline) 2000 mg/day max. Follow-up = 24 weeks
	Kälviäinen, 1996[43] Study ID: TIA107 (M92–775) Related publications: abstracts[164,399]	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 43 participants recruited	TGB 30 mg/day versus placebo. Follow-up = 12 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Kälviäinen, 1998[164] Study ID: TIA107 (M92–775) Related publications: abstracts[43,399]	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories and the Northern European TGB Study Group	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 177 participants recruited	TGB 30 mg/day versus placebo. Follow-up = 22 weeks
	Richens, 1995[146] Study ID: TIA101 Related publications: industry trial report[400]	Literature search, full paper (final analysis). Sponsorship: Novo Nordisk and Abbott Laboratories	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 94 participants recruited	TGB/placebo 12–52 mg/day versus placebo/TGB. Follow-up = 20 weeks
	Sachdeo, 1997[140] Study ID: TIA109/M91–605 Related publications: Sachdeo, 1995[401] (abstract); industry submission, 1994[402]	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 351 participants recruited	TGB 32 mg/day (16 mg b.d.) and 32 mg/day (8 mg q.d.s) versus placebo. Follow-up = 16 weeks
	Schachter, 1995[251] Study ID: not stated Related publications: none	Literature search, full paper (final analysis) from unpublished data. Sponsorship: Abbott Laboratories	Monotherapy, parallel trial, superiority trial, partial onset, refractory, 11 participants recruited	TGB max. 66 mg/day versus placebo. Follow-up = 7 days
	Sommerville, 1998[129] Study ID: M92–825 Related publications: Dodrill, 2000[57] (cognitive data); Cramer, 2001[65] (QoL data); Vasquez, 1998[403] (abstract); Biton, 1998[404] (abstract)	Industry submission, industry trial report. Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 451 participants recruited	TGB (CBZ baseline) 80 mg/day max. versus PHA (CBZ baseline) 600 mg/day max. and TGB (PHT baseline) 80 mg/day max. versus CBZ (PHT baseline) 2000 mg/day max. Follow-up = 16 weeks
	Sveinbjornsdottir, 1994[39] Study ID: TIA101 Related publications: Richens, 1995,[146] presents effectiveness data for all centres participating in TIA101	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories and Novonordisk supplied tiagabine and provided support during the study	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 22 participants recruited	TGB/placebo 20–40 mg/day versus placebo/TGB. Follow-up = 20 weeks
	Uthman, 1998[163] Study ID: TIA106/M91 603 Related publications: Uthman, 1993;[405] Rowan, 1994;[406] Dodrill, 1997[167] (cognitive); trial report, 1994[402]	Literature search, full paper (final analysis). Sponsorship: Abbott Laboratories	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 322 participants recruited	TGB 16, 32 and 56 mg/day versus placebo. Follow-up = 20 weeks
TPM	Aldenkamp, 2000[130] Study ID: not stated Related publications: abstract of final results;[407] National Research Register entries[408,409]	Literature search, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 59 participants recruited	TPM 200–400 mg/day versus VPA 1800 mg/day. Follow-up = 24 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Barrett, 1997[76] Study ID: RWJ-17021–000 Related publications: none	Industry submission, Industry trial report. Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, generalised onset, refractory, 87 participants recruited	TPM 175, 225 or 400 mg/day versus placebo. Follow-up = 20 weeks
	Ben-Menachem, 1996[151] Study ID: Europe Y3 Related publications: abstracts[410,411]	Literature search, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 57 participants recruited	TPM 800 mg/day versus placebo. Follow-up = 13 weeks
	Biton, 1999[79] Study ID: YTC Related publications: none	Literature search, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, generalised onset, refractory, 103 participants recruited	TPM 175–400 mg/day versus placebo. Follow-up = 20 weeks
	Coles, 1999[60] Study ID: not stated Related publications: none	Literature search, abstract (final analysis). Sponsorship: Janssen-Cilag	Adjunctive therapy, parallel trial, superiority trial, combination of partial/generalised, refractory, 128 participants recruited	TPM not stated versus placebo. Follow-up = 28 weeks
	Faught, 1996[67] Study ID: US YD Related publications: Faught, 1995[412]	Literature search, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 233 participants recruited	TPM 200, 400 and 600 mg/day versus placebo. Follow-up = 16 weeks
	Guberman, 2002[150] Study ID: EPAJ-119 Related publications: Guberman, 2001;[413] Guberman, 2001[414]	Industry submission, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 263 participants recruited	TPM 200 mg/day versus placebo. Follow-up = 12 weeks
	Korean Topiramate Study Group, 1999[149] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Janssen-Cilag, Korea	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 235 participants recruited	TPM 600 mg/day versus placebo. Follow-up = 18 weeks
	Meador, 2001[44] Study ID: not stated Related publications: none	Literature search, abstract (final analysis). Sponsorship: Ortho-McNeill Pharmaceutical	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 76 participants recruited	TPM 400 mg/day and VPA 2250 mg/day versus placebo. Follow-up = 24 weeks
	Privitera, 2002[94] Study ID: EPMN105 Related publications: Privitera, 2001[415] (abstract); Wheless, 2001[416] (abstract)	Industry submission, Industry trial report. Sponsorship: Janssen-Cilag	Monotherapy, parallel trial, non-inferiority trial, combination of partial/generalised, newly diagnosed, 621 participants recruited	TPM 100 and 200 mg/day with CBZ 600 mg/day and VPA 1250 mg/day. Follow-up = 6 months

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Privitera, 1996[68] Study ID: US YE Related publications: Privitera, 1995[417]	Literature search, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 240 participants recruited	TPM 600, 800 and 1000 mg/day versus placebo. Follow-up = 18 weeks
	Rosenfeld, 1996[41] Study ID: US YF-YG Related publications: none	Literature search, abstract (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, number of participants recruited not stated	TPM 1000 mg/day versus placebo. Follow-up = 19 weeks
	Sharief, 1996[148] Study ID: Europe Y1 Related publications: Martinez-Lage, 1995[418]	Literature search, full paper (final analysis). Sponsorship: RW Johnson Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, number of participants recruited not stated	TPM 400 mg/day versus placebo. Follow-up = 11 weeks
	Tassinari, 1996[42] Study ID: Europe Y2 Related publications: Tassinari, 1995[419]	Literature search, full paper (final analysis). Sponsorship: R. W. Johnson Pharmaceutical Research Institute	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, number of participants recruited not stated	TPM 600 mg/day versus placebo. Follow-up = 12 weeks
	Yen, 2000[165] Study ID: not stated Related publications: Yu 1999[420]	Literature search, full paper (final analysis). Sponsorship: Taipei Veterans General Hospital and Yen Tjing Ling Medical Foundation	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 46 participants recruited	TPM 300 mg/day versus placebo. Follow-up = 14 weeks
VGB	Beran, 1996[87] Study ID: AUS01 Related publications: none	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 97 participants recruited	VGB/placebo 3 g/day versus placebo/VGB and VGB/placebo 2 g/day versus placebo/VGB. Follow-up = 32 weeks
	Brodie, 1999[66] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy and monotherapy and, parallel trial, superiority trial, partial onset, refractory, 215 participants recruited	VGB 1–4 g/day versus VPA 1–3 g/day. Follow-up = 12 weeks for duotherapy and 12 weeks for monotherapy
	Bruni, 2000[153] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Hoeschst Marion Roussel	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 111 participants recruited	VGB 4 g/day max. versus placebo. Follow-up = 4 weeks
	Chadwick, 1999[92] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Hoechst Marion Roussell	Monotherapy, parallel trial, equivalence trial, partial onset, newly diagnosed, 459 participants recruited	VGB 1–4 g/day versus CBZ 200–1400 mg/day. Follow-up = 52 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	Czapinski, 1997[45] Study ID: not stated Related publications: none	Literature search, abstract (final analysis). Sponsorship: not stated	Monotherapy, parallel trial, superiority trial, partial onset, refractory, 40 participants recruited	VGB 4 g/day max. versus LTG max. 600 mg/day. Follow-up = 12 months
	Dean, 1999[154] Study ID: not stated Related publications: Kälviäinen, 1998;[164] Penry, 1993[326] (abstract); Dodrill, 1995[168] (cognitive and QoL)	Literature search, full paper (final analysis). Sponsorship: Hoechst Marion Roussel	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 203 participants recruited	VGB 1, 3 and 6 g/day versus placebo. Follow-up = 12 weeks
	Dodrill, 1995[168] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Marion Merrell Dow	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 174 participants recruited	VGB 1, 3 and 6 g/day versus placebo. Follow-up = 12 weeks
	Dodrill, 1993[169] Study ID: Study 024 Related publications: efficacy and safety data;[155] abstracts[421,422]	Literature search, full paper (final analysis). Sponsorship: Marion Merrell Dow	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 203 participants recruited	VGB 3 g/day versus placebo. Follow-up = 12 weeks
	French, 1996[155] Study ID: Study 024 Related publications: Dodrill, 1993,[169] reports cognitive function outcome data; abstracts[421,422]	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 203 participants recruited	VGB 3 g/day versus placebo. Follow-up = 12 weeks
	Gillham, 1993[51] Study ID: not stated Related publications: McKee, 1993[54]	Literature search, full paper (final analysis). Sponsorship: Marion Merrell Dow	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 24 participants recruited	VGB/placebo 2–3 g/day versus placebo/VGB. Follow-up = 30 weeks
	Grunewald, 1994[38] Study ID: not stated Related publications: Grunewald, 1993,[423] is an abstract of this study	Literature search, full paper (final analysis). Sponsorship: Marion Merrell Dow	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 45 participants recruited	VGB 3 g/day versus placebo. Follow-up = 18 weeks
	Kälviäinen, 1995[71] Study ID: not stated Related publications: Kälviäinen, 1994;[424] Aikia, 1991;[425] Kälviäinen, 1991[426]	Literature search, full paper (final analysis). Sponsorship: not stated	Monotherapy, parallel trial, superiority trial, combination of partial/generalised, newly diagnosed, 100 participants recruited	VGB individually titrated, 40–60 mg/kg/day versus CBZ individually titrated. Follow-up = 12 months
	Loiseau, 1986[83] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 23 participants recruited	VGB/placebo 3 g/day versus placebo/VGB. Follow-up = 26 weeks

continued

Drug	Author, year, trial ID, related publications	Source, status, sponsorship	Study design, no. of participants	Comparators, length of follow-up
	McKee, 1993[54] Study ID: not stated Related publications: Gillham, 1993[51]	Literature search, full paper (final analysis). Sponsorship: Marion Merrell Dow	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 24 participants recruited	VGB/placebo 2–3 g/day versus placebo/VGB. Follow-up = 30 weeks
	Provinciali, 1996[152] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: not stated	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 40 participants recruited	VGB 2–3 g/day versus placebo. Follow-up = 4 months
	Reynolds, 1991[141] Study ID: not stated Related publications: interim data.[427] Also linked to prior phase reports of Reynolds, 1988[428] (preliminary paper); Ring, 1988[429] (abstract)	Literature search, full paper (final analysis). Sponsorship: Merrell Dow	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 33 participants recruited	VGB 2–3 g/day versus placebo. Follow-up = 8 weeks
	Riekkinen, 1997[59] Study ID: not stated Related publications: Kälviäinen, 1995[71]	Literature search, abstract (final analysis). Sponsorship: not stated	Monotherapy, parallel trial, superiority trial, partial onset, newly diagnosed, 27 participants recruited	VGB (dose not stated) versus CBZ (dose not stated). Follow-up = 1 year
	Rimmer, 1984[49] Study ID: not stated Related publications: Rimmer, 1984[430]	Literature search, full paper (final analysis). Sponsorship: Wellcome Foundation; Drugs supplied by Merrell International Strasbourg	Adjunctive therapy, crossover trial, superiority trial, partial onset, refractory, 24 participants recruited	VGB/placebo 3 g/day versus placebo/VGB. Follow-up = 18 weeks
	Specchio, 1999[61] Study ID: not stated Related publications: none	Literature search, abstract (interim analysis). Sponsorship: not stated	Adjunctive therapy, parallel trial, superiority trial, partial onset, refractory, 404 participants recruited	VGB (dose not stated) and LTG (dose not stated) versus GBP (dose not stated). Follow-up = 18 months
	Tanganelli, 1996[53] Study ID: not stated Related publications: Tanganelli, 1995[431]	Literature search, full paper (final analysis). Sponsorship: none received	Monotherapy, crossover trial, superiority trial, partial onset, newly diagnosed, 58 participants recruited	VGB 3500 mg/day max. versus CBZ 1400 mg/day max. Follow-up = 32 weeks
	Tartara, 1986[86] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Merrell Dow	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 23 participants recruited	VGB/placebo 2 or 3 g/day versus placebo/VGB. Follow-up = 7 weeks
	Tassinari, 1987[85] Study ID: not stated Related publications: none	Literature search, full paper (final analysis). Sponsorship: Merrell Dow	Adjunctive therapy, crossover trial, superiority trial, combination of partial/generalised, refractory, 31 participants recruited	VGB/placebo 2 or 3 g/day versus placebo/VGB. Follow-up = 9 months

NRR, National Research Register.

Appendix 15

Links between included studies

Drug	RCT	RCT	RCT	Industry trial submission
	Effectiveness data	**Cognitive data**	**QoL data**	
GBP	Anhut, 1994[156]			Study ID: not stated
	Brodie, 2002[93]			Study ID: 945-212
	Chadwick, 1996[74]			Study ID: not stated
	Chadwick, 1998[250]			Study ID: Study Group 945-77
	Crawford, 2001[131]			Study ID: not stated
	Leach, 1997[90]			Study ID: not stated
	Lindberger, 2000[132]			Study ID: 945-448-001
	Lopes-Lima, 1999[46]			Study ID: not stated
	Maton, 1998[128]			Study ID: RR-430-00120
	Sivenius, 1991[157]			Study ID: not stated
	UK Gabapentin Study Group, 1990[73]			Study ID: not stated
	US Gabapentin Study Group No. 5, 1993[138]			GBP Study Group No.5. Study ID: not stated
	Wilensky, 1996[69]			Study ID: 945-36/RR720-03733
LTG	Beran, 1998[134]			Beran (GlaxoSmithKline trial report)[432] Study ID: LAM40057
	Binnie, 1987[50]			Industry trial report.[339] Study ID: H34-007
	Binnie, 1989[159]			Industry trial report.[340] Study ID: LAM 30029 (H34/C/85/AWP/55/16) (UK-016)
	Biton, 2001[116]		Sackellares, 2000[126]	GSK ITR[345] Study ID: SCAA4001
	Boas, 1996[136]			Industry submission.[346] Study ID: LAM30022
	Brodie, 1995[121]	Brodie, 1999[47]	Gillham, 2000[77]	GlaxoSmithKline, 1994, industry Submission.[127] Study ID: LAM30039; H34-049-C87/H34-089-C88
	Brodie, 1999[117]			Industry trial report.[352] Study ID: ITR: 105-124-C93
	Chmielewska, 2001[133]			Study ID: not stated
	Cordova, 1995[40]			Study ID: not stated
	Gilliam, 1998[112]			Industry trial report.[356] Study ID: not stated
	GlaxoSmithKline, 2001[62]			GlaxoSmithKline, 2001.[62] Study ID: 105-126
	GlaxoSmithKline (Kerr), 2001[122]		Bryant-Comstock, 2002[113]	GlaxoSmithKline (Kerr), 2001[122] Study ID: SCAB3001
	GlaxoSmithKline, 2000[118]			GlaxoSmithKline, 2000[118] Study ID: 105-405R
	Jawad, 1989[160]			Industry trial report.[360] Study ID: LAM30024 (H34/C/85/AWP/57) (UK-021)

continued

Drug	RCT	RCT	RCT	Industry trial submission
	Effectiveness data	**Cognitive data**	**QoL**	
	Loiseau, 1990[89]			Trial report from GlaxoSmithKline.[360] Study ID: LAM30009
	Martinez, 2002[114]		Nanry, 2000[364] (abstract of QoL data)	Study ID: SCAA4005
	Matsuo, 1993[142]			Industry trial report.[365] Study ID: US-05 (P42-05)/ GSK16
	Matsuo, 1996[328]			Industry submission.[366] Study ID: US14 (P42-14)
	Messenheimer, 1994[158]			Industry trial report.[367] Study ID: P42/06/W7(1)
	Nieto Barrera, 2001[119]			Study ID: 105-136
	Reunanen, 1996[120]			Study ID: LAM30025
	Sander, 1990[135]			Industry submission, 1989.[433] Study ID: H34/C/85/AWP/1(UK-022)
	Schachter, 1995[56]			Industry trial report.[374] Study ID: P42-16
	Schapel, 1993[161]	Banks, 1991[88]		GlaxoSmithKline, 1991[337] (full trial report from GlaxoSmithKline). Study ID: H34-035-C86
	Schmidt, 1993[91]			Study ID: H34-18/C/85/WCY/34 (UK-018)
	Smith, 1993[55]			Industry trial report.[378] Study ID: H34-086-C88
	Steiner, 1999[75]			Industry trial report.[381] Study ID: LAM30026
	Stolarek, 1994[162]			Study ID: not stated
	Veendrick-Meekes, 2000[137]			Study ID: LAM40004
	Yaqub, 1995[82]			Study ID: not stated
LEV	Ben-Menachem, 2000[144]			Study ID: not stated
	Betts, 2000[139]			Study ID: not stated
	Boon, 2002[80]			Study ID: not stated
	Shorvon, 2000[145]			
	Cereghino, 2000[143]		Cramer, 2000[166]	Study ID: N132
OXC	Aikia, 1992[58]			Study ID: not stated
	Barcs, 2000[70]			Study ID: OT/PE1
	Bill, 1997[124]			Study ID: OT/F02
	Christe, 1997[123]			Study ID: OT/F01
	Dam, 1989[125]			Study ID: not stated
	Houtkooper, 1987[84]			Study ID: not stated
	Loiseau, 1998[72]			Loiseau, 1998.[72] Study ID: OT/E25
	Reinikainen, 1987[115]			Study ID: not stated
	Sachdeo, 1998[111]			Sachdeo, 1998.[111] Study ID: 025
	Schachter, 1999[78]			Study ID: Novartis 004
TGB		Aikia, 1999[52]		Study ID: not stated
	Baulac, 2001[329]			Baulac, 2001.[329] Study ID: TIA126
	Crawford, 2001[147]			Industry trial report.[395] Study ID: TIA103

continued

Drug	RCT	RCT	RCT	Industry trial submission
	Effectiveness data	**Cognitive data**	**QoL**	
	Kälviäinen, 1998[164]	Kälviäinen, 1996[43]		Trial report.[434] Study ID: TIA107 M92-775
	Richens, 1995[146]	Sveinbjornsdottir, 1994[39]		Industry trial report.[400] Study ID: TIA101
	Sachdeo, 1997[140]			Industry submission, 1994.[402] Study ID: TIA109 M91-605
	Schachter, 1995[251]			Study ID: not stated
	Sommerville, 1998[129]	Dodrill, 2000[57]	Cramer, 2001[65]	Industry trial report, 1998.[129] Study ID: TIA 128; M92-825
	Uthman, 1998[163]	Dodrill, 1997[167]	Dodrill, 1997[167]	Trial report, 1994.[398] Study ID: TIA106 M91-603
TPM		Aldenkamp, 2000[130]		Study ID: not stated
	Barrett, 1997[76]			Study ID: RWJ-17021-000
	Ben-Menachem, 1996[151]			Study ID: Europe Y3
	Biton, 1999[79]			Study ID: YTC
	Coles, 1999[60]			Study ID: not stated
	Faught, 1996[67]			Study ID: US YD
	Guberman, 2002[150]			Study ID: EPAJ-119
	Korean Topiramate Study Group, 1999[149]			Study ID: not stated
		Meador, 2001[44]		Study ID: not stated
	Privitera, 2002[94]			Study ID: EPMN105
	Privitera, 1996[68]			Study ID: US YE
	Rosenfeld, 1996[41]			Study ID: US YF-YG
	Sharief, 1996[148]			Study ID: Europe Y1
	Tassinari, 1996[42]			Study ID: Europe Y2
	Yen, 2000[165]			Study ID: not stated
VGB	Beran, 1996[87]			Study ID: AUS01
	Brodie, 1999[66]			Study ID: not stated
	Bruni, 2000[153]			Study ID: not stated
	Chadwick, 1999[92]			Study ID: not stated
	Czapinski, 1997[45]			Study ID: not stated
	Dean, 1999[154]	Dodrill, 1995[168]	Dodrill, 1995[168]	Study ID: not stated
	French, 1996[155]	Dodrill, 1993[169]		Study ID: Study 024
	Grunewald, 1994[38]			Study ID: not stated
	Kälviäinen, 1995[71]			Study ID: not stated
	Loiseau, 1986[83]			Study ID: not stated
	McKee, 1993[54]	Gillham, 1993[51]	Gillham, 1993[51]	Study ID: not stated
	Provinciali, 1996[152]			Study ID: not stated
	Reynolds, 1991[141]			Study ID: not stated
	Riekkinen, 1997[59]			Study ID: not stated
	Rimmer, 1984[49]			Study ID: not stated
	Specchio, 1999[61]			Study ID: not stated
	Tanganelli, 1996[53]			Study ID: not stated
	Tartara, 1986[86]			Study ID: not stated
	Tassinari, 1987[85]			Study ID: not stated

Appendix 16

Details of non-English language studies meeting the inclusion criteria but not included in the review

Study details	Study design	Population	Interventions	Comments
Boati, 1998[435]	Multicentre double-blind RCT	Newly diagnosed partial seizures	VGB vs CBZ as add-on therapy	Published in Italian
Canger, 1997[436]	Multicentre double-blind RCT	Newly diagnosed partial seizures	VGB vs CBZ monotherapy	Published in Italian
de Romanis, 1995[437]	RCT	Refractory partial complex and/or partial secondary generalised seizures	LTG vs placebo as add-on therapy	Published in Italian
Regesta, 1997[438]	Randomised conditional crossover trial	Newly diagnosed focal seizures	VGB vs CBZ as add-on therapy	Published in Italian
Sasanelli, 1996[439]	Multicentre RCT	Newly diagnosed	GBP vs CBZ as monotherapy	Published in Italian
Severi, 1993;[371] Severi, 1994[370]	Open RCT	Refractory partial or generalised tonic–clonic seizures	LTG vs CBZ	Published in Italian
Thümler, 1992[440]	Single-blind RCT	Refractory complex partial seizures	VGB vs placebo as add-on therapy	Published in German

Appendix 17

Ongoing studies (adults)

Study details	Study design	Population	Interventions	Comments
Stephen[441]	Open-label RCT	Newly diagnosed	LTG vs VPA	Patients aged ≥ 13 years
Faught, ongoing;[442] Collins, ongoing;[443] Rowan, 2001[444]	RCT	Newly diagnosed	GBP, LTG vs CBZ	Patients aged ≥ 60 years
Chadwick[288]	RCT	Patients currently managed with monotherapy	Physician's choice of CBZ or VPA compared with appropriate comparator new AED. Monotherapy	Patients aged ≥ 5 years. Unblinded study. ITT analysis. Follow-up 6 years. Also assesses psychosocial outcomes
Read, 2001;[445,446] Bird, 2000;[447] Manga, 2001[448]	RCT	Patients with learning disabilities (mental handicap)	TPM compared with placebo	
GlaxoSmithKline	12 trials were commercial-in-confidence			
UCB Pharma	2 trials were commercial-in-confidence			

Appendix 18

Quality assessment of effectiveness studies: randomised controlled trials

Gabapentin – parallel studies (*n* = 10)

Criterion	Anhut, 1994[156]	Brodie, 2002[93]	Chadwick, 1996[74]	Chadwick, 1998[250]	Crawford, 2001[131]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	Yes	Yes	Yes	Yes	Yes
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	Yes	Yes	Yes	NS
Was allocation of treatment concealed?	NS	NS	Yes	Yes	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	No	No
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	No	No
Were participants blind to the treatment allocation?	Yes	Yes	Yes	No	No
Was success of blinding assessed?	NS	NS	NS	NA	NA
Were details of baseline comparability of treatment groups presented?	Partial	Yes	Yes	Partial	Yes
Were adjustments made for differences in baseline characteristics?	NS	NA	NA	NA	NA
Were appropriate doses of intervention drugs used?	Yes	Partial	Yes	Yes	Partial
Were appropriate doses of control drugs used?	NA	Yes	NA	Yes	Yes
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	NS	NS	NS	NS
Were all patients originally considered accounted for at end of study?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included?	No	No	Partial	No	NS
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	Partial	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NA	NA	NS	NA	NS
Was the equivalence margin specified before the study?	NA	Yes	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	Yes	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	Yes	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	Yes	NA	NA	NA
Were treatments applied in optimal fashion?	NA	Partial	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	Yes	NA	NA	NA

continued

Criterion	Lopes-Lima, 1999[46]	Maton, 1998[128]	Sivenius, 1991[157]	UK Gabapentin Study Group, 1990[73]	US Gabapentin Study Group, 1993[138]
Were eligibility criteria specified?	Partial	Yes	Partial	Yes	Yes
Was an *a priori* power calculation performed?	NS	NS	NS	Yes	Yes
Was number of participants randomised stated?	No	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	NS	NS	Yes	NS
Was allocation of treatment concealed?	NS	Yes	NS	NS	NS
Were outcome assessors blind to treatment allocation?	NS	Yes	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	NS	Yes	NS	NS	Yes
Were participants blind to the treatment allocation?	Yes	No	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	No	Yes	N0	Yes	Yes
Were adjustments made for differences in baseline characteristics?	NS	NA	NS	NA	NA
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	Partial
Were appropriate doses of control drugs used?	Yes	Yes	NA	NA	NA
Were any co-interventions identified that could influence the outcomes?	NS	Yes	NS	NS	NS
Was patient compliance assessed?	NS	Yes	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	NS	Yes	Yes	Yes	Yes
Was a valid ITT analysis included?	NS	No	Yes	?	No
Were at least 80% of participants originally included in randomisation process considered at follow-up?	NS	No	Yes	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NA	NS	NS	NA
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

? Unclear; NA, not applicable; NS, not stated (and in all subsequent tables).

Gabapentin – crossover studies ($n = 2$)

Criterion	Leach, 1997[90]	Wilensky, 1996[69]
Were the eligibility criteria for the study specified?	Partial	Yes
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	NS	Yes
Was the number of participants who were randomised stated?	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	Yes	NS
Was the allocation of treatment concealed?	Yes	NS
Were the outcome assessors blind to the treatment allocation?	NS	NS
Were the individuals who administered the intervention blind to the treatment allocation?	NS	NS
Were the participants who received the intervention blind to the treatment allocation?	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS
Were details of the baseline comparability of the treatment groups presented?	No	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NS	NS
Were appropriate doses of the intervention drugs used?	Yes	Yes
Were appropriate doses of the control drugs used?	NA	Yes
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS
Was patient compliance with the assigned treatment assessed?	Yes	NS
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes	No
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	No	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	No	No
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NA	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes	Yes
Was the crossover design appropriate?	Yes	No
Was an appropriate washout period allowed between the different treatments?	Yes	NS
Was an appropriate analysis using paired data performed?	No	No

Lamotrigine – parallel studies (*n* = 20)

Criterion	Biton, 2001[116]	Brodie, 1999[117]	Brodie, 1999[47]	Brodie, 1995[121]	Bryant-Comstock, 2002[113]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Partial
Was an *a priori* power calculation performed?	Yes	NS	Yes	Yes	Yes
Was number of participants randomised stated?	Yes	Yes	No	Yes	Yes
Was method to assign participants really random?	Yes	Yes	Yes	Yes	Yes
Was allocation of treatment concealed?	NS	Yes	Yes	Yes	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	NS	No
Were individuals who administered intervention blind to treatment allocation?	NS	Yes	Yes	Yes	No
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	No
Was success of blinding assessed?	NS	NS	NS	NS	NA
Were details of baseline comparability of treatment groups presented?	Partial	Yes	No	Yes	No
Were adjustments made for differences in baseline characteristics?	NA	NA	NS	NA	NS
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of control drugs used?	Yes	Yes	Yes	Yes	Yes
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	Yes	NS	Yes	NS
Were all patients originally considered accounted for at end of study?	Yes	Yes	NS	Yes	NS
Was a valid ITT analysis included?	Partial	Yes	?	NS	No
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	NS	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NS	NS	NS	NA
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Criterion	Chmielewska, 2001[133]	Gillham, 2000[77]	Gilliam, 1998[112]	GlaxoSmithKline, 2001[62]	Kerr, 2001[122]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	NS	Yes	Yes	NS	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	Yes	NS	NS	Yes
Was allocation of treatment concealed?	NS	Yes	NS	NS	NS
Were outcome assessors blind to treatment allocation?	No	NS	NS	No	No

continued

Criterion	Chmielewska, 2001[133]	Gillham, 2000[77]	Gilliam, 1998[112]	GlaxoSmithKline, 2001[62]	Kerr, 2001[122]
Were individuals who administered intervention blind to treatment allocation?	No	Yes	NS	No	No
Were participants blind to the treatment allocation?	No	Yes	Yes	No	No
Was success of blinding assessed?	NA	NS	NS	NA	NA
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	No	Partial
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	NS	NA
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of control drugs used?	Yes	Yes	Yes	NS	Yes
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	Yes	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	NS	Yes	Yes	Yes	Yes
Was a valid ITT analysis included?	NS	Yes	Yes	Partial	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	?	Yes	No	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	Yes	NS	NS	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Criterion	GlaxoSmithKline, 2000[118]	Martinez, 2002[114]	Matsuo, 1993[142]	Matsuo, 1996[328]	Nieto Barrera, 2001[119]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	Yes	Yes	Yes	NS	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	Yes	NS	NS	Yes	NS
Was allocation of treatment concealed?	Yes	NS	NS	Yes	Yes
Were outcome assessors blind to treatment allocation?	No	No	Yes	NS	No
Were individuals who administered intervention blind to treatment allocation?	No	No	Yes	Yes	No
Were participants blind to the treatment allocation?	No	No	Yes	Yes	No

continued

Criterion	GlaxoSmithKline, 2000[118]	Martinez, 2002[114]	Matsuo, 1993[142]	Matsuo, 1996[328]	Nieto Barrera, 2001[119]
Was success of blinding assessed?	NA	NA	NS	NS	NA
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	Yes	Yes
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	NA	NS
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of control drugs used?	Yes	Yes	NA	NA	Yes
Were any co-interventions identified that could influence the outcomes?	Yes	NS	NS	NS	NS
Was patient compliance assessed?	Yes	NS	Yes	Yes	Yes
Were all patients originally considered accounted for at end of study?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included?	No	Yes	Yes	Yes	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	No	Yes	Yes	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NA	NS	NS	NS	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Criterion	Reunanen, 1996[120]	Sackellares, 2000[126]	Schacter, 1995[56]	Steiner, 1999[75]	Veendrick-Meekes, 2000[137]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	NS	Yes	NS	Yes	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	Yes	Yes	NS	NS
Was allocation of treatment concealed?	NS	NS	Yes	NS	NS
Were outcome assessors blind to treatment allocation?	No	NS	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	No	NS	NS	Yes	NS
Were participants blind to the treatment allocation?	No	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NA	NS	Yes	NS	NS
Were details of baseline comparability of treatment groups presented?	Partial	Partial	Yes	Yes	Yes
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	NA	NA

continued

Criterion	Reunanen, 1996[120]	Sackellares, 2000[126]	Schacter, 1995[56]	Steiner, 1999[75]	Veendrick-Meekes, 2000[137]
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of control drugs used?	Yes	Yes	NA	Partial	NA
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	Yes	NS	Yes	Yes	NS
Were all patients originally considered accounted for at end of study?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included?	NS	No	Yes	No	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	Yes	Partial	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NA	NS	NA	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Lamotrigine – crossover studies (*n* = 15)

Criterion	Banks, 1991[88]	Beran, 1998[134]	Binnie, 1989[159]	Binnie, 1987[50]	Boas, 1996[136]
Were the eligibility criteria for the study specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	Yes	NS	NS	NS	NS
Was the number of participants who were randomised stated?	Yes	Yes	Yes	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	NS	NS	NS	NS	NS
Was the allocation of treatment concealed?	Yes	NS	Yes	NS	Yes
Were the outcome assessors blind to the treatment allocation?	Yes	NS	Yes	Partial	NS
Were the individuals who administered the intervention blind to the treatment allocation?	Yes	NS	No	Yes	NS
Were the participants who received the intervention blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS	NS	NS	NS
Were details of the baseline comparability of the treatment groups presented?	No	No	Yes	No	Yes

continued

Criterion	Banks, 1991[88]	Beran, 1998[134]	Binnie, 1989[159]	Binnie, 1987[50]	Boas, 1996[136]
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NS	NS	NA	NS	NA
Were appropriate doses of the intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of the control drugs used?	NA	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS	NS	NS	NS
Was patient compliance with the assigned treatment assessed?	Yes	Yes	Yes	NS	NS
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	No	No	No	NS	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	Yes	Yes	Yes	Yes	No
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NA	NA	NA	NS	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes	Yes	Yes	NS	Yes
Was the crossover design appropriate?	Yes	Yes	Yes	Yes	Yes
Was an appropriate washout period allowed between the different treatments?	Yes	Yes	Yes	No	Yes
Was an appropriate analysis using paired data performed?	No	Yes	Yes	Yes	Yes

Criterion	Cordova, 1995[40]	Jawad, 1989[160]	Loiseau, 1990[89]	Messenheimer, 1994[158]	Sander, 1990[135]
Were the eligibility criteria for the study specified?	No	Yes	Yes	Yes	Yes
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	NS	Yes	Yes	NS	NS
Was the number of participants who were randomised stated?	No	Yes	Yes	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	NS	NS	Yes	NS	NS
Was the allocation of treatment concealed?	NS	Yes	Yes	NS	Yes
Were the outcome assessors blind to the treatment allocation?	NS	Yes	Yes	Yes	Yes
Were the individuals who administered the intervention blind to the treatment allocation?	NS	No	Yes	Yes	No
Were the participants who received the intervention blind to the treatment allocation?	NS	Yes	Yes	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS	NS	NS	NS
Were details of the baseline comparability of the treatment groups presented?	No	Yes	Partial	Yes	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NS	NA	NA	NA	NS
Were appropriate doses of the intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of the control drugs used?	NA	NA	NA	NA	NA

continued

Criterion	Cordova, 1995[40]	Jawad, 1989[160]	Loiseau, 1990[89]	Messenheimer, 1994[158]	Sander, 1990[135]
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS	Yes	NS	NS
Was patient compliance with the assigned treatment assessed?	NS	Yes	Yes	Yes	Yes
Were all patients who were originally considered for the study accounted for at its conclusion?	NS	Yes	Yes	Yes	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	NS	No	No	No	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	NS	Yes	Yes	Yes	Yes
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NS	NA	NA	NA	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	NS	Yes	Yes	Yes	Yes
Was the crossover design appropriate?	Yes	Yes	Yes	Yes	Yes
Was an appropriate washout period allowed between the different treatments?	NS	Yes	Yes	Yes	Yes
Was an appropriate analysis using paired data performed?	NS	Yes	No	Yes	Yes

Criterion	Schapel, 1993[161]	Schmidt, 1993[91]	Smith, 1993[55]	Stolarek, 1994[162]	Yaqub, 1995[82]
Were the eligibility criteria for the study specified?	Yes	Yes	Yes	Partial	Partial
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	Yes	NS	Yes	NS	NS
Was the number of participants who were randomised stated?	Yes	Yes	Yes	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	NS	NS	Yes	Yes	NS
Was the allocation of treatment concealed?	Yes	Yes	Yes	Yes	NS
Were the outcome assessors blind to the treatment allocation?	Yes	Yes	Yes	NS	NS
Were the individuals who administered the intervention blind to the treatment allocation?	Yes	No	Yes	NS	NS
Were the participants who received the intervention blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS	Yes	NS	NS
Were details of the baseline comparability of the treatment groups presented?	Yes	Yes	No	No	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NA	NA	NS	NS	NS
Were appropriate doses of the intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of the control drugs used?	NA	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS	NS	Yes	NS
Was patient compliance with the assigned treatment assessed?	Yes	Yes	Yes	Yes	Yes

continued

Criterion	Schapel, 1993[161]	Schmidt, 1993[91]	Smith, 1993[55]	Stolarek, 1994[162]	Yaqub, 1995[82]
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	No	No	No	No	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	Yes	Yes	No	Yes	Yes
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NA	NA	NA	NA	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes	Yes	Yes	Yes	NS
Was the crossover design appropriate?	Yes	Yes	Yes	Yes	Yes
Was an appropriate washout period allowed between the different treatments?	Yes	Yes	Yes	Yes	NS
Was an appropriate analysis using paired data performed?	Yes	No	Yes	Yes	NS

Levetiracetam – parallel studies (*n* = 5)

Criterion	Ben-Menachem, 2000[144]	Betts, 2000[139]	Cereghino, 2000[143]	Cramer, 2000[166]	Shorvon, 2000[145]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	Yes	NS	Yes	Yes	Yes
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	Yes	Yes	Yes	Yes
Was allocation of treatment concealed?	NS	Yes	Yes	Yes	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	NS	NS	Yes	Yes	NS
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	Yes	Yes
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	NA	Yes
Were appropriate doses of intervention drugs used?	Yes	Partial	Yes	Yes	Yes
Were appropriate doses of control drugs used?	NA	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes?	NS	NS	Yes	Yes	NS
Was patient compliance assessed?	Yes	NS	NS	NS	Yes
Were all patients originally considered accounted for at end of study?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included?	No	No	Partial	No	Partial

continued

Criterion	Ben-Menachem, 2000[144]	Betts, 2000[139]	Cereghino, 2000[143]	Cramer, 2000[166]	Shorvon, 2000[145]
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	No	Yes	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NA	NA	NS	NA	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Levetiracetam – crossover studies (*n* = 1)

Criterion	Boon, 2002[80]
Were the eligibility criteria for the study specified?	Yes
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	Yes
Was the number of participants who were randomised stated?	Yes
Was the method used to assign participants to the treatment groups really random?	Yes
Was the allocation of treatment concealed?	NS
Were the outcome assessors blind to the treatment allocation?	NS
Were the individuals who administered the intervention blind to the treatment allocation?	NS
Were the participants who received the intervention blind to the treatment allocation?	Yes
Was the success of the blinding procedure assessed?	NS
Were details of the baseline comparability of the treatment groups presented?	Yes
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NA
Were appropriate doses of the intervention drugs used?	Yes
Were appropriate doses of the control drugs used?	NA
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS
Was patient compliance with the assigned treatment assessed?	Yes
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	Partial
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	Yes
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	Yes
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes
Was the crossover design appropriate?	Yes
Was an appropriate washout period allowed between the different treatments?	No
Was an appropriate analysis using paired data performed?	Yes

Oxcarbazepine – parallel studies (*n* = 9)

Criterion	Aikia, 1992[58]	Barcs, 2000[70]	Bill, 1997[124]	Christe, 1997[123]	Dam, 1989[125]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	NS	NS	Yes	Yes	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	NS	Yes	NS	NS
Was allocation of treatment concealed?	NS	NS	NS	NS	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	NS	NS
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	Yes	Yes
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	Yes	NA
Were appropriate doses of intervention drugs used?	NS	Yes	Partial	Yes	Partial
Were appropriate doses of control drugs used?	NS	NA	Partial	Yes	Partial
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	NS	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	Yes	Partial	Yes	Yes	Yes
Was a valid ITT analysis included?	No	Yes	No	No	No
Were at least 80% of participants originally included in randomisation process considered at follow-up?	No	Yes	Yes	Yes	No
Were appropriate methods used to account for missing data in ITT analysis?	NA	NS	NA	NA	NA
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

continued

Criterion	Loiseau, 1998[72] [Data have been designated commercial-in-confidence and have been removed]	Reinikainen, 1987[115]	Sachdeo, 1998[111]	Schachter, 1999[78]
Were eligibility criteria specified?		Yes	Yes	Yes
Was an *a priori* power calculation performed?		NS	Yes	Yes
Was number of participants randomised stated?		Yes	Yes	Yes
Was method to assign participants really random?		NS	NS	Yes
Was allocation of treatment concealed?		NS	Yes	NS
Were outcome assessors blind to treatment allocation?		NS	Yes	NS
Were individuals who administered intervention blind to treatment allocation?		NS	Yes	NS
Were participants blind to the treatment allocation?		Yes	Yes	Yes
Was success of blinding assessed?		NS	NS	NS
Were details of baseline comparability of treatment groups presented?		No	Yes	Yes
Were adjustments made for differences in baseline characteristics?		NS	NA	NA
Were appropriate doses of intervention drugs used?		Yes	Yes	Yes
Were appropriate doses of control drugs used?		Yes	NA	NA
Were any co-interventions identified that could influence the outcomes?		NS	NS	NS
Was patient compliance assessed?		NS	Yes	NS
Were all patients originally considered accounted for at end of study?		Yes	Yes	Yes
Was a valid ITT analysis included?		No	Yes	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?		Yes	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?		NA	NS	Yes
Was the equivalence margin specified before the study?		NA	NA	NA
Was the active control treatment previously found to be effective?		NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?		NA	NA	NA
Was it appropriate to test null hypothesis?		NA	NA	NA
Were treatments applied in optimal fashion?		NA	NA	NA
Was the analysis appropriate for equivalence trial?		NA	NA	NA

Oxcarbazepine – crossover studies (*n* = 1)

Criterion	Houtkooper, 1987[84]
Were the eligibility criteria for the study specified?	Yes
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	NS
Was the number of participants who were randomised stated?	Yes
Was the method used to assign participants to the treatment groups really random?	NS
Was the allocation of treatment concealed?	Yes
Were the outcome assessors blind to the treatment allocation?	NS
Were the individuals who administered the intervention blind to the treatment allocation?	Yes
Were the participants who received the intervention blind to the treatment allocation?	Yes
Was the success of the blinding procedure assessed?	NS
Were details of the baseline comparability of the treatment groups presented?	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NS
Were appropriate doses of the intervention drugs used?	Partial
Were appropriate doses of the control drugs used?	Yes
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS
Was patient compliance with the assigned treatment assessed?	NS
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	Yes
Were appropriate methods used to account for missing follow-up data in the intention to treat analysis?	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes
Was the crossover design appropriate?	Yes
Was an appropriate washout period allowed between the different treatments?	No
Was an appropriate analysis using paired data performed?	Partial

Tiagabine – parallel studies (*n* = 11)

Criterion	Aikia, 1999[52]	Baulac, 2001[329]	Cramer, 2001[65]	Dodrill, 1997[167]
Were eligibility criteria specified?	Partial	Yes	Yes	Yes
Was an *a priori* power calculation performed?	NS	NS	NS	Yes
Was number of participants randomised stated?	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	NS	NS	Yes
Was allocation of treatment concealed?	NS	NS	NS	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	NS
Were participants blind to the treatment allocation?	NS	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Partial	Yes	Yes	Partial
Were adjustments made for differences in baseline characteristics?	NS	NA	NA	NS
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes
Were appropriate doses of control drugs used?	Yes	Yes	Yes	NA
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS
Was patient compliance assessed?	NS	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	Yes	Yes	No	Yes
Was a valid ITT analysis included?	No	NS	No	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	No	No	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NA	NS	NA	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA

Criterion	Dodrill, 2000[57]	Kälviäinen, 1998[164]	Kälviäinen, 1996[43]	Sachdeo, 1997[140]	Schachter, 1995[251]
Were eligibility criteria specified?	Partial	Yes	Yes	Yes	Yes
Was an *a priori* power calculation performed?	NS	Yes	NS	Yes	NS
Was number of participants randomised stated?	Yes	Yes	No	Yes	Yes
Was method to assign participants really random?	Yes	Yes	NS	NS	NS
Was allocation of treatment concealed?	NS	NS	NS	Yes	NS
Were outcome assessors blind to treatment allocation?	NS	NS	Yes	NS	NS
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	Yes	NS
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	Yes	No

continued

Criterion	Dodrill, 2000[57]	Kälviäinen, 1998[164]	Kälviäinen, 1996[43]	Sachdeo, 1997[140]	Schachter, 1995[251]
Were adjustments made for differences in baseline characteristics?	NA	NA	Yes	NA	NS
Were appropriate doses of intervention drugs used?	No	Yes	Yes	Yes	Partial
Were appropriate doses of control drugs used?	Partial	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes?	NS	Yes	NS	NS	NS
Was patient compliance assessed?	NS	Yes	Yes	Yes	NS
Were all patients originally considered accounted for at end of study?	Partial	Yes	No	Yes	Yes
Was a valid ITT analysis included?	No	Yes	NS	Yes	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	No	No	?	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NA	NS	NS	NS	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Criterion	Sommerville, 1998[129] [Data have been designated commercial-in-confidence and have been removed]	Uthman, 1998[163]
Were eligibility criteria specified?		Yes
Was an *a priori* power calculation performed?		Yes
Was number of participants randomised stated?		Yes
Was method to assign participants really random?		Yes
Was allocation of treatment concealed?		Yes
Were outcome assessors blind to treatment allocation?		NS
Were individuals who administered intervention blind to treatment allocation?		Yes
Were participants blind to the treatment allocation?		Yes
Was success of blinding assessed?		NS
Were details of baseline comparability of treatment groups presented?		Yes
Were adjustments made for differences in baseline characteristics?		NA
Were appropriate doses of intervention drugs used?		Partial
Were appropriate doses of control drugs used?		NA
Were any co-interventions identified that could influence the outcomes?		NS
Was patient compliance assessed?		Yes
Were all patients originally considered accounted for at end of study?		Yes
Was a valid ITT analysis included?		Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?		Yes
Were appropriate methods used to account for missing data in ITT analysis?		NS
Was the equivalence margin specified before the study?		NA
Was the active control treatment previously found to be effective?		NA

continued

Criterion	Sommerville, 1998[129] [Data have been designated commercial-in-confidence and have been removed]	Uthman, 1998[163]
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?		NA
Was it appropriate to test null hypothesis?		NA
Were treatments applied in optimal fashion?		NA
Was the analysis appropriate for equivalence trial?		NA

Tiagabine – crossover studies (*n* = 3)

Criterion	Crawford, 2001[147]	Richens, 1995[146]	Sveinbjornsdottir, 1994[39]
Were the eligibility criteria for the study specified?	Yes	Yes	No
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	Yes	Yes	?
Was the number of participants who were randomised stated?	Yes	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	NS	NS	NS
Was the allocation of treatment concealed?	NS	NS	NS
Were the outcome assessors blind to the treatment allocation?	NS	Yes	NS
Were the individuals who administered the intervention blind to the treatment allocation?	NS	Yes	NS
Were the participants who received the intervention blind to the treatment allocation?	Yes	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS	NS
Were details of the baseline comparability of the treatment groups presented?	Partial	No	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NA	NS	NS
Were appropriate doses of the intervention drugs used?	Yes	Yes	Yes
Were appropriate doses of the control drugs used?	NA	NA	NA
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS	NS
Was patient compliance with the assigned treatment assessed?	Yes	Yes	NS
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes	Yes	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	No	No	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	No	Yes	Partial
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NA	NA	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes	Yes	Yes
Was the crossover design appropriate?	Yes	Yes	Yes
Was an appropriate washout period allowed between the different treatments?	Yes	Yes	NS
Was an appropriate analysis using paired data performed?	Yes	Yes	Yes

Topiramate – parallel studies (*n* = 15)

Criterion	Aldenkamp, 2000[130]	Barrett, 1997[76]	Ben-Menachem, 1996[151]	Biton, 1999[79]	Coles, 1999[60]
Were eligibility criteria specified?	Yes	Yes	Yes	Yes	Partial
Was an *a priori* power calculation performed?	Yes	Yes	NS	Yes	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	Yes	Yes	NS	Yes	NS
Was allocation of treatment concealed?	Yes	Yes	NS	Yes	NS
Were outcome assessors blind to treatment allocation?	Yes	NS	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	No	Yes	NS	Yes	NS
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Yes	Yes	No	Yes	No
Were adjustments made for differences in baseline characteristics?	NA	Yes	NS	NA	NS
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	NS
Were appropriate doses of control drugs used?	Yes	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes?	NS	Yes	NS	Yes	NS
Was patient compliance assessed?	NS	Yes	NS	NS	NS
Were all patients originally considered accounted for at end of study?	Yes	Yes	NS	Yes	NS
Was a valid ITT analysis included?	No	Yes	NS	Yes	NS
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	Yes	Yes	NS
Were appropriate methods used to account for missing data in ITT analysis?	NA	NA	NS	Yes	NS
Was the equivalence margin specified before the study?	NA	Yes	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Criterion	Faught, 1996[67]	Guberman, 2002[150]	Korean Topiramate Study Group, 1999[149]	Meador, 2001[44]	Privitera, 2002[94]
Were eligibility criteria specified?	Yes	Yes	Yes	Partial	Yes
Was an *a priori* power calculation performed?	NS	NS	Yes	NS	Yes
Was number of participants randomised stated?	Yes	Yes	Yes	No	Yes
Was method to assign participants really random?	Yes	Yes	NS	NS	Yes
Was allocation of treatment concealed?	Yes	Yes	NS	NS	NS

continued

Criterion	Faught, 1996[67]	Guberman, 2002[150]	Korean Topiramate Study Group, 1999[149]	Meador, 2001[44]	Privitera, 2002[94]
Were outcome assessors blind to treatment allocation?	NS	Yes	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	Yes	Yes	NS	NS	Yes
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	No	Yes
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	NS	NA
Were appropriate doses of intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of control drugs used?	NA	NA	NA	NA	Yes
Were any co-interventions identified that could influence the outcomes?	NS	Yes	NS	NS	NS
Was patient compliance assessed?	NS	NS	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	No	Yes	Yes	NS	Yes
Was a valid ITT analysis included?	Yes	Partial	Yes	No	No
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	Yes	NS	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NS	NS	NA	NA
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NS
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NS
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NS
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NS
Were treatments applied in optimal fashion?	NA	NA	NA	NA	Partial
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	?

Criterion	Privitera, 1996[68]	Rosenfeld, 1996[41]	Sharief, 1996[148]	Tassinari, 1996[42]	Yen, 2000[165]
Were eligibility criteria specified?	Yes	No	Yes	Yes	Yes
Was an *a priori* power calculation performed?	NS	NS	NS	?	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	NS	NS	NS	NS
Was allocation of treatment concealed?	NS	NS	NS	NS	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	NS	NS
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	NS	NS
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was success of blinding assessed?	NS	NS	NS	NS	NS

continued

Criterion	Privitera, 1996[68]	Rosenfeld, 1996[41]	Sharief, 1996[148]	Tassinari, 1996[42]	Yen, 2000[165]
Were details of baseline comparability of treatment groups presented?	Yes	No	Yes	No	Yes
Were adjustments made for differences in baseline characteristics?	NA	NS	NS	NS	NA
Were appropriate doses of intervention drugs used?	Partial	No	Yes	Yes	Yes
Were appropriate doses of control drugs used?	NA	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	NS	NS	NS	NS
Were all patients originally considered accounted for at end of study?	No	NS	Yes	Yes	Yes
Was a valid ITT analysis included?	Yes	NS	Yes	Yes	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	NS	Yes	Yes	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NS	NS	NS	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Vigabatrin – parallel studies (*n* = 14)

Criterion	Brodie, 1999[66]	Bruni, 2000[153]	Chadwick, 1999[92]	Czapinski, 1997[45]	Dean, 1999[154]
Were eligibility criteria specified?	Yes	Yes	Yes	Partial	Yes
Was an *a priori* power calculation performed?	NS	NS	Yes	NS	NS
Was number of participants randomised stated?	Yes	Yes	Yes	No	Yes
Was method to assign participants really random?	NS	NS	Yes	NS	NS
Was allocation of treatment concealed?	NS	NS	Yes	No	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	No	Yes
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	No	Yes
Were participants blind to the treatment allocation?	Yes	Yes	Yes	No	Yes
Was success of blinding assessed?	NS	NS	NS	NA	NS
Were details of baseline comparability of treatment groups presented?	Yes	Yes	Yes	No	Yes
Were adjustments made for differences in baseline characteristics?	NA	Yes	Yes	NS	Yes
Were appropriate doses of intervention drugs used?	Yes	Partial	Yes	No	Partial
Were appropriate doses of control drugs used?	Yes	NA	Yes	No	NA

continued

Criterion	Brodie, 1999[66]	Bruni, 2000[153]	Chadwick, 1999[92]	Czapinski, 1997[45]	Dean, 1999[154]
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	Yes	NS	NS	Yes
Were all patients originally considered accounted for at end of study?	No	Yes	Yes	NS	Yes
Was a valid ITT analysis included?	NS	Yes	No	NS	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	Yes	NS	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NS	NA	NS	NS
Was the equivalence margin specified before the study?	NA	NA	Yes	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	Yes	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NS	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	Yes	NA	NA
Were treatments applied in optimal fashion?	NA	NA	Partial	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	Yes	NA	NA

Criterion	Dodrill, 1993[169]	Dodrill, 1995[168]	French, 1996[155]	Grunewald, 1994[38]	Kälviäinen, 1995[71]
Were eligibility criteria specified?	Yes	Yes	Yes	No	Yes
Was an *a priori* power calculation performed?	NS	NS	NS	NS	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	NS	NS	Yes	NS
Was allocation of treatment concealed?	NS	NS	NS	NS	NS
Were outcome assessors blind to treatment allocation?	NS	NS	NS	NS	Partial
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	NS	NS
Were participants blind to the treatment allocation?	Yes	Yes	Yes	Yes	No
Was success of blinding assessed?	NS	NS	NS	NS	NS
Were details of baseline comparability of treatment groups presented?	Partial	Yes	Yes	Partial	Yes
Were adjustments made for differences in baseline characteristics?	NA	NA	NA	NA	NA
Were appropriate doses of intervention drugs used?	Yes	Partial	Yes	Yes	Yes
Were appropriate doses of control drugs used?	NA	NA	NA	NA	Yes
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS	NS
Was patient compliance assessed?	NS	NS	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	Yes	Yes	Yes	Yes	Partial
Was a valid ITT analysis included?	No	No	No	NS	No
Were at least 80% of participants originally included in randomisation process considered at follow-up?	Yes	Yes	Yes	Yes	No
Were appropriate methods used to account for missing data in ITT analysis?	NA	NA	NA	NS	NA

continued

Criterion	Dodrill, 1993[169]	Dodrill, 1995[168]	French, 1996[155]	Grunewald, 1994[38]	Kälviäinen, 1995[71]
Was the equivalence margin specified before the study?	NA	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA	NA

Criterion	Provinciali, 1996[152]	Reynolds, 1991[141]	Riekkinen, 1997[59]	Specchio, 1999[61]
Were eligibility criteria specified?	Yes	Yes	Partial	Partial
Was an *a priori* power calculation performed?	NS	NS	NS	NS
Was number of participants randomised stated?	Yes	Yes	Yes	Yes
Was method to assign participants really random?	NS	NS	NS	NS
Was allocation of treatment concealed?	NS	NS	NS	NS
Were outcome assessors blind to treatment allocation?	Yes	NS	NS	No
Were individuals who administered intervention blind to treatment allocation?	NS	NS	NS	No
Were participants blind to the treatment allocation?	No	Yes	Yes	No
Was success of blinding assessed?	NS	NS	NS	NA
Were details of baseline comparability of treatment groups presented?	Yes	No	Partial	No
Were adjustments made for differences in baseline characteristics?	NS	NS	NS	NS
Were appropriate doses of intervention drugs used?	Yes	Yes	NS	NS
Were appropriate doses of control drugs used?	NA	NA	NS	NS
Were any co-interventions identified that could influence the outcomes?	NS	NS	NS	NS
Was patient compliance assessed?	NS	Yes	NS	NS
Were all patients originally considered accounted for at end of study?	NS	Yes	NS	Partial
Was a valid ITT analysis included?	NS	No	NS	Yes
Were at least 80% of participants originally included in randomisation process considered at follow-up?	NS	Yes	NS	Yes
Were appropriate methods used to account for missing data in ITT analysis?	NS	NA	NS	NS
Was the equivalence margin specified before the study?	NA	NA	NA	NA
Was the active control treatment previously found to be effective?	NA	NA	NA	NA
Were the study participants/outcome variables similar to those in original trials establishing efficacy of active control?	NA	NA	NA	NA
Was it appropriate to test null hypothesis?	NA	NA	NA	NA
Were treatments applied in optimal fashion?	NA	NA	NA	NA
Was the analysis appropriate for equivalence trial?	NA	NA	NA	NA

Vigabatrin – crossover studies (*n* = 8)

Criterion	Beran, 1996[87]	Gillham, 1993[51]	Loiseau, 1986[83]	McKee, 1993[54]	Rimmer, 1984[49]
Were the eligibility criteria for the study specified?	Yes	Partial	Yes	Partial	Partial
Was an *a priori* power calculation for adequate sample population size performed? (this should be appropriate to test the null hypothesis)	NS	NS	NS	Yes	NS
Was the number of participants who were randomised stated?	Yes	Yes	Yes	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	Yes	NS	NS	NS	NS
Was the allocation of treatment concealed?	NS	NS	NS	NS	NS
Were the outcome assessors blind to the treatment allocation?	NS	Partial	NS	NS	Partial
Were the individuals who administered the intervention blind to the treatment allocation?	Yes	NS	NS	NS	NS
Were the participants who received the intervention blind to the treatment allocation?	Yes	Yes	Yes	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS	NS	Yes	NS
Were details of the baseline comparability of the treatment groups presented?	No	No	Partial	No	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NS	NS	NA	NS	NS
Were appropriate doses of the intervention drugs used?	Yes	Yes	Yes	Yes	Yes
Were appropriate doses of the control drugs used?	NA	NA	NA	NA	NA
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS	NS	NS	NS
Was patient compliance with the assigned treatment assessed?	NS	Yes	NS	Yes	Yes
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	No	NS	No	No	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	Yes	No	Yes	No	Yes
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NA	NS	NA	NA	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	Yes	Yes	Yes	Yes	NS
Was the crossover design appropriate?	Yes	Yes	Yes	Yes	Yes
Was an appropriate washout period allowed between the different treatments?	NS	Yes	No	Yes	No
Was an appropriate analysis using paired data performed?	Yes	Yes	NS	Yes	No

continued

Criterion	Tanganelli, 1996[53]	Tartara, 1986[86]	Tassinari, 1987[85]
Were the eligibility criteria for the study specified?	Yes	Yes	Yes
Was an *a priori* power calculation for adequate sample population size performed? (This should be appropriate to test the null hypothesis)	Yes	NS	NS
Was the number of participants who were randomised stated?	Yes	Yes	Yes
Was the method used to assign participants to the treatment groups really random?	NS	NS	NS
Was the allocation of treatment concealed?	NS	NS	NS
Were the outcome assessors blind to the treatment allocation?	NS	NS	NS
Were the individuals who administered the intervention blind to the treatment allocation?	NS	NS	NS
Were the participants who received the intervention blind to the treatment allocation?	NS	Yes	Yes
Was the success of the blinding procedure assessed?	NS	NS	NS
Were details of the baseline comparability of the treatment groups presented?	Yes	No	No
Were adjustments made for differences in the baseline characteristics of the treatment groups?	NA	NS	NS
Were appropriate doses of the intervention drugs used?	Yes	Yes	Yes
Were appropriate doses of the control drugs used?	Yes	NA	NA
Were any co-interventions identified that could influence the outcomes for the treatment groups?	NS	NS	NS
Was patient compliance with the assigned treatment assessed?	Yes	NS	Yes
Were all patients who were originally considered for the study accounted for at its conclusion?	Yes	Yes	Yes
Was a valid ITT analysis included? (were all participants included in the final analysis according to the treatment group to which they were originally randomised?)	Yes	No	No
Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments?	Yes	Yes	Yes
Were appropriate methods used to account for missing follow-up data in the ITT analysis?	NS	NA	NA
Did all participants have established epilepsy with a constant and predictable seizure frequency and type?	No	Yes	Yes
Was the crossover design appropriate?	No	Yes	Yes
Was an appropriate washout period allowed between the different treatments?	?	No	No
Was an appropriate analysis using paired data performed?	No	Yes	Yes

Appendix 19

Summary of main quality issues of RCTs

Drug	Study	Random	Conceal	Blinding[a]	Comments
GBP	Leach, 1997[90]	Yes	Yes	NS	Details of statistical assessment were lacking and not clear if appropriate paired analyses performed
	Wilensky, 1996[69]	NS	NS	NS	Discontinued prior to full enrolment so considered underpowered. Insufficient details to assess quality
	Anhut, 1994[156]	NS	NS	NS	Small but significant differences in baseline duration of epilepsy and other characteristics between treatment groups. Not clear if data consider the differences
	Brodie, 2002[93]	Yes	NS	NS	**[Data have been designated commercial-in-confidence and have been removed]**
	Chadwick, 1996[74]	Yes	Yes	NS	Data for large number of patients missing so per protocol analysis may be insufficiently powered and not clear how ITT analysis accounts for these data. Unlicensed indication
	Chadwick, 1998[250]	Yes	Yes	No	Difficult to assess the proportion of missing follow-up data and how this was dealt with in the ITT analysis
	Crawford, 2001[131]	NS	NS	No	Unclear how to tell how many participants were originally randomised and included in the final analysis. Specifically examines participants with intellectual disabilities so findings may not apply to general population
	Lindberger, 2000[132]	Yes	Yes	NS	Baseline differences between treatment groups in duration of epilepsy. Unclear if analysis has taken this into account. Study discontinued prematurely, sample size small so may be underpowered. 22.55% of patients excluded from per protocol analysis for protocol violation. Two doses of GBP and VGB above those recommended
	Lopes-Lima, 1999[46]	NS	NS	NS	Not possible to carry out proper quality assessment as this is only published in abstract form
	Maton, 1998[128]	NS	Yes	Yes	Study was terminated owing to poor recruitment, so likely to be underpowered. Concurrent medications were taken, which may influence outcomes
	Sivenius, 1991[157]	NS	NS	NS	No *a priori* sample calculation performed. Sample seems small so it is likely the study is insufficiently powered
	UK Gabapentin Study Group, 1990[73]	Yes	NS	NS	Absolute numbers of participants and denominators for outcome data lacking
	US Gabapentin Study Group, 1993[138]	NS	NS	NS	Only patients deemed likely to complete the trial were included so findings may not be applicable to the general population
LTG	Banks, 1991[88]	NS	Yes	Yes	Study reports cognitive assessments on very small sample of patients from an RCT. RCT sample size calculations based on differences in seizure frequency so unlikely cognitive assessment is sufficiently powered. Not clear if paired analysis performed

continued

Drug	Study	Random	Conceal	Blinding[a]	Comments
	Beran, 1998[134]	NS	NS	Partial	Not clear to which treatment group patients who withdrew were randomised. Baseline characteristics of treatment groups not presented, unclear if comparable. Sample size seems small and no sample size calculation reported
	Binnie, 1989[159]	NS	Yes	Partial	Data missing for 4 withdrawals and not clear how this has been dealt with
	Binnie, 1987[50]	NS	NS	Partial	Difficult to assess baseline comparability between treatment groups from the report. Baseline period only 1 week so difficult to assess whether seizure frequency constant
	Boas, 1996[136]	NS	Yes	Partial	Eligibility criteria altered during study. One patient was receiving lamotrigine as monotherapy
	Cordova, 1995[40]	NS	NS	NS	
	Jawad, 1989[160]	NS	Yes	Partial	Difficult to assess whether participants had constant/predictable seizure frequency required for crossover study
	Loiseau, 1990[89]	Yes	Yes	Yes	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)
	Messenheimer, 1994[158]	NS	NS	Yes	
	Sander, 1990[135]	NS	Yes	Partial	
	Schapel, 1993[161]	NS	Yes	Yes	Appropriate paired analysis does not appear to have been conducted
	Schmidt, 1993[91]	NS	Yes	Partial	
	Smith, 1993[55]	Yes	Yes	Yes	Testing of blinding suggested may not have been effective. Max. 74% of participants included in follow-up. Not clear how missing data replaced in ITT analysis
	Stolarek, 1994[162]	Yes	Yes	Partial	
	Yaqub, 1995[82]	NS	NS	Partial	Quality assessment incomplete as only abstract available. Not possible to assess the extent of participant withdrawal
	Biton, 2001[116]	Yes	NS	Partial	No baseline comparability data and not clear if epilepsy is newly diagnosed or refractory
	Brodie, 1999[117]	Yes	Yes	Partial	
	Brodie, 1999[47]	Yes	Yes	Partial	Specifically examines effectiveness in elderly participants, so findings may not be generally applicable
	Brodie, 1995[121]	Yes	Yes	Partial	Dose of CBZ lower than recommended
	Bryant-Comstock, 2002[113]	Yes	NS	No	
	Chmielewska, 2001[133]	NS	NS	No	Open-label study, which may have influenced findings of more subjective QoL assessments. Number completing the study is not stated
	Gillham, 2000[77]	Yes	Yes	Partial	
	Gilliam, 1998[112]	NS	NS	Partial	25.64% of participants withdrew from study

continued

Drug	Study	Random	Conceal	Blinding[a]	Comments
	GlaxoSmithKline, 2000[118]	Yes	Yes	No	Open-label study. Power calculations suggest evaluable population of 1000. Less than half this number included so probably underpowered. Physicians allowed to choose whether patients received VPA or CBZ (after randomisation to LTG or comparator). Some patients received concomitant medications, which may have affected study findings
	GlaxoSmithKline, 2001[62]	NS	NS	No	
	Kerr, 2001[122]	Yes	NS	No	Includes adults and children, but data are not always presented separately for the two groups. Participants were assigned to LTG vs CBZ or LTG vs VPA randomisation branches according to physician's choice
	Martinez, 2002[114]	NS	NS	No	Physicians chose which of the conventional therapies (CBZ, PHT or VPA) participants received after randomisation to LTG or conventional therapy groups
	Matsuo, 1993[142]	NS	NS	Yes	
	Matsuo, 1996[328]	Yes	Yes	Partial	Not clear whether study assessors blinded since unblinding possibly occurred before analysis
	Nieto Barrera, 2001[119]	NS	Yes	No	Open-label trial. Seizure freedom only included patients who had ≥ 18 weeks of data. LTG group had higher baseline seizure rate than CBZ group. Unclear if findings consider this
	Reunanen, 1996[120]	NS	NS	No	CBZ dose lower than usual suggested min. dose. Time to first seizure excluded participants withdrawing before day 42 (data not provided)
	Sackellares, 2000[126]	Yes	NS	Partial	
	Schacter, 1995[56]	Yes	Yes	Partial	
	Steiner, 1999[75]	NS	NS	Partial	
	Veendrick-Meekes, 2000[137]	NS	NS	Partial	Specifically looks at patients with intellectual disabilities so findings may not be applicable to the general population
LEV	Boon, 2002[80]	Yes	NS	Partial	No washout period, only cross-titration at crossover
	Ben-Menachem, 2000[144]	NS	NS	Partial	Only small proportion of original sample entered monotherapy phase. Power calculations suggest 258 participants required, but only 46 included in monotherapy, so possibly underpowered
	Betts, 2000[139]	Yes	Yes	Partial	4000 mg/day dose exceeded the recommended dose of 3000 mg/day
	Cereghino, 2000[143]	Yes	Yes	Partial	Concomitant AEDs allowed included new AEDs GBP, LTG and TGB – may have affected study findings
	Cramer, 2000[166]	Yes	Yes	Partial	Concomitant AEDs allowed included new AEDs GBP, LTG and TGB – may have affected study findings
	Shorvon, 2000[145]	Yes	NS	Partial	
OXC	Houtkooper, 1987[84]	NS	Yes	Partial	OXC (600–2400 mg/day) dose range outwith that recommended (900–3600 mg/day). No washout period was reported. Potential treatment/period effects, not assessed. No paired analysis
	Aikia, 1992[58]	NS	NS	Partial	Only participants who completed entire 12-month follow-up were included in analysis
	Barcs, 2000[70]	NS	NS	Partial	Numbers of withdrawals and reasons not clearly stated

continued

Drug	Study	Random	Conceal	Blinding[a]	Comments
	Bill, 1997[124]	Yes	NS	Partial	Analysis only included participants who did not discontinue prior to and who had at least one seizure assessment in maintenance phase
	Christe, 1997[123]	NS	NS	Partial	Analysis only included participants who did not discontinue prior to and who had at least one seizure assessment in maintenance phase
	Dam, 1989[125]	NS	NS	Partial	Not stated if participants comparable in terms of baseline seizure frequency. SDs suggest may not be and unclear if this given consideration. Data for 165/235 participants available, not clear how missing data dealt with
	Loiseau, 1998[72]				**[Data have been designated commercial-in-confidence and have been removed]**
	Reinikainen, 1987[115]	NS	NS	Partial	No sample size calculation, but study seems fairly small, so may be underpowered
	Sachdeo, 1998[111]	NS	Yes	Yes	
	Schachter, 1999[78]	Yes	NS	Partial	Specifically includes patients undergoing evaluation for surgery, so findings may not be generally applicable
TGB	Crawford, 2001[147]	NS	NS	Partial	Response conditional study, participants must achieve certain reduction in seizure frequency on TGB to remain in study
	Richens, 1995[146]	NS	NS	Yes	Response conditional study. 21% withdrew after pretrial phase. 78%/38% remaining were ineligible as failed to achieve ≥ 25% reduction in seizure frequency on TGB
	Sveinbjornsdottir, 1994[39]	NS	NS	Partial	The authors do not justify choice of washout period and do not investigate possibility of carryover effect
	Sommerville, 1998[129]	Yes	Yes	Yes	**[Data have been designated commercial-in-confidence and have been removed]**
	Aikia, 1999[52]	NS	NS	NS	This is an abstract and few details about the trial design and quality are available
	Baulac, 2001[329]	NS	NS	Partial	**[Data have been designated commercial-in-confidence and have been removed]**
	Cramer, 2001[65]	NS	NS	Partial	
	Dodrill, 1997[167]	Yes	NS	Partial	
	Dodrill, 2000[57]	Yes	NS	Partial	Doses of all drugs appear to be high compared with current recommendations. Neuropsychological outcomes appear to be based on population selected postrandomisation
	Kälviäinen, 1998[164]	Yes	NS	Partial	VGB allowed as concurrent medication (15 TGB and 14 placebo patients received VGB) – may have affected results
	Kälviäinen, 1996[43]	NS	NS	Partial	Total no. of participants in each group not stated. Prerandomisation drop-out not stated. Significant difference between no. of seizures at baseline, but considered in MANOVA. No sample size calculations reported, but numbers seem small so may be underpowered
	Sachdeo, 1997[140]	NS	Yes	Partial	Specifically looks at patients with intellectual disabilities, so findings may not be applicable to general population
	Schachter, 1995[251]	NS	NS	Partial	
	Uthman, 1998[163]	Yes	Yes	Partial	

continued

Drug	Study	Random	Conceal	Blinding[a]	Comments
TPM	Aldenkamp, 2000[130]	Yes	Yes	Partial	
	Barrett, 1997[76]	Yes	Yes	Partial	Baseline difference in seizure rate (higher rates in TPM group). Unclear if findings consider this
	Ben-Menachem, 1996[151]	NS	NS	Partial	
	Biton, 1999[79]	Yes	Yes	Partial	Concomitant medications included new AEDs (GBP and LTG)
	Coles, 1999[60]	NS	NS	Partial	Incomplete quality assessment as only abstract available
	Faught, 1996[67]	Yes	Yes	Partial	
	Guberman, 2002[150]	Yes	Yes	Yes	Concomitant medications included new AEDs (VGB and LTG)
	Korean Topiramate Study Group, 1999[149]	NS	NS	Partial	
	Meador, 2001[44]	NS	NS	Partial	Incomplete quality assessment due to poor reporting
	Privitera, 2002[94]	Yes	NS	Partial	Non-inferiority trial powered with intention of combining both TPM doses if 200 mg/day group did not appear more effective – probably underpowered to detect difference in first place. Outcome data presented inconsistently, sometimes combining treatment groups across randomisation branches. Data include children and are not presented separately for adults. Physicians allowed to choose which randomisation branch (TPM vs CBZ or TPM vs VPA) patients entered. CBZ dose lower than usual suggested min. dose. Treat with great caution
	Privitera, 1996[68]	NS	NS	Partial	
	Rosenfeld, 1996[41]	NS	NS	Partial	Incomplete quality assessment as only abstract available
	Sharief, 1996[148]	NS	NS	Partial	
	Tassinari, 1996[42]	NS	NS	Partial	Unclear whether sample size calculations performed *a priori*
	Yen, 2000[165]	NS	NS	Partial	No information about baseline comparability
VGB	Beran 1996[87]	Yes	NS	Partial	
	Gillham, 1993[51]	NS	NS	Partial	Extent of missing data unclear. Limited information provided on neuropsychological testing protocol so not clear whether possible time of day effects were taken into account
	Loiseau, 1986[83]	NS	NS	Partial	No washout period (only crossover titration)
	McKee, 1993[54]	NS	NS	Partial	
	Rimmer, 1984[49]	NS	NS	Partial	Unclear whether patients had constant/predictable seizure frequency/type. No washout period. Unclear if paired analysis used. Includes patients with intellectual disabilities, so findings may not be applicable to the general population
	Tanganelli, 1996[53]	NS	NS	NS	Relatively small sample size and lack of power suggest caution
	Tartara, 1986[86]	NS	NS	Partial	

continued

Drug	Study	Random	Conceal	Blinding[a]	Comments
	Tassinari 1987[85]	NS	NS	Partial	No washout period but report no statistically significant period effect/treatment by period interaction. However, report patients ($n = 4$) who responded to VGB experienced episodes of quasi-continuous seizures during first days following change from VGB to placebo, indicating possibility of withdrawal/rebound effect. Specifically looks at participants with intellectual disabilities, so findings may not be applicable to general population
	Brodie, 1999[66]	NS	NS	Partial	Unclear how many participants were initially recruited and prerandomisation withdrawal rate. Response conditional study requiring patients to achieve ≥ 50% seizure reduction without AEs in pretrial period to enter study. Looks specifically at individuals with intellectual disabilities so findings may not apply to general population
	Bruni, 2000[153]	NS	NS	Partial	8 patients found not to satisfy inclusion criteria after randomisation
	Chadwick, 1999[92]	Yes	Yes	Partial	
	Czapinski 1997[45]	NS	No	No	No sample size calculation, sample seems fairly small for monotherapy phase so may be underpowered
	Dean, 1999[154]	NS	NS	Partial	6-g dose of VGB higher than normally used
	Dodrill, 1993[169]	NS	NS	Partial	
	Dodrill, 1995[168]	NS	NS	Partial	
	French, 1996[155]	NS	NS	Partial	
	Grunewald, 1994[38]	Yes	NS	Partial	
	Kälviäinen, 1995[71]	NS	NS	Partial	Unclear why some successfully treated participants were excluded from neuropsychological analysis. Clinical outcome analysis (including and excluding non-compliant patients) reported because of possibility of unrecognised drug-related difference in the drop-out rate. AE analysis excluded non-compliant patients
	Provinciali, 1996[152]	NS	NS	Partial	Significant baseline differences for 3 cognitive tests (VGB performing more poorly). Authors suggest a 'floor effect' but do not appear to consider this in the findings. Sample size appears small
	Reynolds, 1991[141]	NS	NS	Partial	No sample size calculation, but numbers seem fairly small so may be underpowered. Baseline comparability is unclear
	Riekkinen, 1997[59]	NS	NS	Partial	Incomplete quality assessment as only abstract available
	Specchio, 1999[61]	NS	NS	No	Incomplete quality assessment as only abstract available

MANOVA, multivariate analysis of variance; NS not stated.

[a] Blinding refers to three categories of individuals: patients, clinicians and study assessors. In many cases one or two categories of individuals were blinded to the treatment assignment, but not all. Such studies were described as partially fulfilling the criterion. See Appendix 18 for more details.

Appendix 20

Serious, rare and long-term adverse events: quality assessment of included studies

Gabapentin – uncontrolled trials

Criterion	Fisher, 2001[173]	McLean, 1999;[174] Morrell, 2000[449]	Mayer, 1999[175]	Wilson, 1998[176]	Baulac, 1998[177]	Mauri, 2001;[178] Laini, 1999[450]	Schaffer, 1999[179]	Knoll, 1998[451]	McElroy, 1997[181]
Eligibility criteria	Yes	Yes	Yes	No	NA	Yes	Yes	Yes	Yes
Power calculation	NS	NA	NS	NA	NA	NA	NA	NA	NA
Number randomised	Yes	NA	NA	NA	NA	NA	NA	NA	NA
Randomisation	?	NA	NA	NA	NA	NA	NA	NA	NA
Allocation concealment	?	NA	NA	NA	NA	NA	NA	NA	NA
Assessor blind	NS	NA	NA	NA	NA	NA	NA	NA	NA
Administrator blind	NS	NA	NA	NA	Yes	NA	NA	NA	NA
Participant blind	Yes	NA	NA	NA	NA	NA	NA	NA	NA
Blinding success	NS	NA	NA	NA	Yes	NA	NA	NA	NA
Baseline comparability	Yes	NA	NA	NA	NS	NA	NA	NA	NA
Baseline adjustment	NA	NA	NA	NA	Yes	NA	NA	NA	NA
Dose AED	Partial	Partial	Yes	Partial	Yes	Yes	Partial	Partial	Partial
Dose control	NA	NA	NA	NA	NA	NA	NA	NA	NA
Co-interventions	Yes	Partial	NS	NS	NA	NS	NS	Partial	NS
Compliance	Yes	Yes	NS	?	NA	NS	NS	NS	NS
All participants accounted for	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes
80% follow-up	Partial	Partial	Yes	Yes	NA	Yes	Yes	Yes	Yes
ITT	No	NA	NA	NA	NA	NA	NA	NA	NA
ITT methods appropriate	No	NA	NA	NA	NA	NA	NA	NA	NA

?, Unclear; NA, not applicable; NS, not stated (and in all subsequent tables).

Gabapentin – cohort study

Criterion	Putzke, 2002[186]
Sample	Yes
Control group appropriate	NA
Exposure	NS
Groups comparable	NA
Adjustment for confounding	NA
Dose–response	NS
Blinding of outcome assessment	NA
Duration of follow-up	Yes
Proportion followed up	78%
Reasons for drop-out	NA
Data	Yes
Analysis	No

Gabapentin – open-label extension studies

Criterion	Beydoun, 1998[182]	Anhut, 1995[183]	Sivenius, 1994[184]	US Gabapentin Study Group[185]
Sample	Yes	Yes	Yes	Yes
Dose AED	No	Yes	?	Yes
Follow-up duration	Partial	Partial	Yes	Partial

Lamotrigine – uncontrolled trials

Criterion	Pimentel, 1999[193]	Calabrese, 1999[194]	Cocito, 1994[195]	Mikati, 1989[196]	Sander, 1990[197]
Eligibility criteria	Yes	Yes	Yes	Yes	Yes
Power calculation	NA	NA	NA	NA	NA
Number randomised	NA	NA	NA	NA	NA
Randomisation	NA	NA	NA	NA	NA
Allocation concealment	NA	NA	NA	NA	NA
Assessor blind	NA	NA	NA	NA	NA
Administrator blind	NA	NA	NA	NA	NA
Participant blind	NA	NA	NA	NA	NA
Blinding success	NA	NA	NA	NA	NA
Baseline comparability	NA	NA	NA	NA	NA
Baseline adjustment	NA	NA	NA	NA	NA
Dose AED	Partial	Partial	Yes	Yes	Partial
Dose control	NA	NA	NA	NA	NA
Co-interventions	NS	NS	NS	NS	NS
Compliance	NS	NS	NS	Yes	?
All participants accounted for	Yes	Yes	Yes	Yes	?
80% follow-up	Yes	Yes	Yes	Yes	?
ITT	NA	NA	NA	NA	NA
ITT methods appropriate	NA	NA	NA	NA	NA

Lamotrigine – cohort studies

Criterion	Huber, 1998[198]	Leetsma, 1997[199]	Buchanan, 1996[200]	Martin, 1994[201]
Sample	Partial	Yes	NS	Partial
Control group appropriate	NA	NA	NA	NA
Exposure	NS	NS	NS	NS
Groups comparable	NA	NA	NA	NA
Adjustment for confounding	NA	NA	NA	NA
Dose–response	Yes	No	NS	?
Blinding of outcome assessment	NA	NA	NA	NA
Duration of follow-up	?	Partial	Partial	Partial
Proportion followed up	94%	100%	99.5%	96%
Reasons for drop-out	NA	NA	NA	NA
Data	No	Yes	No	No
Analysis	No	Yes	No	No

Lamotrigine – case-control study

Criterion	Rzany, 1999[192]
Case definition	Yes
Event validated	Yes
Control selection	NS
Exposure	Yes
Analysis	Yes?

Oxcarbazepine – open-label extension studies

Criterion	Beydoun, 2001[204]	Schachter, 2001[203]
Sample	Partial	Yes
Dose AED	?	?
Follow-up duration	No	No

Tiagabine – RCT and uncontrolled trial

Criterion	Biraben, 2001[206]	Striano, 2002[207]
Eligibility criteria	Yes	NA
Power calculation	No	NA
Number randomised	Yes	NA
Randomisation	NS	NA
Allocation concealment	NS	NA
Assessor blind	No	NA
Administrator blind	No	NA
Participant blind	No	NA
Blinding success	NA	NA
Baseline comparability	Yes	NA
Baseline adjustment	NA	NA
Dose AED	Partial	Partial
Dose control	NA	NA
Co-interventions	NS	NS
Compliance	No	No
All participants accounted for	Yes	NS
80% follow-up	Yes	Yes
ITT	?	NA
ITT methods appropriate	NS	NA

Tiagabine – cohort study

Criterion	Nousiainen, 2000[208]
Sample	Yes
Control group appropriate	No
Exposure	NS
Groups comparable	No
Adjustment for confounding	No
Dose–response	No
Blinding of outcome assessment	NS
Duration of follow-up	Yes
Proportion followed up	94%
Reasons for drop-out	NA
Data	Yes
Analysis	Yes

Tiagabine – open-label extension study

Criterion	Kälviäinen, 1999[209]
Sample	Partial
Dose AED	Partial
Follow-up duration	Partial

Topiramate – uncontrolled trials

Criterion	Singh, 2002[211]	Mecarelli, 2001[212]	Abou-Khalil, 2000[213]	Pellock, 2000[214]	Canger, 1997[215]	Tartara, 1996[216]
Eligibility criteria	Yes	No	Yes	Yes	Yes	Yes
Power calculation	NA	NA	NA	NA	NS	NA
Number randomised	NA	NA	NA	NA	NA	NA
Randomisation	NA	NA	NA	NA	NA	NA
Allocation concealment	NA	NA	NA	NA	NA	NA
Assessor blind	NA	NA	NA	NA	NA	NA
Administrator blind	NA	NA	NA	NA	NA	NA
Participant blind	NA	NA	NA	NA	NA	NA
Blinding success	NA	NA	NA	NA	NA	NA
Baseline comparability	NA	NA	NA	NA	NA	NA
Baseline adjustment	NA	NA	NA	NA	NA	NA
Dose AED	Yes	Yes	Partial	NS	Yes	Yes
Dose control	NA	NA	NA	NA	NA	NA
Co-interventions	NS	NS	NS	NS	NS	NS
Compliance	NS	NS	NS	NS	NS	NS
All participants accounted for	Yes	NS	No	?	?	Yes
80% follow-up	Yes	NS	Yes	?	?	Yes
ITT	NA	NA	NA	NA	NA	NA
ITT methods appropriate	NA	NA	NA	NA	NA	NA

Topiramate – open-label extension study

Criterion	Biton, 1997;[217] Montouris, 2000[210]
Sample	Partial
Dose AED	?
Follow-up duration	Partial

Vigabatrin – non-randomised controlled trial and uncontrolled trials

Criterion	Cocito, 1989[221]	de Feo, 1994[233] 1998[452]	Arzimanoglou, 1997[234]	Russ, 1995[235]	Buchanan, 1994[236]	Pedersen, 1985[238]	Dam, 1989[237]
Eligibility criteria	Yes	Partial	Yes	Yes	No	No	No
Power calculation	NS	NA	NA	NA	NA	NA	NS
Number randomised	NA	NA	NA	NA	NA	NA	NA
Randomisation	NA	NA	NA	NA	NA	NA	NA
Allocation concealment	NA	NA	NA	NA	NA	NA	NA
Assessor blind	No	NA	NA	NA	NA	NA	NA
Administrator blind	No	NA	NA	NA	NA	NA	NA
Participant blind	?	NA	NA	NA	NA	NA	NA
Blinding success	NS	NA	NA	NA	NA	NA	NA
Baseline comparability	NA	NA	NA	NA	NA	NA	NA
Baseline adjustment	NA	NA	NA	NA	NA	NA	NA
Dose AED	Partial	?	?	Partial?	Partial?	Partial	NS
Dose control	NA	NA	NA	NA	NA	NA	NA
Co-interventions	NS	NS	NS	NS	NS	NS	NS
Compliance	NS	NS	NS	NS	NS	NS	NS
All participants accounted for	Yes	Yes	?	Yes	Yes	Yes	NS
80% follow-up	Yes	Yes	?	Yes	Yes	Yes	NS
ITT	NA	NA	NA	NA	NA	NA	NA
ITT methods appropriate	NA	NA	NA	NA	NA	NA	NA

Vigabatrin – cohort studies

Criterion	Comaish, 2002[222]	Jensen, 2002[223]	Nousiainen, 2001[224]	Toggweiler, 2001[225]	Manuchehri, 2000[226]	Midelfart, 2000[227]
Sample	Yes	Partial	No	Yes	Yes	Yes
Control group appropriate	Yes	Yes	No	Yes	Yes	?
Exposure	NS	NS	?	?	?	NS
Groups comparable	Partial	Yes	No	Yes	Partial	?
Adjustment for confounding	NS	NA	No	NA	No	NS
Dose–response	NS	Yes	NS	Yes	Yes	NS
Blinding of outcome assessment	NS	Yes	NS	No	NS	?
Duration of follow-up	Yes	Yes	Yes	Yes	Yes	Yes
Proportion followed up	100	100	85	88	95	90
Reasons for drop-out	NA	NA	?	NA	NA	NA
Data	No	Yes	No	No	Yes	No
Analysis	Yes	Yes	Yes	Yes?	Yes	?

Criterion	Lawden, 1999[228]	van der Torren, 2002;[229] Graniewski-Wijnands, 2002[453]	Malmgren, 2001[230]	Ponjavic, 2001[231]	Arndt, 1999[232]
Sample	Yes	Yes	Partial	Yes	Partial
Control group appropriate	Partial	NA	NA	NA	NA
Exposure	?	?	?	NS	NS
Groups comparable	Partial	NA	NA	NA	NA
Adjustment for confounding	NS	NA	NA	NA	NA
Dose–response	NS	Yes	Yes	NS	NS
Blinding of outcome assessment	?	NS	Partial	NS	NS
Duration of follow-up	Yes	Yes	Yes	Yes	Yes
Proportion followed up	76	88	63	100	86
Reasons for drop-out	NA	NA	NA	NA	NA
Data	Yes	No	No	No	Yes
Analysis	No	Yes	?	No	No

Vigabatrin – open-label extension/follow-up studies

Criterion	Guberman, 2000[239]	Michelucci, 1994[240]	Sivenius, 1991[243]	Reynolds, 1991[242]	Browne, 1991[241]	Schmitz, 2002[244]	Paul, 2001[245]	Kälviäinen, 1999[246]	Pitkänen, 1993;[248] Matilainen, 1988[454]	Remy, 1989,[249] Cosi, 1988,[455] 1989[456]	Tartara, 1997,[247] 1994[457]
Sample	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dose AED	Partial	Partial	Partial	Yes	Partial	Partial	Partial	NS	Yes	Partial	Partial
Follow-up duration	No	Yes	Yes	No	Partial	Yes	Yes	Yes	Partial?	Partial	Partial

Mixed AEDs – cohort studies

Criterion	Samren, 1999[205]	Kwan, 2001[202]	Lhatoo, 2000[187]
Sample	Yes	Yes	Yes
Control group appropriate	No	NA	NA
Exposure	NS	NS	NS
Groups comparable	No	NA	NA
Adjustment for confounding	Partial	NA	NA
Dose–response	Partial	NS	NS
Blinding of outcome assessment	NS	NA	NA
Duration of follow-up	NS	NS	Yes
Proportion followed up	100	?	100
Reasons for drop-out	NA	?	NA
Data	Yes	No	Yes
Analysis	Yes	Yes	Yes

Appendix 21

Quality assessment of cost-effectiveness studies

Published studies

Monotherapy studies (*n* = 4)

Checklist	Questions	Bryant, 1998[252]	Heaney, 1998[253]	Heaney, 2000[254]	Shakespeare, 1998[255]
Study question	Costs and effects examined	Yes	Yes	Yes	Yes
	Alternatives compared	Yes	Yes	Yes	Yes
	The viewpoint(s)/perspective of the analysis is clearly stated	Yes	Yes	Yes	Yes
Selection of alternatives	All relevant alternatives are compared	Yes	Yes	Yes	Yes
	The alternatives being compared are clearly described	Yes	Yes	Yes	Yes
	The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	Yes
Form of evaluation	The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	Yes	Yes
	If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	Yes	Yes	Unclear	Yes
Effectiveness data	The source(s) of effectiveness estimates used are stated	Yes	Yes	Yes	Yes
	Effectiveness data from RCT or review of RCTs	Yes	Yes	Yes	Yes
	Potential biases identified (especially if data not from RCTs)	Yes	No	No	Yes
	Details of the method of synthesis or meta-analysis of estimates are given	Yes	No	No	NA
Costs	All the important and relevant resource use included	Yes	Yes	Yes	Yes
	All the important and relevant resource use measured accurately	Unclear	Unclear	Unclear	Unclear
	Appropriate unit costs estimated	Yes	Yes	Unclear	Yes
	Unit costs reported separately from resource use data	Yes	Yes	Yes	Yes
	Productivity costs treated separately from other costs	NA	NA	NA	NA
	The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	No	Yes	No	Yes
Benefit measurement	The primary outcome measure(s) for the economic evaluation are clearly stated	Yes	NA	NA	NA
and valuation	Methods to value health states and other benefits are stated	NA	NA	NA	NA
	Details of the individuals from whom valuations were obtained are given	NA	NA	NA	NA
Decision modelling	Details of any decision model used are given	Yes	Yes	Yes	Yes
	The choice of model used and the key input parameters on which it is based are adequately detailed and justified	No	Unclear	No	Yes
	All model outputs described adequately	Yes	Yes	Yes	Yes

continued

Checklist	Questions	Bryant, 1998[252]	Heaney, 1998[253]	Heaney, 2000[254]	Shakespeare, 1998[255]
Discounting	Discount rate used for both costs and benefits	No	No	Unclear	NA
	Do discount rates accord with NHS guidance?	NA	NA	Unclear	NA
Allowance for uncertainty	Details of statistical tests and confidence intervals are given for stochastic data	No	No	No	No
(patient-level data)	Uncertainty around cost-effectiveness expressed	No	NA	No	NA
	Sensitivity analysis used to assess uncertainty in non-stochastic variables	No	NA	No	NA
	Are all appropriate input parameters included with uncertainty?	No	No	No	No
Allowance for uncertainty	Is second-order uncertainty included rather than first-order?	NA	No	NA	No
(decision models)	Are the probability distributions adequately detailed and appropriate?	NA	NA	NA	NA
	Sensitivity analysis used to assess uncertainty in non-stochastic variables and analytic decisions	Yes	Yes	Yes	Yes
Allowance for uncertainty	The approach to sensitivity analysis is given	Not stated	Yes	Yes	Yes
(deterministic analysis)	The choice of variables for sensitivity analysis is justified	No	Yes	No	No
	The ranges over which the variables are varied are stated	Yes	Yes	Yes	Yes
Presentation of results	Incremental analysis is reported using appropriate decision rules	No	NA	No	No
	Major outcomes are presented in both a disaggregated and aggregated form	Yes	No	No	Yes
	Applicable to the NHS setting	Yes	Yes	Yes	Yes

Adjunct studies (*n* = 7)

Checklist	Questions	Hughes, 1996[256]	Markowitz, 1998[258]	Messori, 1998[261]	O'Neill, 1995[262]	Reinharz, 1995[259]	Schachter, 1999[260]	Selai, 1999[257]
Study question	Costs and effects examined	No	Yes	Yes	Yes	No	Yes	Yes
	Alternatives compared	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	The viewpoint(s)/perspective of the analysis is clearly stated	Yes	Yes	Yes	No	Yes	No	No
Selection of alternatives	All relevant alternatives are compared	Yes	Yes	Yes	Yes	Yes	Unclear	No
	The alternatives being compared are clearly described	Yes	Yes	Yes	Yes	Yes	No	No
	The rationale for choosing the alternative programmes or interventions compared is stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Form of evaluation	The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	Yes	NA	NA	NA	NA	NA	NA
Effectiveness data	The source(s) of effectiveness estimates used are stated	Yes	Yes	Yes	Yes	NA	Yes	Yes
	Effectiveness data from RCT or review of RCTs	No	Yes	No	Unclear	NA	Yes	No
	Potential biases identified (especially if data not from RCTs)	No	Unclear	No	No	NA	No	Unclear
	Details of the method of synthesis or meta-analysis of estimates are given	No	No	NA	NA	NA	NA	NA
Costs	All the important and relevant resource use included	Yes	Yes	Yes	Unclear	Unclear	Unclear	No
	All the important and relevant resource use measured accurately	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
	Appropriate unit costs estimated	Unclear	Unclear	No	Yes	Unclear	Unclear	Unclear
	Unit costs reported separately from resource use data	Yes	Yes	No	No	No	No	No
	Productivity costs treated separately from other costs	Yes	NA	NA	NA	NA	NA	NA
	The year and country to which unit costs apply are stated with appropriate adjustments for inflation and/or currency conversion	Unclear	Unclear	No	Unclear	Yes	No	No
Benefit measurement and valuation	The primary outcome measure(s) for the economic evaluation are clearly stated	NA	Yes	Yes	Yes	NA	Yes	Yes
	Methods to value health states and other benefits are stated	NA	NA	Yes	NA	NA	NA	Yes
	Details of the individuals from whom valuations were obtained are given	NA	NA	Yes	NA	NA	NA	Yes

continued

Checklist	Questions	Hughes, 1996[256]	Markowitz, 1998[258]	Messori, 1998[261]	O'Neill, 1995[262]	Reinharz, 1995[259]	Schachter, 1999[260]	Selai, 1999[257]
Decision modelling	Details of any decision model used are given	Yes	Yes	Unclear	Yes	Yes	No	NA
	The choice of model used and the key input parameters on which it is based are adequately detailed and justified	Yes	No	No	Yes	Yes	No	NA
	All model outputs described adequately	Yes	Yes	Yes	Yes	Yes	No	NA
Discounting	Discount rate used for both costs and benefits	NA	Yes	Yes	NA	No	No	No
	Do discount rates accord with NHS guidance?	NA	No	No	NA	NA	NA	NA
Allowance for uncertainty (patient-level data)	Details of statistical tests and confidence intervals are given for stochastic data	NA	No	Yes	No	No	No	No
	Uncertainty around cost-effectiveness expressed	No	No	No	No	No	No	No
	Sensitivity analysis used to assess uncertainty in non-stochastic variables	Yes	Yes	No	Yes	Yes	No	No
	Are all appropriate input parameters included with uncertainty?	No	Unclear	Unclear	No	No	No	NA
Allowance for uncertainty (decision models)	Is second-order uncertainty included rather than first-order?	NA	Unclear	No	NA	No	No	NA
	Are the probability distributions adequately detailed and appropriate?	NA	No	NA	NA	NA	No	NA
	Sensitivity analysis used to assess uncertainty in non-stochastic variables and analytic decisions	No	Yes	No	Yes	Yes	No	NA
Allowance for uncertainty (deterministic analysis)	The approach to sensitivity analysis is given	Yes	Yes	No	Yes	Yes	NA	NA
	The choice of variables for sensitivity analysis is justified	No	Yes	Yes	Yes	Yes	NA	NA
	The ranges over which the variables are varied are stated	Yes	Yes	Yes	Yes	Yes	NA	NA
Presentation of results	Incremental analysis is reported using appropriate decision rules	No	Yes	Unclear	Unclear	No	No	No
	Major outcomes are presented in both a disaggregated and aggregated form	Yes	Yes	Yes	Yes	No	No	No
	Applicable to the NHS setting	Yes	Unclear	Unclear	Yes	No	Unclear	Yes

Appendix 22

Extraction tables for systematic reviews included in the assessment of effectiveness (*n* = 13)

Review details	Review methods	Data synthesis and results	Conclusions and comments
Ramaratnam, 2002[108] **Source:** Literature search **Objective:** To examine the effects of LTG on seizures, side-effects, cognition and QoL, when used as an add-on treatment for patients with drug-resistant partial epilepsy	**Inclusion criteria** **Interventions:** Conventional AED with adjunct LTG vs conventional AED with adjunct matched placebo. No treatment control groups will also be included **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence. These side-effects were chosen as they were considered to be common and important side-effects of AEDs. The proportion of participants reporting the five most common side-effects (if different from above) was also recorded 4. Any outcomes relating to cognitive effects 5. Any outcomes relating to QoL **Participants:** Participants (any age) with drug-resistant partial epilepsy (simple partial, complex partial or SGTC seizures)	**Synthesis methods:** The fixed-effects model was used to combine data provided no significant source of heterogeneity was detected. Results were expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI was calculated for individual side-effects to make allowance for multiple testing. All analyses were on an ITT basis, including all allocated participants in groups to which they were allocated. Sensitivity analyses (best and worse case) concerning the participants excluded from analyses were performed as follows: primary ITT analysis (participants not completing follow-up or with inadequate seizure data were assumed non-responders), worst case (participants not completing follow-up or with inadequate seizure data were assumed non-responders in the LTG group and responders in the placebo group), and best case (participants not completing follow-up or with inadequate seizure data were assumed responders in the LTG group and non-responders in the placebo group) For the primary outcome of seizure frequency dose-response relationships were to be examined using logistic regression, but there were insufficient data No attempt was made to combine data relating to QoL and cognitive effects data. These data were summarised in table form **Heterogeneity assessment:** Clinical heterogeneity was assessed by comparing the distribution of important factors such as age, seizure type, duration of epilepsy, number of antiepileptic drugs taken at time of randomisation, randomisation concealment, blinding and losses to follow-up. Statistical heterogeneity was assessed using a χ^2 test ($p < 0.05$ was considered statistically significant) **Number of studies included:** Eleven double-blind randomised placebo-controlled studies of add-on LTG were included in the review. Three were of a parallel design and eight used a crossover design. Ten studies included only adults and one study included only children. All of the studies were sponsored by the manufacturer (GlaxoSmithKline). In total the studies included 1243 participants (199 children and 1044 adults). The doses of LTG used varied from 75 to 500 mg/day	**Authors' conclusions:** LTG add-on therapy is effective in reducing the seizure frequency, in patients with drug-resistant partial epilepsy. Further trials are needed to assess the long-term effects of lamotrigine, and to compare it with other add-on drugs **Comments:** This is a well-conducted review. However, only data from the first period of crossover trials were considered in the analysis Both children and adults were considered in the overall analysis; however, both were also analysed separately, as were crossover and parallel studies

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	Study design: Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used. 2. Double-blind, single or unblinded trials 3. Placebo controlled 4. Parallel or crossover study. Only data from the first crossover period were used **Literature sources searched:** 1. CCTR (Cochrane Library, Issue 1, 2001) 2. Controlled Trials Register of Cochrane Epilepsy Group 3. MEDLINE (Jan. 1966–Nov. 2001) 4. GlaxoSmithKline (manufacturer of LTG) 5. Bibliographies of retrieved articles were checked for additional references **Validity assessment criteria:** 1. Method of randomisation concealment 2. Method of blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of lamotrigine used	Banks, 1991[88] Binnie, 1989[159] Boas, 1996[136] Duchowny, 1999[295] (children only) Jawad, 1989[160] Loiseau, 1990[89] Matsuo, 1993[142] Messenheimer, 1994[158] Schachter, 1995[56] Schapel, 1993[161] Schmidt, 1993[375] Smith, 1993[55] **Results:** At least 50% reduction in seizure frequency (compared with placebo): ITT analysis (all studies) RR = 2.71 (95% CI: 1.87 to 3.91), $\chi^2 = 5.50$, df = 9, $p = 0.79$ Best case scenario, RR = 4.32 (95% CI: 3.10 to 6.01) Worse case scenario, RR = 1.38 (95% CI: 0.98 to 1.95) Children only (n = 1 study), RR = 3.54 (95% CI: 1.92 to 6.54) Crossover studies only (n = 8 studies), RR = 2.81 (95% CI: 1.54 to 5.15) Treatment withdrawal (compared with placebo): RR = 1.12 (95% CI: 0.78 to 1.61), indicating that there was insufficient evidence to conclude that patients are more likely to withdraw from lamotrigine than placebo QoL and neuropsychological measures: Overall, the limited data available precluded any conclusions about the effects of LTG on cognition and QoL, although there may be minor benefits in affect balance (happiness) and mastery Side-effects (compared with placebo): Ataxia, RR = 3.14 (99% CI: 1.99 to 4.95) Dizziness, RR = 2.57 (99% CI: 1.80 to 3.69) Fatigue, RR = 0.84 (99% CI: 0.48 to 1.46) Nausea, RR = 1.88 (99% CI: 1.21 to 2.91) Somnolence, RR = 1.54 (99% CI: 0.97 to 2.43) Diplopia, RR = 3.40 (99% CI: 2.05 to 5.62) Headache, RR = 1.18 (99% CI: 0.77 to 1.81)	

Review details	Review methods	Data synthesis and results	Conclusions and comments
Chaisewikul, 2002[97] **Source:** Literature search **Objective:** To evaluate the effects of LEV on seizures, side-effects, QoL and cognition, when used as an add-on treatment for patients with a drug-resistant localisation related (partial) epilepsy	**Inclusion criteria** **Interventions:** Conventional AED with adjunct LEV vs conventional AED with adjunct matched placebo **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period as compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration, the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence. These side-effects were chosen as they were considered to be common and important side-effects of AEDs. The proportion of participants reporting the five most common side-effects (if different from above) was also recorded 4. Any outcomes relating to cognitive effects 5. Any outcomes relating to QoL **Participants:** Participants of any age with a drug-resistant localisation related epilepsy (i.e. experiencing simple partial, complex partial or SGTC seizures)	**Synthesis methods:** The fixed-effects model was used to combine data provided no significant source of heterogeneity was detected. Results were expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI were calculated for individual side-effects to make allowance for multiple testing. All analyses were on an ITT basis, including all allocated participants in groups to which they were allocated. Sensitivity analyses (best and worse case) concerning the participants excluded from analyses were performed as follows: primary ITT analysis (participants not completing follow-up or with inadequate seizure data were assumed non-responders), worst case (participants not completing follow-up or with inadequate seizure data were assumed non-responders in the LEV group and responders in the placebo group), and best case (participants not completing follow-up or with inadequate seizure data were assumed responders in the LEV group and non-responders in the placebo group) For the primary outcome of seizure frequency dose–response relationships were examined using logistic regression, and probabilities for the following were calculated for different doses: % participants with 50% response and the difference in % participants responding to each dose compared with placebo No attempt was made to combine data relating to QoL and cognitive effects data. These data will be summarised in table form **Heterogeneity assessment:** Statistical heterogeneity was investigated using a χ^2 test for heterogeneity ($p < 0.05$ was judged to be significant) **Number of studies included:** Four randomised double-blind placebo controlled add-on trials. Three used a parallel design and one used a crossover design (1023 participants in total). All of the trials included adults only and were sponsored by the manufacturer UCB. Doses ranged from 1000 to 4000 mg/day N051[145] N052[139] N132[143,166] N138 UCB industry information, unpublished	**Authors' conclusions:** LEV reduces seizure frequency when used as an add-on treatment for patients with a drug-resistant localisation related (partial) epilepsy, and seems well tolerated. Minimum effective and maximum tolerated doses have not been identified. The trials reviewed were of 16–24 weeks duration and results cannot be used to confirm longer term effects. Our results cannot be extrapolated to monotherapy or to patients with other seizure types or epilepsy syndromes. Great care should also be taken with any attempt to apply these results to children **Comments:** This was a well-conducted review. Three trials provided data on QoL and cognitive outcomes but only 595 out of the 737 participants randomised to these studies were assessed Five participants were excluded from the reported analyses and contributed to the best and worse case scenario analyses. Only data from the first treatment period of the crossover trial were used in the analysis

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	Study design: Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used 2. Double-blind, single or unblinded trials 3. Placebo controlled 4. Parallel or crossover study 5. Minimum treatment period of 8 weeks **Literature sources searched:** 1. Cochrane Epilepsy Group trials register 2. CCTR (Cochrane Library, Issue 2, 2002) 3. UCB (manufacturers of LEV) 4. Experts were contacted to check for missing trials **Validity assessment criteria:** 1. Method of randomisation concealment 2. Method of blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of LEV used	**Results:** At least 50% reduction in seizure frequency (compared with placebo): ITT analysis, RR = 3.81 (95% CI: 2.78 to 5.22), $\chi^2 = 0.76$, df = 2, $p = 0.68$ 1000 mg, RR = 4.48 (95% CI: 2.69 to 7.47) 2000 mg, RR = 5.87 (95% CI: 3.04 to 11.37) 3000 mg, RR = 4.08 (95% CI: 2.71 to 6.15) Best case scenario, RR = 3.87 (95% CI: 2.83 to 5.29), $\chi^2 = 0.74$, df = 2, $p = 0.69$ Worse case scenario, RR = 3.66 (95% CI: 2.68 to 5.00), $\chi^2 = 1.04$, df = 2, $p = 0.59$ Dose–response regression: There was significant heterogeneity due to differences in response rates between trials. There were no important differences between trials with respect to design or participants recruited. In summary, there was strong evidence for an effect of LEV with an increase in effect with increasing dose. The improvement expected for additional 1000-mg decreases, so the gain from an increase from 1000 to 2000 mg is larger than the gain for an increase from 2000 to 3000 mg. Owing to heterogeneity it was not possible to give a generally valid estimate of the response rates which could be expected for people on a particular dose of drug. However, with placebo rates in the 5–12% range, at least an additional 15% of patients would experience at least a 50% decrease in seizure frequency on a 1000-mg dose and 20–30% for a 3000-mg dose Treatment withdrawal (compared with placebo): RR = 1.25 (95% CI: 0.87 to 1.80), $\chi^2 = 0.46$, df = 3, $p = 0.93$, indicating that there is insufficient evidence to conclude that patients are more likely to withdraw from LEV than placebo, but the CI is wide Side-effects (compared with placebo): Dizziness, RR = 2.36 (99% CI: 1.21 to 4.61) Infection, RR = 1.82 (99% CI: 1.05 to 3.14) Accidental injury, RR = 0.55 (99% CI: 0.32 to 0.93) Ataxia, RR = 1.55 (99% CI: 0.46 to 5.18) Fatigue, RR = 1.51 (99% CI: 0.90 to 2.53) Headache, RR = 0.98 (99% CI: 0.58 to 1.64) Nausea, RR = 0.85 (99% CI: 0.36 to 1.99) Somnolence, RR = 1.65 (99% CI: 0.98 to 2.79) Cognitive effects and QoL: Overall, the findings from two studies suggest that LEV does have some positive effects on some aspects of QoL	

Review details	Review methods	Data synthesis and results	Conclusions and comments
Jette, 2002[98] **Source:** Literature search **Objective:** To evaluate the effects of topiramate when used as an add-on treatment for drug-resistant partial epilepsy	**Inclusion criteria** **Interventions:** Conventional AED with adjunct TPM vs conventional AED drug with adjunct matched placebo **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence. These side-effects were chosen as they were considered to be common and important side-effects of AEDs. The proportion of participants reporting the five most common side-effects (if different from above) was also recorded **Participants:** Participants (any age) with drug-resistant partial epilepsy (simple partial, complex partial or SGTC seizures) **Study design:** Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used 2. Double-blind trials in which both participant and clinician treating/assessing the outcome were blinded to the treatment allocation	**Synthesis methods:** The fixed-effects model was used to combine data provided no significant source of heterogeneity was detected. Results were expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI were calculated for individual side-effects to make allowance for multiple testing. All analyses were on an ITT basis, including all allocated participants in groups to which they were allocated. The authors planned to carry out sensitivity analyses (best and worse case) concerning the participants excluded from analyses but none of the studies excluded participants For the primary outcome of seizure frequency dose–response relationships were examined using logistic regression, and probabilities for the following were calculated for different doses: % participants with 50% response, difference in % participants responding to each dose compared with placebo **Heterogeneity assessment:** Statistical heterogeneity was investigated using a χ^2 test for heterogeneity ($p < 0.05$ was judged to be significant) **Number of studies included:** Nine parallel, double-blind, randomised placebo-controlled trials (1049 participants in total). All were sponsored by Johnson and Johnson. The doses of TPM tested varied from 200 to 1000 mg/day. Eight trials included only adults (≥ 18 years), one trial included only children (2–16 years) Elterman, 1999[458] (children only) Ben-Menachem, 1996[151] Faught, 1996[67] Korean Topiramate Study Group, 1999[149] Privitera, 1996[68] Rosenfeld, 1996[41] Sharief, 1996[148] Tassinari, 1996[42] Yen, 2000[165]	**Authors' conclusions:** TPM has efficacy as an add-on treatment for drug-resistant partial epilepsy. However, trials reviewed were of relatively short duration and provide no evidence for long-term efficacy of TPM. Results cannot be extrapolated to monotherapy or treating other epilepsy types. **Comments:** This is a well-conducted systematic review. Dose–response regression was only performed for those trials including adult participants ($n = 8$)

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	3. Placebo controlled 4. Parallel or crossover study (no crossover studies were found) 5. Minimum treatment period of 8 weeks 6. Studies with a response conditional design were excluded (none were found) **Literature sources searched:** Cochrane Epilepsy Group's specialised register (28 March 2002), CCTR (Cochrane Library, Issue 1, 2002). In addition, the manufacturer of TPM (Johnson and Johnson) and experts in the field were also contacted to obtain information about published and unpublished trials **Validity assessment criteria:** 1. Method of randomisation 2. Method of double blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of topiramate used	**Results:** At least 50% reduction in seizure frequency (compared with placebo): RR = 3.32 (95% CI: 2.52 to 4.39). Dose regression analysis showed an increasing effect with increasing dose, but found no advantage for doses over 300 mg/day Treatment withdrawal (compared with placebo): RR = 2.06 (95% CI: 1.38 to 3.08) Side-effects (compared with placebo): Five most frequent, RR = 1.95 (99% CI: 1.04 to 3.65) Dizziness, RR = 1.55 (99% CI: 1.07 to 2.24) Fatigue, RR = 2.21 (99% CI: 1.42 to 3.45) Nausea, RR = 2.75 (99% CI: 1.36 to 5.57) Somnolence, RR = 2.26 (99% CI: 1.48 to 3.46) 'Thinking abnormally', RR = 5.54 (99% CI: 2.34 to 13.12)	

Review details	Review methods	Data synthesis and results	Conclusions and comments
Marson, 2002[105] **Source:** Literature search **Objective:** To evaluate the efficacy and tolerability of GBP when used as an add-on treatment for patients with drug-resistant partial epilepsy	**Inclusion criteria** **Interventions:** Conventional AED with adjunct GBP vs conventional AED with adjunct matched placebo **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence. These side-effects were chosen as they were considered to be common and important side-effects of AEDs. The proportion of participants reporting the five most common side-effects (if different from above) was also recorded **Participants:** Participants (any age) with drug-resistant partial epilepsy (simple partial, complex partial or SGTC seizures) **Study design:** Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used 2. Double-blind trials in which both participant and clinician treating/assessing the outcome were blinded to the treatment allocation	**Synthesis methods:** The fixed-effects model was used to combine data provided no significant source of heterogeneity was detected. Results were expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI were calculated for individual side-effects to make allowance for multiple testing. All analyses were on an ITT basis, including all allocated participants in groups to which they were allocated. Sensitivity analyses (best and worse case) concerning the participants excluded from analyses were performed as follows: primary ITT analysis (participants not completing follow-up or with inadequate seizure data were assumed non-responders), worse case (participants not completing follow-up or with inadequate seizure data were assumed non-responders in the GBP group and responders in the placebo group), and best case (participants not completing follow-up or with inadequate seizure data were assumed responders in the GBP group and non-responders in the placebo group) For the primary outcome of seizure frequency dose–response relationships were examined using logistic regression, and probabilities for the following were calculated for different doses: % participants with 50% response, difference in % participants responding to each dose compared with placebo and the number needed to treat (NNT) for each dose **Heterogeneity assessment:** Statistical heterogeneity was investigated using a χ^2 test for heterogeneity ($p < 0.05$ was judged to be significant) **Number of studies included:** Five parallel, double-blind, randomised placebo-controlled trials (997 participants in total). All were sponsored by Parke Davis. The doses of GBP tested varied from 600 to 1800 mg/day. Four trials included only adults (750 participants in total) and one trial included only children (247 participants). A total of 61 participants were excluded from the reported analyses, 38 of whom did not complete the treatment phase and nine who had inadequate seizure data recorded. These 47 participants contribute to the best and worse case scenario analyses	**Authors' conclusions:** GBP has efficacy as an add-on treatment in patients with drug resistant epilepsy. However, the trials reviewed were of relatively short duration, and provided no evidence for the long term efficacy of GBP. Results cannot be extrapolated to monotherapy or patients with other epilepsy types **Comments:** This is a well-conducted systematic review Outcomes were pooled for both studies of adults and children with the exception of dose response regression, which was only performed for those trials including adult participants ($n = 4$)

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	3. Placebo controlled 4. Parallel or crossover study (no crossover studies were found) **Literature sources searched:** Cochrane Epilepsy Group's specialised register, CCTR (Cochrane Library, Issue 1, 2000). In addition, the manufacturer of TPM (Parke Davis) and experts in the field were also contacted to obtain information about published and unpublished trials **Validity assessment criteria:** 1. Method of randomisation 2. Method of double blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of GBP used	Anhut, 1994[156] Appleton, 1999[459] (children only) Sivenius, 1991[157] UK Gabapentin Study Group, 1990[73] US Gabapentin Study Group, 1993[138] **Results:** At least 50% reduction in seizure frequency (compared with placebo): ITT analysis, RR = 1.93 (95% CI: 1.37 to 2.71), $\chi^2 = 2.50$, df = 4, $p = 0.84$ Best case scenario, RR = 2.55 (95% CI: 1.86 to 3.50), $p = 0.17$ Worse case scenario, RR = 1.49 (95% CI: 1.07 to 2.08), $p = 0.97$ **Dose–response regression:** ITT analysis (log odds) was best summarised using a linear dose–response. The log odds increased by 0.215 [standard error of the mean (SEM) 0.052] for a 330-mg increase in daily dose, which is roughly a 25% increase in the odds of response for a 300-mg increase in dose. The reduction in deviance due to dose was 17.93 on 1 df and the residual deviance was 6.19 on 10 df Best case scenario (log odds) was best summarised using a linear dose–response. The log odds increased by 0.265 (SEM 0.048) for a 330-mg increase in daily dose Worse case scenario (log odds) was best summarised using a linear dose–response. The log odds increased by 0.133 (SEM 0.049) for a 330 mg increase in daily dose. Treatment withdrawal (compared with placebo): RR = 1.05 (95% CI: 0.68 to 1.61), $\chi^2 = 4.90$, df = 4, $p = 0.30$, indicating that there is insufficient evidence to conclude that patients are more likely to withdraw from GBP than placebo, but that there is a substantial withdrawal rate Side-effects (compared with placebo): Dizziness, RR = 2.22 (99% CI: 1.28 to 3.85) Fatigue, RR = 2.28 (99% CI: 1.15 to 4.52) Somnolence, RR = 2.01 (99% CI: 1.24 to 3.28) Ataxia, RR = 2.04 (99% CI: 1.00 to 4.12) Headache, RR = 0.70 (99% CI: 0.37 to 1.33) Nausea, RR = 0.87 (99% CI: 0.44 to 1.74)	

Review details	Review methods	Data synthesis and results	Conclusions and comments
Castillo, 2002[96] **Source:** Literature search **Objective:** To evaluate the effects of OXC when used as an add-on treatment for drug-resistant partial epilepsy	**Inclusion criteria** **Interventions:** Conventional AED with adjunct OXC vs conventional AED with adjunct matched placebo **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence, headache, hyponatraemia, vertigo, diplopia and rash 4. Any outcomes relating to cognitive effects 5. Any outcomes relating to QoL **Participants:** Patients of any age with drug-resistant partial epilepsy. Seizures will be considered drug-resistant if they continue despite trying monotherapy with at least two of the standard AEDs **Study design:** Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used 2. Double-blind, single or unblinded trials 3. Placebo controlled 4. Add-on studies	**Synthesis methods:** The fixed-effects model was used to combine data provided no significant source of heterogeneity was detected. Results were expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI was calculated for individual side-effects to make allowance for multiple testing. All analyses were on an ITT basis, including all allocated participants in groups to which they were allocated. Sensitivity analyses (best and worse case) concerning the participants excluded from analyses were performed as follows: primary ITT analysis (participants not completing follow-up or with inadequate seizure data were assumed non-responders), worse case (participants not completing follow-up or with inadequate seizure data were assumed non-responders in the OXC group and responders in the placebo group), and best case (participants not completing follow-up or with inadequate seizure data were assumed responders in the OXC group and non-responders in the placebo group) For the primary outcome of seizure frequency dose–response relationships were examined using logistic regression, and probabilities for the following were calculated for different doses: % participants with 50% response and difference in % participants responding to each dose compared to placebo No attempt was made to combine data relating to QoL and cognitive effects data. These data were summarised in table form **Heterogeneity assessment:** Clinical heterogeneity was assessed by comparing the distribution of important factors such as age, seizure type, duration of epilepsy, number of AEDs taken at time of randomisation, randomisation concealment, blinding and losses to follow-up. Statistical heterogeneity was assessed using a χ^2 test ($p < 0.05$ was considered statistically significant) **Number of studies included:** Two double-blind randomised parallel add-on trials were included. Both were unpublished and sponsored by the drug manufacturer (Novartis). One study recruited only children ($n = 694$) and the other only adults ($n = 694$). In total, 961 participants were recruited. In one study OXC was titrated according to patient weight and in the other study three	**Authors' conclusions:** OXC has efficacy as an add-on treatment in patients with drug-resistant partial epilepsy, in both adults and children. However, trials reviewed were of relatively short duration, and provide no evidence about the long-term effects of OXC. Results cannot be extrapolated to monotherapy or to patients with other types of epilepsy **Comments:** This is a well-conducted review. Studies including children and adults were included, but analysed separately

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	5. Parallel or crossover study. Only data from the first crossover period were used	different doses (600, 1200 and 2400 mg/day) were compared with placebo	
	Literature sources searched: 1. CCTR (Cochrane Library, Issue 1, 2000) 2. Controlled Trials Register of Cochrane Epilepsy Group 3. MEDLINE (Jan. 1966–Dec. 1999) 4. Novartis (manufacturer of OXC) 5. Experts in the field were also contacted for missing studies	**Results:** At least 50% reduction in seizure frequency (compared with placebo): ITT analysis (both studies), RR = 2.96 (95% CI: 2.20 to 4.00), χ^2 =1.27, df = 1, p = 0.26 As only three participants in the paediatric study and two in the adult study were excluded from the analyses, the authors report that they considered the best and worst case scenarios would be similar to the overall analysis.	
	Validity assessment criteria: 1. Method of randomisation concealment 2. Method of blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of OXC used	Children only (n = 1 study), RR = 2.33 (95% CI: 1.39 to 3.90) Adults only (n = 1 study), RR = 3.35 (95% CI: 2.32 to 4.83) Treatment withdrawal (compared with placebo): RR = 2.17 (95% CI: 1.59 to 2.97), χ^2 = 0.02, df = 1, p = 0.89, indicating that patients are significantly more likely to withdraw from OXC than placebo. Estimates for individual doses indicate that patients were increasingly more likely to withdraw from OXC with increasing dose: 600 mg, RR = 0.76 (95% CI: 0.47 to 1.23); 1200 mg, RR = 2.08 (95% CI: 1.35 to 3.21); and 2400 mg, RR = 6.08 (95% CI: 3.99 to 9.26) QoL and neuropsychological measures: These outcomes were not assessed in the two included studies Side-effects (compared with placebo): Ataxia, RR = 2.39 (99% CI: 1.72 to 4.99) Dizziness, RR = 3.05 (99% CI: 1.99 to 4.67) Fatigue, RR = 1.80 (99% CI: 1.02 to 3.19) Nausea, RR = 2.88 (99% CI: 1.77 to 4.69) Somnolence, RR = 2.55 (99% CI: 1.84 to 3.55) Diplopia, RR = 4.32 (99% CI: 2.65 to 7.04) Hyponatraemia, no data reported.	

Review details	Review methods	Data synthesis and results	Conclusions and comments
Marson, 2001[104] **Source:** Literature search **Objective:** To undertake a systematic review and meta-analysis of placebo-controlled add-on trials of LEV, OXC, remacemide and zonisamide (ZNS) for patients with drug-resistant localisation-related epilepsy	**Inclusion criteria** **Interventions:** Adjunct LEV, OXC, remacemide or zonisamide vs placebo **Outcomes:** The primary outcome measure was the proportion of participants experiencing at least a 50% reduction in seizure frequency during treatment as compared with a prerandomisation period. The secondary outcome measure was the number of treatment withdrawals **Participants:** Participants of any age with drug-resistant localisation-related epilepsy (i.e. experiencing simple partial, complex partial or SGTC seizures). **Study design:** To be included studies must be: 1. Adequately randomised placebo-controlled trials 2. Double, single or unblinded trials 3. Parallel or crossover design (only the first-phase data were used for crossover studies) **Literature sources searched:** 1. Cochrane Library (Issue 4, 2000) 2. Controlled Trial Register of the Cochrane Epilepsy Group 3. Manufacturers' databases **Validity assessment criteria:** 1. Adequate method of randomisation. 2. Adequate method of allocation concealment	**Synthesis methods:** ITT data were used based on all randomised patients. RRs (95% CI) and RD (risk difference) for the number of responders (at least 50% reduction in seizure frequency) were calculated and pooled if there was no significant heterogeneity. A p-value of ≤ 0.05 was considered statistically significant. The effect of drug dose was considered using a regression model **Heterogeneity assessment:** Clinical heterogeneity was considered by comparing important factors such as method of randomisation, length of treatment and baseline periods, baseline seizure frequency and age of participants. Statistical heterogeneity was assessed using a χ^2 test ($p < 0.05$ was considered statistically significant) **Number of studies included:** 11 RCTS: Adjunct LEV vs placebo ($n = 3$ parallel studies, $n = 1$ crossover study) Adjunct OXC vs placebo ($n = 2$ parallel studies) Adjunct remacemide vs placebo ($n = 2$ parallel studies) Adjunct ZNS vs placebo ($n = 3$ parallel studies) **Results:** Ignoring the effect of dose, RRs for the number of 50% responders were: LEV 3.78 (95% CI: 2.62 to 5.44), OXC 2.51 (95% CI: 1.88 to 3.33), remacemide 1.59 (95% CI: 0.91 to 2.97) and ZNS 2.46 (95% CI: 1.61 to 3.79). There was evidence for increasing effect with increasing dose for LEV, OXC and remacemide. The RRs for the number of treatment withdrawals were LEV 1.21 (95% CI: 0.88 to 1.66), OXC 1.72 (95% CI: 1.35 to 2.18), remacemide 1.90 (95% CI: 1.00 to 3.60) and ZNS 1.64 (95% CI: 1.02 to 2.62)	**Authors' conclusions:** These data suggest a useful effect for LEV, OXC and ZNS. LEV has a more favourable 'responder-withdrawal ratio' followed by ZNS and OXC **Comments:** This is a well-conducted review

Review details	Review methods	Data synthesis and results	Conclusions and comments
Marson, 1997[100] **Source:** Literature search **Objective:** To report a series of meta-analyses of randomised placebo-controlled add-on trials in which GBP, LTG, TGB, TPM, VGB and ZNS were tested in patients with partial epilepsy, the purpose being to provide an estimate of each drug's efficacy and tolerability compared with placebo. In addition, the estimates will be compared across drugs to give broad estimates of comparative efficacy and tolerability	**Inclusion criteria** **Interventions:** Adjunct GBP, LTG, TGB, TPM, VGB or ZNS vs placebo **Outcomes:** Seizure outcomes must be reported **Participants:** Only patients with partial epilepsy were included **Study design:** To be included trials must be: 1. RCTs 2. Parallel or crossover design (only the first-phase data were used for crossover studies) 3. Treatment period of at least 8 weeks The following types of study design were excluded: 1. Response conditional trials 2. Trials with a surgical paradigm 3. Trials with a treatment replacement paradigm **Literature sources searched:** 1. Controlled Trials Register of Cochrane Epilepsy Group (1995) 2. Manufacturers' databases and records **Validity assessment criteria:** Not stated	**Synthesis methods:** ITT data were used based on all randomised patients. ORs (95% CI) for the number of responders (at least 50% reduction in seizure frequency) were calculated and pooled if there was no significant heterogeneity using the fixed Peto OR method. ORs (99% CI) were used to report the incidence of AEs and summary estimates reported again using the fixed Peto OR method if there was no significant heterogeneity. A p-value of ≤ 0.05 was considered statistically significant **Heterogeneity assessment:** Statistical heterogeneity was assessed using a χ^2 test ($p < 0.05$ was considered statistically significant) **Number of studies included:** 29 studies were included representing 4091 participants: Adjunct GBP vs placebo ($n = 4$ parallel RCTs) Adjunct LTG vs placebo ($n = 2$ parallel RCTs, $n = 8$ crossover RCTs) Adjunct TGB vs placebo ($n = 3$ parallel RCTs) Adjunct TPM vs placebo ($n = 6$ parallel RCTs) Adjunct VGB vs placebo ($n = 3$ parallel RCTs, $n = 1$ crossover RCT) Adjunct ZNS vs placebo ($n = 2$ parallel RCTs) **Results:** The ORs for 50% response were GBP 2.29 (95% CI: 1.53 to 3.43), LTG 2.32 (95% CI: 1.47 to 3.68), TGB 3.03 (95% CI: 2.01 to 4.58), TPM 4.07 (95% CI: 2.87 to 5.78), VGB 3.67 (95% CI: 2.44 to 5.51) and ZNS 2.7 (95% CI: 1.36 to 4.47) The ORs for discontinuation were GBP 1.36 (95% CI: 0.75 to 2.49), LTG 1.19 (95% CI: 0.79 to 1.79), TGB 1.81 (95% CI: 1.21 to 2.70), TPM 2.56 (95% CI: 1.64 to 4.00), VGB 2.58 (95% CI: 1.26 to 5.27) and ZNS 4.23 (95% CI: 1.71 to 10.49)	**Authors' conclusions:** There is clear evidence that each of the drugs is better than placebo at preventing seizures. When results were compared across drugs, the CIs overlap, and there is no conclusive evidence of differences in efficacy or tolerability **Comments:** Indirect comparisons were made between the AEDs in the absence of studies making direct comparisons. Such analyses are subject to potentially large biases, so caution should be exercised when interpreting the findings across drugs

Review details	Review methods	Data synthesis and results	Conclusions and comments
Adab, 2004[95] **Source:** Literature search **Objective:** To assess the AEs of commonly used AEDs on maternal and fetal outcomes in pregnancy in women with epilepsy	**Inclusion criteria** **Interventions:** Exposure to any of the following at any stage of pregnancy: PB, PHT, CBZ, OXC, VPA, LTG, TPM, GBP, VGB, TGB, ZNS **Outcomes:** 1. Primary maternal outcome – mortality 2. Secondary maternal outcomes – maternal complications of pregnancy (antepartum haemorrhage, pre-eclampsia, premature delivery, postpartum haemorrhage), modes of delivery (normal, Caesarian section, forceps, ventouse) 3. Primary fetal outcomes – major malformations (congenital heart defects, neural tube defects, craniofacial defects, genitourinary malformations, limb defects), developmental delay 4. Secondary fetal outcomes – perinatal death, fetal death, infant mortality, minor malformations (eyes, ears, nose, mouth, digits), intrauterine growth restriction and microcephaly **Participants:** 1. RCTs including women with epilepsy requiring treatment (prior to conception or at any stage of pregnancy) who are planning or are already pregnant, randomised to an AED suitable for their type of epilepsy. Prospective follow-up is preferred though RCTs of effectiveness of monotherapy in epilepsy who have reported pregnancy outcomes are eligible 2. Prospective controlled cohort studies that consecutively enroll pregnant women with epilepsy, categorised according to AED exposure (one or more AEDs), who were followed up for the outcome of interest. Eligible control groups include pregnant women in the general population or pregnant women with epilepsy not taking AEDs 3. Case–control studies where cases (children and/or mothers) have the condition of interest (see outcome measures) compared with an unaffected control group (children and/or mothers) in terms of their exposure to AEDs and any other factors **Study design:** See participant criteria	**Synthesis methods:** For each outcome a pooled estimate of treatment effect (OR, RR or weighted mean difference) will be calculated. A separate analysis will be used for each study type and in addition control groups which included women with epilepsy will be examined separately to control groups which include women in the general population. The analysis comparing any AED regime with none will be subgrouped by monotherapy or polytherapy **Heterogeneity assessment:** Clinical heterogeneity will be assessed by examining differences in patient characteristics across studies (e.g. type of epilepsy, population setting, accrual period, maternal age, maternal seizures, timing of exposure to AEDs, adequate folic acid supplementation and social class). Any characteristics identified as potentially important will be used to drive subsequent subgroup analyses and meta regression. A χ^2 test will be used to assess statistical heterogeneity ($p < 0.1$ will be considered significant) **Number of studies included:** This review has now been published please refer to the Cochrane Library for further details **Results:** Not applicable	**Authors' conclusions:** Not applicable **Comments:** This review has now been published please refer to the Cochrane Library for further details

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	Literature sources searched: 1. MEDLINE, EMBASE, Pharmline, Reprotox and Teris from 1966 to present 2. Literature reviews and textbooks 3. Journals were handsearched (*Neurology*, *Epilepsia*, *Journal of Neurology, Neurosurgery and Psychiatry*, *Epilepsy Research*, *Journal of Paediatrics, Archives of Disease in Childhood*, *Developmental Medicine and Clinical Neurology*, *Reproductive Toxicology*, *Teratology* and *American Journal of Medical Genetics*) 4. Trial authors were contacted for additional trials 5. Conference abstracts were searched 6. Pharmaceutical companies were contacted **Validity assessment criteria:** 1. Explicit recording of classification of epilepsy 2. Timing of recruitment 3. Adequate matching of controls 4. Attention to confounding factors 5. Clear recording of exposure 6. Standard and valid criteria used to assess outcomes 7. Blinding of assessors to allocation 8. Completeness of follow-up		

Review details	Review methods	Data synthesis and results	Conclusions and comments
White, 2002[110] **Source:** Literature search **Objective:** To compare the efficacy and tolerability of CBZ and LTG when used as monotherapy in patients with POSs or GTC seizures	**Inclusion criteria** **Interventions:** CBZ or LTG as monotherapy **Outcomes:** 1. Time on allocated treatment (retention time). A combined outcome reflecting both efficacy and tolerability. This is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the ILAE 2. Time to 6, 12 and 23 months remission from seizures 3. Time to first seizure postrandomisation 4. Time to treatment withdrawal due to AEs 5. Incidence of side-effects 6. Incidence of side-effects leading to treatment withdrawal **Participants:** 1. Children or adults with POSs (simple partial, complex partial, or SGTC seizures) or generalised onset tonic–clonic seizures 2. A new diagnosis of epilepsy, or a relapse following antiepileptic drug withdrawal **Study design:** 1. Randomised controlled monotherapy studies comparing CBZ and LTG. Studies may be double, single or unblinded 2. Studies using either quasi or adequate methods of randomisation **Literature sources searched:** 1. Cochrane Library 2. Controlled Trials Register of Cochrane Epilepsy Group 3. Ciba Geigy (manufacturer of CBZ) 4. GlaxoSmithKline (manufacturer of LTG) 4. Original investigators of relevant trials found **Validity assessment criteria:** 1. Randomisation method 2. Method of concealment of allocation 3. Stratification factors 4. Blinding methods	**Synthesis methods:** The primary analysis will be ITT using individual patient data. Sensitivity analyses will be undertaken including all studies and only those using adequate methods of concealment. With 'time to event' outcomes (time to treatment withdrawal, time to first seizures, time to period remission), stratified log-rank tests will be used to combine data and regression models. Data on neurological signs, computed tomography (CT) and magnetic resonance imaging (MRI) scans and EEG results will be described, and a summary of the distribution of available covariates will be provided. If sufficient information is available, the impact of these factors on outcome will be assessed. Hierarchical modes will be explored in order to examine the effects of study factors such as blinding and allocation concealment **Heterogeneity assessment:** Clinical heterogeneity will be assessed by reviewing the differences across trials in the characteristics of randomised participants and dosing protocols. Estimates of the effects of variables which might contribute to heterogeneity will be investigated in regression models **Number of studies included:** This review is still in the protocol stage **Results:** Not applicable	**Authors' conclusions:** Not applicable **Comments:** This protocol has been withdrawn. The review has been delayed owing to problems in obtaining individual patient data

Review details	Review methods	Data synthesis and results	Conclusions and comments
Pereira, 2002[107] **Source:** Literature search **Objective:** To evaluate the effects of add-on treatment with TGB upon seizures, side-effects, cognition and QoL for people with drug-resistant localisation-related seizures	**Inclusion criteria** **Interventions:** Conventional AED with adjunct TGB vs conventional AED with adjunct matched placebo **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence. These side-effects were chosen as they were considered to be common and important side-effects of AEDs. The proportion of participants reporting the five most common side-effects (if different from above) was also recorded 4. Any outcomes relating to cognitive effects 5. Any outcomes relating to QoL **Participants:** People of any age with drug-resistant localisation-related seizures (i.e. experiencing simple partial, complex partial or SGTC seizures) **Study design:** Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used 2. Double-blind, single or unblinded trials 3. Placebo controlled	**Synthesis methods:** The fixed-effects model was used to combine data provided no significant source of heterogeneity was detected. Results were expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI was calculated for individual side-effects to make allowance for multiple testing. All analyses were on an ITT basis, including all allocated participants in groups to which they were allocated. Sensitivity analyses (best and worse case) concerning the participants excluded from analyses were performed as follows: primary ITT analysis (participants not completing follow-up or with inadequate seizure data were assumed non-responders), worse case (participants not completing follow-up or with inadequate seizure data were assumed non-responders in the TGB group and responders in the placebo group) and best case (participants not completing follow-up or with inadequate seizure data were assumed responders in the TGB group and non-responders in the placebo group) For the primary outcome of seizure frequency dose–response relationships were examined using logistic regression No attempt was made to combine data relating to QoL and cognitive effects data. These data were summarised in table form **Heterogeneity assessment:** Clinical heterogeneity was assessed by comparing the distribution of important factors such as age, seizure type, duration of epilepsy, number of AEDs taken at time of randomisation, randomisation concealment, blinding and losses to follow-up. Statistical heterogeneity was assessed using a χ^2 test ($p < 0.05$ was considered statistically significant) **Number of studies included:** Five randomised double-blind placebo-controlled add-on trials (858 participants in total) were included. Three were parallel trials and two used a crossover design. All of the trials were originally sponsored by Novo Nordisk, the original drug manufacturer (patent now owned by Sanofi-Synthelabo) and all included only adults	**Authors' conclusions:** TGB reduces seizure frequency but is associated with some side-effects when used as an add-on for people with drug-resistant localisation-related seizures **Comments:** This is a well-conducted review Three trials provided data on QoL and cognitive outcomes; however, only 199 and 221 (respectively) out of the 858 participants randomised to these studies were assessed There were insufficient data from the crossover trials to be included in analysis. However, the authors only planned to use data from the first treatment period of the crossover trials in the analysis. This data will be incorporated into the next update of the review once it becomes available. In addition, both of the crossover trials used a response conditional design so the participants were highly selected. Hence the authors intend to consider the two trial designs (parallel and crossover separately)

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	4. Parallel or crossover study 5. Minimum treatment period of 8 weeks **Literature sources searched:** 1. Cochrane Epilepsy Group Trials register (28 March 2002) 2. CCTR (Cochrane Library, Issue 1, 2002) 3. MEDLINE (1966–Nov. 2001) 4. Sanofi-Synthelabo (manufacturer of TGB) 5. Experts were contacted to check for missing trials **Validity assessment criteria:** 1. Method of randomisation concealment 2. Method of blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of TGB used	Crawford, 2001[131] Kälviäinen, 1996,[43] 1998[164] Richens, 1995[146,400] Uthman, 1998,[163] Dodrill, 1997[167] **Results:** 1. Parallel trials At least 50% reduction in seizure frequency (compared with placebo): ITT analysis, RR = 3.16 (95% CI: 1.97 to 5.07), $\chi^2 = 0.81$, df = 2, p = 0.67 Best case scenario, RR = 3.32 (95% CI: 2.08 to 5.32), $\chi^2 = 1.09$, df = 2, $p = 0.58$ Worse case scenario, RR = 2.70 (95% CI: 1.75 to 4.19), $\chi^2 = 0.41$, df = 2, $p = 0.81$ **Dose–response regression:** Owing to differences in the response rates in the individual trials, it was not possible to give valid estimates of precise responses to individual doses. However, there is strong evidence of an effect for daily dose of 30–56 mg. With placebo rates in the range 6–10%, at least an additional 13% and possibly 20% of people would experience at least a 50% reduction in seizure frequency on a dose of 30 mg/day The best-case scenario findings were very similar. The reduction in deviance due to dose, adjusting for trial effects, was 47.7 on 1 df, $p = 0.001$. With a contrast of trials included, the residual deviance was 6.7 on 5 df. For the worse case scenario, the findings were also very similar to the ITT findings. The reduction in deviance due to dose, adjusting for trial effects, was 35.4 on 1 df, $p = 0.001$. With a contrast of trials included, the residual deviance was 4.5 on 5 df Treatment withdrawal (compared with placebo): RR = 1.81 (95% CI: 1.25 to 2.62), $\chi^2 = 1.75$, df = 2, $p = 0.42$, indicating that patients are significantly more likely to withdraw from TGB than placebo Side-effects (compared with placebo): Dizziness, RR = 1.69 (99% CI: 1.31 to 2.18) Fatigue, RR = 1.38 (99% CI: 1.04 to 1.82) Nervousness, RR = 10.65 (99% CI: 2.00 to 56.70) Tremor, RR = 4.56 (99% CI: 1.73 to 12.08)	

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
		Ataxia, RR = 1.24 (99% CI: 0.54 to 2.84) Nausea, RR = 1.24 (99% CI: 0.85 to 1.80) Somnolence, RR = 1.18 (99% CI: 0.89 to 1.56) Headache, RR = 1.15 (99% CI: 0.66 to 2.03) Infection, RR = 1.00 (99% CI: 0.52 to 1.91) 2. Crossover trials At least 50% reduction in seizure frequency (compared with placebo): There were insufficient data to carry out the planned analysis Dose–response regression: There were insufficient data to carry out the planned analysis Treatment withdrawal was not considered for crossover trials Side-effects (compared with placebo): For crossover trials one trial reports $n = 8$ reported side-effects whilst taking TGB (including $n = 2$ dizziness, $n = 2$ in coordination and $n = 3$ accidental injury; all other effects were only reported each a single individual) and $n = 10$ while taking placebo. The other trial failed to provide a detailed breakdown of AEs 3. All trials Cognitive effects: The trials used numerous tests which varied. Overall there was insufficient evidence to conclude that TGB has an effect on cognition QoL: Only two studies assessed QoL and neither found a significant difference between TGB and placebo, hence there is insufficient evidence to conclude that TGB has an effect on QoL	

Review details	Review methods	Data synthesis and results	Conclusions and comments
Rashid, 2002[109] **Source:** Literature search **Objective:** To evaluate the efficacy and tolerability of VGB when used as an add-on treatment for patients with drug-resistant partial epilepsy	**Inclusion criteria** **Interventions:** Conventional AED with adjunct VGB vs conventional AED with adjunct matched placebo **Outcomes:** 1. Primary outcome was number of participants with at least 50% reduction in seizure frequency in treatment period as compared with prerandomisation period 2. Treatment withdrawal was also recorded and used as a measure of global effectiveness. Treatment may be withdrawn owing to side-effects, lack of efficacy or a combination of both. In trials of short duration, the most likely reason for withdrawal is side-effects 3. The proportion of participants reporting the following side-effects was recorded: ataxia, dizziness, fatigue, nausea, somnolence. These side-effects were chosen as they were considered to be common and important side-effects of AEDs. The proportion of participants reporting the five most common side-effects (if different from above) was also recorded 4. Any outcomes relating to cognitive effects 5. Any outcomes relating to QoL **Participants:** Participants (any age) with drug-resistant partial epilepsy (simple partial, complex partial or SGTC seizures) **Study design:** Studies had to fulfil all of the following: 1. RCTs in which an adequate method of concealment of randomisation was used 2. Double-blind, single or unblinded trials 3. Placebo controlled 4. Parallel or crossover study (no crossover studies were found) 5. Minimum treatment period of 8 weeks	**Synthesis methods:** The fixed-effects model will be used to combine data provided no significant source of heterogeneity is detected. Results will be expressed as RR with 95% CI for 50% reduction in seizure frequency and treatment withdrawal. RR with 99% CI will be calculated for individual side-effects to make allowance for multiple testing. All analyses will be on an ITT basis, including all allocated participants in groups to which they were allocated. Sensitivity analyses (best and worse case) concerning the participants excluded from analyses will be performed as follows: primary ITT analysis (participants not completing follow-up or with inadequate seizure data will be assumed non-responders), worse case (participants not completing follow-up or with inadequate seizure data will be assumed non-responders in the VGB group and responders in the placebo group) and best case (participants not completing follow-up or with inadequate seizure data will be assumed responders in the VGB group and non-responders in the placebo group) For the primary outcome of seizure frequency dose–response relationships will be examined using logistic regression, and probabilities for the following will be calculated for different doses: % participants with 50% response, difference in % participants responding to each dose compared with placebo and the NNT for each dose No attempt will be made to combine data relating to QoL and cognitive effects data. These data will be summarised in table form **Heterogeneity assessment:** Clinical heterogeneity will be assessed by comparing the distribution of important factors such as age, seizure type, duration of epilepsy and number of AEDs taken at time of randomisation. Statistical heterogeneity will be assessed using a χ^2 test ($p < 0.05$ will be considered statistically significant)	**Authors' conclusions:** Not applicable **Comments:** This is only published as a protocol

continued

Review details	Review methods	Data synthesis and results	Conclusions and comments
	Literature sources searched: 1. Cochrane Library (Issue 3, 1999) 2. Controlled Trials Register of Cochrane Epilepsy Group 3. Hoechst Marrion Rousell (manufacturer of VGB) 4. Experts in the field will be asked to identify any missing studies **Validity assessment criteria:** 1. Method of randomisation 2. Method of double blinding 3. Whether any participants had been excluded from the reported analyses 4. Length of baseline period 5. Length of treatment period 6. Dose(s) of VGB used	**Number of studies included:** This review is still in the protocol stage. The completed review is expected to be published in the Cochrane Library, Issue 4, 2002 **Results:** Not applicable	
Kälviäinen, 2002[99] **Source:** Literature search **Objective:** Not stated	**Inclusion criteria** **Interventions:** Not stated **Outcomes:** Not stated **Participants:** Not stated **Study design:** Not stated **Literature sources searched:** Not stated **Validity assessment criteria:** Not stated	**Synthesis methods:** Not stated **Heterogeneity assessment:** Not stated **Number of studies included:** Not applicable **Results:** Not applicable	**Authors' conclusions:** Not applicable **Comments:** This protocol has been withdrawn. The review has been delayed owing to problems in obtaining individual patient data

Review details	Review methods	Data synthesis and results	Conclusions and comments
Muller, 2002[106] **Source:** Literature search **Objective:** To review the effects of OXC compared with PHT when used as monotherapy in patients with epilepsy	**Inclusion criteria** **Interventions:** OXC or PHT as monotherapy **Outcomes:** 1. Time on allocated treatment (retention time). A combined outcome reflecting both efficacy and tolerability. This is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the ILAE 2. Time to 6, 12 and 23 months remission from seizures 3. Time to first seizure postrandomisation **Participants:** Children or adults with epilepsy **Study design:** 1. RCTs using either: (a) an adequate method of allocation concealment (b) a quasi method of randomisation 2. Studies may be double blind, single blind or unblinded **Literature sources searched:** 1. Cochrane Library 2. Controlled Trials Register of Cochrane Epilepsy Group 3. Novartis (manufacturer of OXC) 4. Parke-Davis (manufacturer of PHT) 4. Original investigators of relevant trials found 5. *Epilepsia*, *Epilepsy Research* and *Acta Neurologica Scandinavica* will be handsearched 6. Bibliographies of retrieved papers will be checked 7. Appropriate conference abstracts will be searched 8. Foreign language publications will be included **Validity assessment criteria:** 1. Randomisation method 2. Method of concealment of allocation 3. Stratification factors 4. Blinding methods	**Synthesis methods:** The primary analysis will be ITT using individual patient data. Sensitivity analyses will be undertaken including all studies, and only those using adequate methods of concealment. With 'time to event' outcomes (time to treatment withdrawal, time to first seizures, time to period remission), stratified log-rank tests will be used to combine data and regression models. Data on neurological signs, CT and MRI scans and EEG results will be described, and a summary of the distribution of available covariates will be provided. If sufficient information is available, the impact of these factors on outcome will be assessed. Hierarchical modes will be explored in order to examine the effects of study factors such as blinding and allocation concealment. Primary analyses will use original seizure classification. Secondary analyses utilising reclassification data from individual studies (where available) will be undertaken to examine the potential impact of misclassification on estimates of treatment effect **Heterogeneity assessment:** Clinical heterogeneity will be assessed by reviewing the differences across trials in the characteristics of randomised participants, dosing protocols and trial design. Estimates of the effects of variables which might contribute to heterogeneity will be investigated **Number of studies included:** This review is still in the protocol stage **Results:** Not applicable	**Authors' conclusions:** Not applicable **Comments:** This is only published as a protocol

Appendix 23

Extraction tables for clinical effectiveness studies

Six studies of new versus new AEDs have been included only once in the clinical effectiveness tables, despite being eligible for inclusion in more than one section. The chart below gives details of these studies.

Study	GBP	LTG	LEV	OXC	TGB	TPM	VGB
Brodie, 2002[93]	In GBP extraction tables	See GBP extraction tables					
Chmielewska, 2001[133]		In LTG extraction tables			See LTG extraction tables		
Crawford, 2001[131]	In GBP extraction tables	See GBP extraction tables					
Czapinski, 1997[45]	See VGB extraction tables						In VGB extraction tables
Lindberger, 2000[132]	In GBP extraction tables						See GBP extraction tables
Specchio, 1999[61]	See VGB extraction tables	See VGB extraction tables					In VGB extraction tables

Gabapentin (licensed use)

Crossover studies (n = 2)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Leach, 1997[90] **Related publications** None **Country** UK **Source** Literature search **Aim** To assess the effect of different doses of GBP on cognitive function in treated epileptic patients **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Coin tossing; after pretrial period	**Number of participants** 27 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 21): 36.6 years; total (n = 21): 16–67 years **Gender** Total (n = 21): men = 10; women = 11 **Age at onset of seizures** Mean duration of epilepsy: Total (n = 21): 19.7 years (range 2–62 years) **Pretrial medication** Not stated **Ongoing concurrent medication** CBZ, VPA, PHT, PRM, PB, VGB, LTG, OXC **Co-morbidities** Not stated	**Intervention 1** GBP/placebo; 2400 mg/day; 12 weeks No. randomised: 14 No. completed: 11 **Comparator** Placebo/GBP; NA; 12 weeks No. randomised: 13 No. completed: 10	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total (n = 27): withdrew consent (n = 1); AEs (n = 5); incomplete data (n = 1) **Adverse events** **Intervention 1** Total: 19 (79%) reported 47 AEs on GBP. The side-effect scores showed a significant difference compared with placebo while on the highest dose of GBP only (p = 0.006). There was a strong correlation between the side-effect score and seizure frequency (r = 0.61, p < 0.001) during both placebo (r = 0.72, p = 0.001) and GBP treatment (r = 0.50, p = 0.02) **Comparator** Total: 15 (63%) reported 30 AEs on placebo	**Authors' conclusions** Gabapentin is a well-tolerated and effective AED which had no measurable effect on cognition but did produce sedation at the highest dose. This study also supports the suggestion that seizures can cause cognitive impairment **Comments** The authors state that the dose titration in the study design caused dose and length of time on treatment to be confounded in the analysis, hence no direct comparisons were made between dose levels. The primary analysis grouped together data for all dose levels. When individual doses were evaluated this was done by comparing data for a particular dose level with data from the corresponding dose of placebo One participant reported only 3 seizures per month at baseline contrary to the inclusion criteria stated by the study authors Information on randomisation was obtained from the author directly Total numbers of participants reported for individual outcome categories are not stated in most

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period One month after a screening visit, patients were randomised into the first 12-week treatment period (GBP or placebo). After the three dose levels had been tested, participants entered a 4-week washout before commencing the second treatment phase (placebo or GBP). During each 12-week treatment phase the dose of GBP or matched placebo was increased stepwise at intervals of 4 weeks (1200, 1800 and 2400 mg/day in three daily doses). A total of 10 tests were given at each 4-weekly visit (4 psychomotor tests and 6 tests of memory). Tests of subjective well-being comprised the SEALS questionnaire, a side-effect score, and a visual analogue scale for drowsiness. Composite psychomotor tests and memory tests were calculated by subtraction of the mean and division by the SD to give each assessment a mean of zero and an SD of 1. Addition of each score then provided a composite score which gave equal weighting to each test **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Seizure frequencies were normalised by log transformation before analysis of variance (ANOVA) Individual cognitive function tests were analysed using Wilcoxon signed rank tests. Composite scores for memory and psychomotor performance were constructed by summation of normalised scores for related assessments and compared using ANOVA	**Baseline seizure frequency** Mean number of seizures per month: total (n = 21): 26.95 (range 3–212) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: participants had epilepsy refractory to one or two AEDs, the doses of which had remained unchanged for at least 3 months prior to recruitment. Seizures were partial with or without secondary generalisation. All patients reported at least four seizures per month for the previous 3 months (see Comments)			cases. It is not clear what the total number of participants reporting AEs was for each treatment group from the data provided in the report Additional data not extracted here in the form of subgroup analysis data are provided in the paper

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
The five SEALS subscores, the side-effects scores and the visual analogue scale for drowsiness were analysed using analysis of covariance (ANCOVA), fitting the week 0 and week 16 scores as the covariate. All ANOVA and ANCOVA models used fitted patient, period, and treatment effects **Length of trial/frequency of follow-up** 28 weeks; psychomotor and cognitive testing were carried out every 4 weeks, before increasing the dose of gabapentin or placebo				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure frequency; the median monthly seizure frequency **Intervention 1** GBP (n = 21): 4.3, p = 0.02 (GBP vs placebo) **Comparator** Placebo (n = 11): not stated	**Outcome** Proportion of responders; responders were defined as having at least a 50% reduction in total seizure frequency **Intervention 1** GBP: 9/21 (43%) **Comparator** Placebo (n = 21): not stated	**Outcome** Proportion of seizure-free patients; number of participants seizure free throughout the active treatment phase **Intervention 1** GBP (n = 21): 2 **Comparator** Placebo (n = 21): 0	**Outcome** Neuropsychological testing; psychomotor and memory tests, the SEALS questionnaire and a visual analogue scale for drowsiness **Intervention 1** Psychomotor tests: comparison of individual tests and composite psychomotor scores at each treatment level with the corresponding placebo phase failed to show any significant difference Memory tests: the paired associate learning test was improved on 2400 mg/day GBP (score = 17) vs placebo (score = 12), $p < 0.05$. No other memory test showed a significant difference between GBP and placebo at any dose. There was no difference in composite memory scores between GBP and placebo treatment SEALS: none of the five SEALS subscores was significantly affected by GBP Tiredness: the mean tiredness score was significantly increased only during treatment with 2400 mg/day GBP (mean score = 43, SD 29) compared with corresponding placebo phase (mean score = 36, SD 27), $p < 0.03$ Composite psychomotor (r = –0.47, $p < 0.01$), tiredness (r = 0.42, $p < 0.01$), and side-effect (r = 0.61, $p < 0.001$) scores correlated significantly with seizure frequency but not with GBP dose **Comparator** Placebo: see Intervention 1 box

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Wilensky, 1996[69] **Related publications** Abstract[336] **Country** USA **Source** Industry submission **Aim** To assess the efficacy and safety of GBP monotherapy (1200 mg/day) compared with CBZ monotherapy (1200 mg/day) and combination GBP/CBZ therapy (1200 mg/day each) **Type of publication** Industry trial report **Funding** Parke-Davis and National Institutes of Health **Trial ID** 945-36/RR720-03733 **Study design** Combination; new vs old and new vs new; crossover trial; equivalence trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 22 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** [Data have been designated commercial-in-confidence and have been removed]	**Intervention 1** GBP; 1200 mg/day; 16–28 weeks No. randomised: 7 No. completed: not stated **Intervention 2** CBZ; 1200 mg/day; 16–28 weeks No. randomised: 7 No. completed: not stated **Intervention 3** GBP/CBZ; 1200 mg/day each; 16–28 weeks No. randomised: 6 No. completed: not stated **Comparator** NA	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** [Data have been designated commercial-in-confidence and have been removed] **Adverse events** **Intervention 1** [Data have been designated commercial-in-confidence and have been removed] **Intervention 2** [Data have been designated commercial-in-confidence and have been removed] **Intervention 3** [Data have been designated commercial-in-confidence and have been removed] **Comparator** NA	**Authors' conclusions** [Data have been designated commercial-in-confidence and have been removed] **Comments** [Data have been designated commercial-in-confidence and have been removed]

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period [Data have been designated commercial-in-confidence and have been removed] **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Sample size calculations were not stated, however it was reported that 60 patients were planned for the study **Analysis methods** [Data have been designated commercial-in-confidence and have been removed] **Length of trial/frequency of follow-up** 16–28 weeks; not stated				
Results				
Outcome 1		**Outcome 2**		
Outcome [Data have been designated commercial-in-confidence and have been removed]		**Outcome** [Data have been designated commercial-in-confidence and have been removed]		

Parallel studies (*n* = 7)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Anhut, 1994[156] **Related publications** None **Country** Multinational **Source** Literature search **Aim** To evaluate the efficacy and safety of GBP as add-on therapy in patients with refractory partial seizures receiving one to two standard AEDs in a multicentre, double-blind, randomised placebo-controlled study **Type of publication** Full paper (final analysis) **Funding** Parke-Davis and Warner-Lambert **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 272 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (*n* = 272): 32 years; total (*n* = 272): 12–67 years **Gender** Total (*n* = 272): men = 152 (56%), women = 120 (44%) **Age at onset of seizures** Median duration of epilepsy: GBP 1200 mg/day (*n* = 52): 22 years; GBP 900 mg/day (*n* = 111): 19 years; placebo (*n* = 109):19 years **Pretrial medication** See concurrent medication **Ongoing concurrent medication** Total (*n* = 272) 1 concurrent AED: 24%; 2 concurrent AEDs: 68% Total (*n* = 272): CBZ 75%; VPA 31%; PHT 28% **Co-morbidities** Not stated	**Intervention 1** GBP; 1200 mg/day; 12 weeks No. randomised: 52 No. completed: not stated **Intervention 2** GBP; 900 mg/day; 12 weeks No. randomised: 111 No. completed: not stated **Comparator** Placebo; 12 weeks No. randomised: 109 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** GBP 1200 mg: AEs (*n* = 2); GBP 900 mg: AEs (*n* = 9), lack of efficacy (*n* = 1); placebo: AEs (*n* = 4), lack of efficacy (*n* = 2). There were also 3 withdrawals due to protocol violations or for administrative reasons (the treatment group is not specified) **Adverse events** **Intervention 1** *n* = 52 Number experiencing an AE: 33 (64%) Most frequently occurring AEs: somnolence (*n* = 7, 13.5%); dizziness (*n* = 7, 13.5%); fatigue (*n* = 6, 11.5%); nausea and/or vomiting (*n* = 2, 3.8%); ataxia (*n* = 1, 1.9%); headache (*n* = 3, 5.8%); diplopia (*n* = 2, 3.8%); increased appetite (*n* = 3, 5.8%); tremor (*n* = 4, 7.7%) **Intervention 2** *n* = 111 Number experiencing an AE: 76 (69%) Most frequently occurring AEs: somnolence (*n* = 24, 21.6%); dizziness (*n* = 23, 20.7%); fatigue (*n* = 10, 9.0%); nausea and/or	**Authors' conclusions** GBP is safe and effective in treating some patients with refractory partial seizures **Comments** After the double-blind phase patients could continue blinded treatment in a 4-week interim phase to allow collection of case report forms before the randomisation code was broken. Data collected during this phase were evaluated for safety but not included in the efficacy analysis. After the interim phase patients could continue open-label treatment for 12 weeks and those who demonstrated a response were eligible for a separate, long-term open-label study. Only the data for the double-blind phase have been extracted The authors state that study medication was introduced in a 2-day period at the beginning of the double-blind phase. This seems to be a very short titration period if this is the full titration period as implied The treatment group of three of the study withdrawals is not specified, therefore it is not possible to state accurately how many of the participants in each

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 12-week baseline phase during which patients received stable doses of 1 or 2 concurrent AEDs. Serum concentrations of these agents were not to vary more than 25% (20% for PHT) above or below the average value. Patients with a minimum of 6 partial seizures during baseline were eligible for the 12-week double-blind phase. They were randomised to: placebo, 900 mg/day GBP or 1200 mg/day GBP. All three groups received identical capsules. Study medication was introduced in a 2-day period at the beginning of the double-blind phase. The dosage of concurrent AEDs was to remain stable during the double-blind phase. Dosage changes were made only to maintain plasma concentrations within the defined range; decreasing dosage was permitted if toxicity occurred. In the event of intercurrent illness or severe AE, additional medication was allowed at the investigator's discretion. **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** A sample size of 180 patients was planned based on an estimate that 90 evaluable patients in each group would be sufficient to detect a 20% difference in responder rates at $p < 0.05$, two-sided, with a power of 80% and assuming a placebo responder rate of 15%. A group of 45 patients treated with 1200 mg/day GBP was considered sufficient for description of dose–response characteristics; no inferential statistical testing was planned for this group	**Baseline seizure frequency** Median seizure frequency: total: 10.2 (range 0.5–634.3) **Other characteristics** Seizure type: Simple partial: total (n = 272): 105 (38.6%); GBP 1200 mg/day (n = 52): 23 (44.2%); GBP 900 mg/day (n = 111): 42 (37.8%); placebo (n = 109): 40 (36.7%) Complex partial: total (n = 272): 245 (90.1%); GBP 1200 mg/day (n = 52): 48 (92.3%); GBP 900 mg/day (n = 111): 99 (89.2%); placebo (n = 109): 98 (89.9%) Partial secondarily generalised: total (n = 272): 150 (55.1%); GBP 1200 mg/day (n = 52): 31(59.6%); GBP 900 mg/day (n = 111): 61 (55.0%); placebo (n = 109): 58 (53.2%) Other: total (n = 272): 50 (18.4%); GBP 1200 mg/day (n = 52): 3 (5.8%); GBP 900 mg/day (n = 111): 28 (25.2%); placebo (n = 109): 19 (17.4%) **Inclusion/exclusion criteria** Inclusion: partial seizures; failure to respond to standard AED therapy at maximum tolerated dosages; an average of 4 clearly recognisable partial seizures/month during the 3 months before screening despite treatment with one or two currently available AEDs at a stable dosage; seizures included simple partial,		vomiting (n = 7, 6.3%); ataxia (n = 12, 10.8%); headache (n = 2, 1.8%); convulsions (n = 8, 7.2%); diplopia (n = 5, 4.5%); increased appetite (n = 3, 2.7%); tremor (n = 2, 1.8%). One death as a result of a seizure 54 days after discontinuing GBP therapy **Comparator** n = 109 Number experiencing an AE: 57 (52%) Most frequently occurring AEs: somnolence (n = 13, 11.9%); dizziness (n = 9, 8.3%); fatigue (n = 5, 4.6%); nausea and/or vomiting (n = 10, 9.2%); ataxia (n = 3, 2.8%); headache (n = 8, 7.3%); convulsions (n = 3, 2.8%); diplopia (n = 2, 1.8%); increased appetite (n = 2, 1.8%); tremor (n = 2, 1.8%)	group completed the trial. There were 21 withdrawals in total, i.e. 251 in total completed the study Data on baseline characteristics are only given for GBP and placebo groups combined, not separately Data for 245 patients were included in the evaluable-patient analysis; data for 27 patients were excluded Serum concentrations of the four most frequently used concurrent AEDs (CBZ, PHT, VPA and PB) were not influenced by treatment with GBP. Clinical laboratory assessments showed no clinically important changes, with no indication of hepatic or hematopoietic effects. Results for physical and neurological examinations, EEGs and electrocardiograms did not reflect any medically important trends The authors report that the ITT analysis agreed closely with the analysis extracted above for the evaluable population. However, the ITT analysis did not appear to use a properly defined ITT population. The authors defined the population as all patients who were randomised to treatment and received the study drug with the exception of two patients

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods Demographic data for the three treatment groups were compared by the Kruskal–Wallis test for ordinal data and a χ^2 test for categorical data. Body mass was measured by the Broca index Fisher's exact test was used to compare responder rates between treatment groups. The response ratio was analysed by ANOVA. The model included effects due to treatment, centre and treatment × centre interactions. While all 3 treatment groups were included in the analysis, a significance test was performed only for the difference between the 900 mg/day group and placebo groups, as planned *a priori*. All tests were two-sided and significant if $p < 0.05$. No statistical testing was done for percentage change since it is a monotonic function of response ratio In the ITT analysis (which included data for all patients who were randomised to treatment and received study drug), responder rate was analysed by Fisher's exact test and RR by the Wilcoxon test. For the secondary assessments, descriptive analyses were performed for RR by seizure type. Global evaluations for the three treatment groups were compared by a χ^2 test **Length of trial/frequency of follow-up** 12 weeks; not stated	complex partial, partial seizures secondarily generalised or other seizures; ≥ 12 years with a body weight of 40–110 kg; use of adequate contraception by those of childbearing potential. Exclusion: atypical absence or non-epileptic seizures; progressive structural lesions in the CNS; severe hepatic or renal disease, low white blood cell count (WBC: $<3000/mm^3$) or neutrophil counts ($<1500/mm^3$); chronic drug or alcohol abuse; use of other investigational AEDs in the previous 3 months or more than one dose of two investigational drugs in the past year; pregnant or breastfeeding women			who did not have partial seizures during the baseline and double-blind phases

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Seizure frequency; median number of seizures per 28 days during baseline and double-blind phase **Intervention 1** (*n* = 52) All partial: Baseline data: 9.8. Follow-up data: 6.8 Simple partial: Baseline data: 5.0. Follow-up data: 5.5 Complex partial: Baseline data: 6.3. Follow-up data: 4.4 Partial secondarily generalised: Baseline data: 1.3. Follow-up data: 0.6 **Intervention 2** (*n* = 111) All partial: Baseline data: 10.3. Follow-up data: 7.7 Simple partial: Baseline data: 8.3. Follow-up data: 6.5 Complex partial: Baseline data: 7.0. Follow-up data: 5.7 Partial secondarily generalised: Baseline data: 2.0. Follow-up data: 1.0 **Comparator** (*n* = 109) All partial: Baseline data: 9.3. Follow-up data: 8.1 Simple partial: Baseline data: 3.8. Follow-up data: 3.8 Complex partial: Baseline data: 7.8. Follow-up data: 7.4 Partial secondarily generalised: Baseline data: 1.0. Follow-up data: 1.0	**Outcome** Change in seizure frequency; median percentage of change in frequency of partial seizures during treatment relative to baseline **Intervention 1** Evaluable-patient analysis (*n* = 50) –17.8% (SD 62.1) **Intervention 2** Evaluable-patient analysis (*n* = 96) –21.8% (SD 53.7) **Comparator** Evaluable-patient analysis (*n* = 99) –0.3% (SD 53.8)	**Outcome** Proportion of responders; the percentage of patients with at least a 50% reduction in seizure frequency (no absolute values given) **Intervention 1** Evaluable-patient analysis (n = 50) All partial seizures: 28.0% (GBP 1200 mg vs placebo, $p = 0.008$) Simple partial seizures: 42.9% Complex partial seizures: 43.5% Secondarily generalised seizures: 45% ITT analysis All partial seizures: 27% **Intervention 2** Evaluable-patient analysis (*n* = 96) All partial seizures: 22.9% (GBP 900 mg vs placebo, $p = 0.020$) Simple partial seizures: 33.3% Complex partial seizures: 22.0% Secondarily generalised seizures: 45.5% ITT analysis All partial seizures: 22% (GBP 900 mg vs placebo, $p = 0.026$) **Comparator** Evaluable-patient analysis (*n* = 99) All partial seizures: 10.1% Simple partial seizures: 26.8% Complex partial seizures: 13.8% Secondarily generalised seizures: 33.3% ITT analysis All partial seizures: 10.1%	**Outcome** Response ratio; adjusted mean response ratio calculated from the formula (treatment – baseline)/(treatment + baseline). It compares seizure frequency during baseline and double-blind treatment. It ranges between +1 and –1. Negative values indicate a reduction in seizure frequency. **Intervention 1** Evaluable-patient analysis (*n* = 50) –0.157 (SE 0.047) (GBP 1200 mg vs placebo, $p = 0.0055$) ITT analysis –0.184 **Intervention 2** Evaluable-patient analysis (*n* = 96) –0.136 (SE 0.026) (GBP 900 mg vs placebo, $p = 0.0046$) ITT analysis –0.138 (GBP 900 mg vs placebo, $p = 0.0002$) **Comparator** Evaluable-patient analysis (*n* = 99) –0.025 (SE 0.022) ITT analysis –0.017

continued

Results	
Outcome 5	**Outcome 6**
Outcome Global evaluation; evaluation by patient or parent of patients' overall ability to perform activities of daily living	**Outcome** Global evaluation; investigator evaluation of patients' overall ability to perform activities of daily living
Intervention 1 Number evaluated by patient: GBP 1200 mg (n = 50): 49 (98.0%); Better: GBP 1200 mg: 28 (57.1%); Same: GBP 1200 mg: 19 (38.8%); Worse: GBP 1200 mg: 2 (4.1%); p = 0.034	**Intervention 1** Number evaluated by physician: GBP 1200 mg (n = 50): 48 (96.0%); Better: GBP 1200 mg: 26 (54.2%); Same: GBP 1200 mg: 21 (43.8%); Worse: GBP 1200 mg: 1 (2.1%); p = 0.002
Intervention 2 Number evaluated by patient: GBP 900 mg (n = 96): 96 (100.0%); Better: GBP 900 mg: 46 (47.9%); Same: GBP 900 mg: 47 (49.0%); Worse: GBP 900 mg: 3 (3.1%)	**Intervention 2** Number evaluated by physician: GBP 900 mg (96): 96 (100.0%); Better: GBP 900 mg: 37 (38.5%); Same: GBP 900 mg: 59 (61.5%); Worse: GBP 900 mg: 0 (0.0%)
Comparator Number evaluated by patient: placebo (n = 99): 98 (99.0%); Better: placebo: 32 (32.7%); Same: placebo: 58 (59.2%); Worse: placebo: 8 (8.2%)	**Comparator** Number evaluated by physician: placebo (n = 99): 99 (100.0%); Better: placebo: 26 (26.3%); Same: placebo: 67 (67.7%); Worse: placebo: 6 (6.1%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Crawford, 2001[131] **Related publications** None **Country** UK **Source** Literature search **Aim** To evaluate the efficacy and safety of GBP in patients with learning disabilities and resistant epilepsy, comparing the effects of GBP with LTG on efficacy, behaviour and mood **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** Not stated **Study design** Add-on therapy; new vs new; parallel trial; superiority trial **Setting** Inpatients and outpatients **Method/timing of randomisation** The medication was randomised in blocks of six. Each patient number was unique. These were assigned sequentially and this determined the	**Number of participants** 109 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** GBP (n = 39): 38 years (SD 11.1); LTG (n = 44): 33 years (SD 11.5); GBP (n = 39): 16–59 years; LTG (n = 44): 15–57 years **Gender** GBP (n = 39): men = 24 (61.5%), women = 15 (38.5%); LTG (n = 44): men = 29 (65.9%), women = 15 (34.1%) **Age at onset of seizures** Not stated **Pretrial medication** CBZ, VPA, diazepam (DZP), PHT, CZP, VGB, PB, CLB, ethosuximide, TPM and PRM **Ongoing concurrent medication** CBZ (69.9%), VPA (65.1%), DZP (13.3%), PHT (12%), CZP (10.8%), VGB (7.2%), PB (6%), CLB (3.6%), ethosuximide (2.4%), TPM (1.2%), and PRM (1.2%) **Co-morbidities** The study population were all identified as having a learning disability and to meet any level of the DSM-IV criteria of mental retardation. In addition, in terms of mobility, 39% of those randomised were either unable to walk or were only capable of	**Intervention 1** GBP; 3600 mg/day; 24 weeks No. randomised: 39 No. completed: 34 **Comparator** LTG; 400 mg/day; 24 weeks No. randomised: 44 No. completed: 35	**Withdrawals prerandomisation** Total: n = 26 (reasons for total 26, i.e. not divided by treatment group, are provided in the paper) **Withdrawals postrandomisation** GBP (n = 39): AEs (n = 3, 7.7%), other (n = 1, 2.6%), protocol violation (n = 1, 2.6%). LTG (n = 44): AEs (n = 4, 9%), carer withdrew consent (n = 1, 2.3%), other (n = 4, 9%) **Adverse events** **Intervention 1** GBP (n = 39): serious AEs (n = 4, 10%), drug-related AEs (n = 13, 33%), death (n = 1). Number of patients with AEs = 24 (62%) **Comparator** LTG (n = 44): serious AEs (n = 5, 11%), drug-related AEs (n = 11, 25%), death (n = 0). Number of patients with AEs = 22 (50%)	**Authors' conclusions** For learning disabled patients with resistant epilepsy, GBP and LTG provide safe and effective treatment, with positive benefits on behaviour. This study has shown the positive impacts of AEDs on a difficult to control population **Comments** Sample size calculations stated 100 participants in each study group to be an adequate number of participants in this study. The authors had to adjust for the lower number of participants actually enrolled in the study The maximum dose of GBP (3600 mg/day) exceeds the recommended limits (2400 mg/day) Intervention 1 dose: 3600 mg/day, mean 1749 ± 35 mg/day. Comparator dose: 400 mg/day, mean 207 ± 38 mg/day 24-week follow-up period included 14-week titration period No participants withdrew during the baseline 8-week period

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
treatment the patient would receive; after pretrial period **Details of pretrial period** There was an initial baseline period of 8 weeks. Participants were then randomised to either GBP or LTG. The dosages were increased over a titration period of up to 14 weeks to a maximum of 3600 mg/day GBP (taken in three divided doses) and 400 mg/day LTG (taken in two divided doses). For participants taking concurrent VPA the LTG dose was 200 mg/day. The treatment was then evaluated for a minimum of 10 weeks **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The protocol assumed a standard deviation of the response ratio of 0.2526, requiring 100 patients per treatment group to attain 80% power to detect a difference of 0.1 in the response ratio as a statistically significant difference ($p \leq 0.5$). As fewer than expected patients were recruited, 80% power was achieved for detection of a slightly larger difference of 0.15 **Analysis methods** All patients randomised to study treatment and who took at least one dose of study medication were used in the analysis. The frequency of	walking with supervision. In terms of dressing and feeding, 72% were unable to dress adequately without a degree of supervision and 59% required a degree of supervision for adequate feeding. 30% could not talk **Baseline seizure frequency** Median (standardised 28-day period): GBP (n = 39): 15.1 (SD 24.9); LTG (n = 42): 11.8 (SD 123.2) **Other characteristics** Patients on a stable dose of monoamine oxidase inhibitor or antidepressants were allowed to enter the study, provided that this medication was maintained at a constant dose throughout the study. Intermittent use of benzodiazepines as rescue medication, for example rectal DZP, was also permitted. Seizure type: GBP (n = 39): simple partial (n = 7, 9%), complex partial (n = 39, 49%), secondary generalised (n = 27, 34%), absence (n = 2, 3%), tonic (n = 0), other (n = 4, 5%); LTG (n = 44): simple partial (n = 9, 13%), complex partial (n = 29, 43%), secondary generalised (n = 25, 37%), absence (n = 1, 2%), tonic (n = 1, 2%), other (n = 2, 3%) **Inclusion/exclusion criteria** Inclusion: 12 years and older; of either sex; with localisation-related epilepsy which was not satisfactorily controlled by existing AEDs; taking one, two or three standard AEDs (not including GBP or LTG) but still not achieving satisfactory seizure control; a minimum of 4 seizures in each 28-day			

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
seizures was compared by analysis of variance of the response ratio Responder rates for GBP and LTG were compared using logistic regression. Group differences in the Key Carer Visual Analogue Scales were assessed using two-sampled *t*-tests, and changes from baseline were assessed using paired *t*-tests. Individual aspects and total scores from the Whelan and Speake Rating Scale and Crichton Scale were assessed non-parametrically using the Wilcoxon rank sum test and the Wilcoxon signed rank test All statistical tests were two-sided ($p < 0.05$). In considering the significance of all tests carried out on the behavioural and carer rating scales, no adjustment was made for multiple comparisons **Length of trial/frequency of follow-up** 24 weeks; not stated	period and no seizure-free 28-day period in the preceding 3 months; patients had to have a degree of learning disability and to meet any level of the DSM-IV criteria of mental retardation. Exclusion: individuals with primary generalised seizures; symptomatic generalised epilepsy of a history of non-epileptic seizures; concurrent therapy with antacids or recent participation in any clinical trial; women were ineligible 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 GBP or LTG or significant renal or hepatic dysfunction also excluded enrolment			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of seizure-free patients; the number of patients who were seizure free during the evaluation phase of the trial **Intervention 1** GBP (n = 39): 3 (7.7%) **Comparator** LTG (n = 44): 5 (11.4%)	**Outcome** Proportion of responders (at least 50% or other specified criteria); reported as the percentage of participants with at least a 50% reduction in the seizure frequency during the treatment period as compared with baseline **Intervention 1** GBP (n = 39): 50% (n = 17), 95% CI: –22.2 to 25.0, NS (GBP vs LTG). Mean reduction in seizures over the course of the study was 50.6% **Comparator** LTG max. dose 400 mg/day (n = 44): 48.6% (n = 17). Mean reduction in seizures over the course of the study was 50.8%	**Outcome** Mean response ratio; NA **Intervention 1** GBP (n = 33): –0.37 (SD 0.38), (95% CI: –0.242 to 0.234) **Comparator** LTG (n = 32): –0.37 (SD 0.49)	**Outcome** Change in functional capacity; measured using the Key Carer/Worker Visual Analogue Scale, the Crichton Royal Behavioural Rating Scale, the Challenging Behaviour (Whelan and Speake) and the Physician's Global Rating Scale **Intervention 1** GBP vs LTG: Key Carer/Worker Visual Analogue Scale: no statistically significant differences Crichton Royal Behavioural Rating Scale: a significant improvement in favour of GBP for cooperation, communication and restlessness ($p < 0.05$) Challenging Behaviour (Whelan and Speake): both drugs were similar on this scale Physician's Global Rating Scale: no statistically significant differences GBP (within-group analysis): Key Carer/Worker Visual Analogue Scale: a significant improvement in seizure severity, sleeping pattern, attention, and general health; $p < 0.05$ Crichton Royal Behavioural Rating Scale: a significant improvement for co-operation and restlessness; $p < 0.01$ Challenging Behaviour (Whelan and Speake): reduced the level of challenging behaviour as a total score over the duration of the trial Physician's Global Rating Scale: a significant improvement in seizure severity and general health ($p < 0.01$) **Comparator** LTG (within-group analysis): Key Carer/Worker Visual Analogue Scale: a significant improvement for seizure severity; $p < 0.05$ Crichton Royal Behavioural Rating Scale: no significant improvement Challenging Behaviour (Whelan and Speake): reduced the level of challenging behaviour as a total score over the duration of the trial Physician's Global Rating Scale: a significant improvement for challenging behaviour and general health ($p < 0.01$)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Lindberger, 2000[132] **Related publications** Abstract[460] **Country** Sweden **Source** Literature search **Aim** The objective was to compare the efficacy and safety of GBP and VGB as first-line add-on treatment in patients with partial epilepsy **Type of publication** Full paper (final analysis) **Funding** Parke-Davis Scandinavia **Trial ID** 945-448-001 **Study design** Add-on therapy; new vs new; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Central randomisation centre; after pretrial period **Details of pretrial period** After an 8-week retrospective or prospective baseline period patients were	**Number of participants** 102 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Median age: GBP (n = 50): 34.5 years; VGB (n = 52): 33.0 years; GBP (n = 50): 13–68 years; VGB (n = 52): 14–56 years **Gender** GBP (n = 50): men = 28 (56%), women = 22 (44%); VGB (n = 52): men = 23 (44%), women = 29 (56%) **Age at onset of seizures** Median duration of epilepsy: GBP (n = 50): 3.5 years (range, 0–36 years); VGB (n = 52): 9.5 (range, 0–43 years) **Pretrial medication** Number who tried one monotherapy: total (n = 102): 49; GBP (n = 50): 25 (50%); VGB (n = 52): 24 (46%) Number who tried multiple monotherapies: total (n = 102): 53; GBP (n = 50): 25 (50%); VGB (n = 52): 28 (54%) **Ongoing concurrent medication** Monotherapy at randomisation CBZ: total: n = 66/102;	**Intervention 1** GBP; 1800–3600 mg/day; max. 24 weeks No. randomised: 50 No. completed: 35 **Comparator** VGB; 1000–4000 mg/day; max. 24 weeks No. randomised: 52 No. completed: 44	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** It is stated that 15 GBP patients and 8 VGB patients were excluded from the per protocol analysis owing to protocol violation. There were also 7 withdrawals from each group due to AEs. It is not clear whether the withdrawals due to AEs are included as part of the per protocol violations **Adverse events** **Intervention 1** GBP: serious AEs (n = 3): status epilepticus (n = 1), pyelonephritis (n = 1), psychiatric problems (n = 1) One or more AEs of any type (n = 38, 76%) Most common AEs: tiredness, dizziness, respiratory infection, headache and diarrhoea (similar in type and frequency for the two groups) 32 GBP participants who underwent perimetry had records suitable for evaluation: no participants had clearly abnormal results; 1 had borderline findings **Comparator** VGB: serious AEs (n = 4): agitative depression (n = 1),	**Authors' conclusions** Approximately one-third of the patients in both groups became seizure free. Although no major differences were seen in terms of the improvement rate between the groups, equivalence between the groups was not found **Comments** Although the authors carried out a sample size calculation, the trial was discontinued prematurely (in response to other studies which suggested that VGB could induce visual field defects (VFDs)) and the estimated required sample size was not reached The range for duration of epilepsy started at zero, which does not seem possible given the inclusion criteria The length of treatment and length of follow-up are difficult to ascertain from this study. The authors described the primary outcome as the proportion of patients with a reduction in seizure frequency of at least 50% without AEs causing withdrawal during the 8-week evaluation period compared with baseline. The authors state that the maximum treatment period at each dosage level was 8 weeks, and that dosage changes were allowed after a 4-week period of receiving each dosage level if the

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
randomised to receive GBP or VGB as add-on treatment to their previous monotherapy provided they had at least 4 seizures during baseline and 2 or more seizures in the month before inclusion. GBP patients received 900 mg/day as an initial dosage which was titrated up during 5 days to the first maintenance dosage level of 1800 mg/day. VGB patients received 1000 mg/day as the first maintenance dosage level from day 1. The dosage could be increased stepwise to two further levels if seizures persisted (2400 and 3600 mg/day GBP; 2000 and 4000 mg/day VGB). It could be reduced if patients were seizure free but experienced intolerable side-effects (2000 mg and 3200 mg/day GBP; 1500 and 3500 mg/day VGB). The 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. Unless prohibited by adverse effects, all patients who continued to have seizures on a specific dosage level proceeded to the next level even if they had experienced a marked reduction in seizure frequency because the goal for each patient was complete seizure control. Patients with at least a 50% reduction in seizure frequency during the evaluation period could continue to receive study medication in a masked fashion until the clean file procedure **ITT analysis performed/method** Authors state yes; not stated	GBP: *n* = 32/50; VGB: *n* = 34/52 OXC: total: *n* = 13/102; GBP: *n* = 5/50; VGB: *n* = 8/52 VPA: total: *n* = 19/102; GBP: *n* = 9/50; VGB: *n* = 10/52 LTG: total: *n* = 2/102; GBP: *n* = 2/50; VGB: *n* = 0/52 CZP: total: *n* = 1/102; GBP: *n* = 1/50; VGB: *n* = 0/52 PRM: total: *n* = 1/102; GBP: *n* = 1/50; VGB: *n* = 0/52 **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: partial epilepsy; had tried no more than 2 AED monotherapy regimens; at least 4 seizures during an 8-week retrospective or prospective baseline period and 2 or more seizures during the last month before inclusion Exclusion: status epilepticus in the previous 6 months; progressive encephalopathy; progressive structural lesions in the CNS; psychosis; severe liver or renal disease; previous treatment with GBP or VGB; pregnancy or breastfeeding; treatment with PHT, antipsychotic or antidepressant drugs or antacids		weight gain (*n* = 1), mononucleosis (*n* = 1), secondary generalised seizure (*n* = 1) One or more AEs of any type (*n* = 45, *n* = 86.5%) Most common AEs: tiredness, dizziness, respiratory infection, headache and diarrhoea (similar in type and frequency for the two groups) 32 VGB participants who underwent perimetry had records suitable for evaluation: 3 participants had clearly abnormal results; 1 had borderline findings	patients had experienced seizures or intolerable side-effects. No indication is given of the proportion of patients who received each possible dosing level The 3200 and 3600 mg/day doses of GBP are above the suggested maximum of 2400 mg/day. The 3500 and 4000 mg/day doses of VGB are above the suggested maximum of 3000 mg/day A retrospective baseline was used for some participants (GBP 54%, VGB 56%) and a prospective used for others. A retrospective baseline is likely to be an unreliable method of assessing seizure frequency. It is not clear why the prospective method was used for some patients and not others or how these participants may have differed from those for whom the retrospective method was used Information on the following was obtained directly from the author: study ID, method of randomisation, source of funding Authors do not state what mean/median dose of drugs was achieved Data from per protocol population analyses for the efficacy outcomes are not

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sample size calculation The study was designed to exclude a difference of 15 percentage points in favour of VGB with respect to the difference in improvement rates. The primary statistical null hypothesis considered was that VGB is superior to GBP by at least 15 percentage points. Under the assumption of a true common improvement rate of 35%, the sample size needed to achieve a power of 80% to reject the null hypothesis testing at the 5% significance level would be 2 groups of 125 participants each. With an estimated 12% of patients being not fully evaluable, it was considered necessary to include two groups of 140 participants each **Analysis methods** Data were analysed on an ITT basis. For primary and secondary measures, two-sided 90% CIs and 95% CIs were calculated Length of trial/frequency of follow-up 24 weeks; QoL at baseline and at the end of the evaluation period				extracted here but are available in the paper Data from analyses examining the duration of epilepsy in relation to treatment response are reported in the paper (but not extracted here); duration of epilepsy did not appear to have an impact on the treatment response The authors comment that the primary outcome variable of improvement rate was a problematic one. Patients who responded at one dosage level according to the criterion of at least 50% seizure reduction but who continued to have seizures proceeded to the next dosage level. If at that higher level AEs prompted treatment withdrawal, the patient was classified as a failure according to the criteria for improvement; this was the case with 3 patients taking VGB

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of responders; the proportion of patients achieving at least a 50% reduction in seizure frequency during the 8-week evaluation phase without experiencing any side-effects causing withdrawal **Intervention 1** ITT population: GBP: *n* = 24/50 (48%) Estimated difference –0.08 (90% CI: –0.24 to 0.08) (95% CI: –0.27 to 0.12) **Comparator** VGB: *n* = 29/52 (56%)	**Outcome** Proportion of responders; the proportion of patients with at least a 50% reduction in seizure frequency irrespective of side-effects **Intervention 1** ITT population: GBP: *n* = 27/50 (54%) Estimated difference –0.10 (90% CI: –0.26 to 0.06), (95% CI: –0.29 to 0.09) **Comparator** VGB: *n* = 34/52 (65%)	**Outcome** Proportion of seizure-free patients; the proportion of seizure-free patients without side effects during the 8-week evaluation phase **Intervention 1** ITT population: GBP: *n* = 13/50 (26%) Estimated difference –0.11 (90% CI: –0.25 to 0.04) (95% CI: –0.28 to 0.07) **Comparator** VGB: *n* = 18/52 (35%)	**Outcome** Change in patient-related QoL; health-related quality of life (HRQoL) assessed by QOLIE-89 **Intervention 1** There were no significant differences between the groups in HRQoL scores in the epilepsy-targeted, cognitive, mental health and physical factors of QOLIE-89 **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Maton, 1998[128] **Related publications** NRR entry giving very brief study design details[461] **Country** UK **Source** Industry submission **Aim** To compare the efficacy, safety and QoL of treatment with GBP and VPA in patients with refractory partial seizures **Type of publication** Industry trial report **Funding** Parke-Davis **Trial ID** RR-430-00120 **Study design** Add-on therapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was an 8-week baseline	**Number of participants** 32 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 25): mean = not stated; GBP (n = 10): mean = 30.3 years (SD 7.9 years); VPA (n = 15): mean = 37.0 years (SD 12.8 years); not stated **Gender** Total (n = 25): men = 12, women = 13; GBP (n = 10): men = 4, women = 6; VPA (n = 15): men = 8, women = 7 **Age at onset of seizures** Duration of disease Total (n = 25): mean = not stated; GBP (n = 10): mean = 16.7 years (SD 10.7 years); VPA (n = 15): mean = 17.8 years (SD 12.8 years) **Pretrial medication** Total no. of participants having previously tried: AZM (n = 1); CBZ (n = 5); CLB (n = 0); CZP (n = 1); DZP (n = 1); LTG (n = 2); PB (n = 7); PHT (n = 4); PRM (n = 1); VGB (n = 1); valproic acid/sodium valproate (n = 7) Ongoing concurrent medication Total no. of participants with concurrent medications: AZM (n = 1); CBZ (n = 14), CLB (n = 2); clonazepam (n = 1); DZP (n = 0); LTG (n = 3); PB (n = 2); PHT (n = 11);	**Intervention 1** GBP; 1200, 1800 or 2400 mg/day; 14–18 weeks No. randomised: 10 No. completed: 5 **Comparator** VPA; 1000, 1500 or 2000 mg/day; 14–18 weeks No. randomised: 15 No. completed: 12	**Withdrawals prerandomisation** Total withdrawals n = 7/32 (22%) (reasons not stated) **Withdrawals postrandomisation** GBP (n = 10) Total withdrawals n = 5 (all withdrew owing to AEs: tired, teasy, dizzy (n = 1), loss of balance, shakiness, dizziness, confusion (n = 1), drunk feeling (n = 1), abdominal pain/discomfort, dizziness (n = 1), worsening hair loss, nose bleed (n = 1) VPA (n = 15) Total withdrawals n = 3 (2 were due to adverse events; flu-like feeling all over (n = 1), poor concentration, unsteady (n = 1), 1 was due to lack of compliance) **Adverse events** **Intervention 1** No. of participants experiencing possibly drug-related AEs: n = 5/10 (50%) Fatigue (n = 1/10); headache (n = 1/10); malaise (n = 0/10); viral infection (n = 0/10); nausea and/or vomiting (n = 1/10); anorexia (n = 0/10); abdominal pain (n = 1/10); ataxia (n = 1/10); confusion (n = 1/10); dizziness (n = 4/10); somnolence (n = 0/10); amnesia (n = 1/10);	**Authors' conclusions** Although there were promising trends in seizure data, no statistical conclusions can be drawn owing to poor recruitment **Comments** This study was identified through the NRR and after specifically requesting information from the manufacturer an unpublished trial report was obtained This study failed to recruit the required 120 participants and was terminated prematurely. Although collected, the QoL data were not assessed 32 participants were recruited and entered the study at baseline, but 7 failed to complete baseline and were not randomised Clinical laboratory measurements were also recorded but are not reported in this table

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
period. Patients were then randomised to receive either GBP or VPA. The dose was titrated for 2–6 weeks after which participants were treated on their maintenance dose for 12 weeks **ITT analysis performed/method** Authors state no; not applicable **Sample size calculation** The authors state that 120 participants were required, but give no further details. Only 25 participants were randomised, so the trial was terminated prematurely **Analysis methods** Response ratio was calculated and the proportion of 50% and seizure-free responders calculated and used in a regression analysis accounting for study centre. A comparison of response ratios was made using an ANOVA. Hypothesis tests were 2-sided and significance was noted at 0.05. The planned (but not carried out) analysis of QoL data was to use an ANOVA **Length of trial/frequency of follow-up** 14–18 weeks; start and end of baseline phase and 12-week maintenance phase; every 2 weeks during titration	PRM (n = 1); VGB (n = 1); valproic acid/sodium valproate (n = 0) No. of participants receiving no. of concurrent medications: 1 medication (n = 15); 2 medications (n = 9); 3 medications (n = 1) **Co-morbidities** Not stated **Baseline seizure frequency** See seizure frequency outcome data **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: ≥ 12 years; seizures classified as simple partial, complex partial or partial becoming secondarily generalised according to ILAE classification; having at least 2 seizures per 28 days despite treatment with up to 3 standard AEDs for 3 months (not including GBP or VPA); no seizure-free interval of 8 or more weeks for 12 weeks prior to study entry Exclusion: pregnant or lactating; any female of child-bearing age not using adequate method of contraception; significant renal dysfunction; known hypersensitivity to either study drug; primary generalised seizures, pseudoseizures, symptomatic generalised epilepsy or a history of non-epileptic seizures; active liver disease; concurrent therapy with monoamine oxidase inhibitors, antidepressants or antacids; participation in any concurrent medication trial or having participated in one within last 30 days		depression (n = 0/10); nervousness (n = 2/10); thinking abnormal (n = 0/10); deafness (0/10) No. of deaths: n = 0/10 (0%) No. of participants experiencing serious possibly drug-related AEs: n = 0/10 (0%) No. of withdrawals due to possibly drug-related AEs: n = 5/10 (50%) **Comparator** No. of participants experiencing possibly drug-related AEs: n = 8/15 (53%) Fatigue (n = 2/15); headache (n = 0/15); malaise (n = 1/15); viral infection (n = 1/15); nausea and/or vomiting (n = 3/15); anorexia (n = 1/15); abdominal pain (n = 1/15); ataxia (n = 1/15); confusion (n = 0/15); dizziness (n = 0/15); somnolence (n = 3/15); amnesia (n = 0/15); depression (n = 2/15); nervousness (n = 0/15); thinking abnormal (n = 1/15); deafness (1/15) No. of deaths: n = 0/15 (0%) No. of participants experiencing serious possibly drug-related AEs: n = 0/15 (0%) Withdrawals due to possibly drug-related AEs: n = 2/15 (13%)	

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of responders; responders were defined as having experienced at least a 50% reduction in seizure frequency from baseline to follow-up at 12 weeks **Intervention 1** *n* = 2/5 (40%) (per protocol) *n* = 2/10 (20%) (ITT) **Comparator** *n* = 6/12 (50%) (per protocol) *n* = 6/15 (40%) (ITT)	**Outcome** Proportion of seizure-free patients; defined as experiencing no seizures during the 12-week maintenance phase **Intervention 1** *n* = 1/5 (20%) (per protocol) *n* = 1/10 (10%) (ITT) **Comparator** *n* = 0/12 (0%) (per protocol) *n* = 0/15 (0%) (ITT)	**Outcome** Seizure frequency; defined as mean number of seizures (SD) per 28 days, grouped according to seizure type **Intervention 1** Mean reduction in seizure frequency = 70% (follow-up compared with baseline), *p*-value not stated All seizures (*n* = 5): baseline, mean = 12.8 (SD 12.3); maintenance, mean = 3.9 (SD 5.1) Simple partial (*n* = 3): baseline, mean = 0.5 (SD 0.9); maintenance, mean = 0.5 (SD 0.8) Complex partial (*n* = 2): baseline, mean = 17.2 (SD 0.9); maintenance, mean = 6.3 (SD 8.9) Secondarily generalised (*n* = 0): generalised (*n* = 4): baseline, mean = 7.0 (SD 6.1); maintenance, mean = 1.4 (SD 1.9) **Comparator** Mean reduction in seizure frequency = 42% (follow-up compared with baseline) All seizures (*n* = 12): baseline, mean = 11.7 (SD 9.1); maintenance, mean = 6.8 (SD 5.4) Simple partial (*n* = 6): baseline, mean = 10.0 (SD 8.2); maintenance, mean = 5.0 (SD 4.5) Complex partial (n = 8): baseline, mean = 5.3 (SD 4.6); maintenance, mean = 4.3 (SD 4.3) Secondarily generalised (*n* = 7): baseline, mean = 4.2 (SD 4.6); maintenance, mean = 1.6 (SD 2.4) Generalised (*n* = 3): baseline, mean = 2.6 (SD 1.7); maintenance, mean = 2.3 (SD 2.6)	**Outcome** QoL; types of assessments performed not stated **Intervention 1** No outcome data reported owing to lack of trial recruitment **Comparator** No outcome data reported owing to lack of trial recruitment

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sivenius, 1991[157] **Related publications** None **Country** Finland **Source** Literature search **Aim** To report a double-blind, placebo-controlled study of GBP as add-on therapy in partial and secondarily generalised seizures **Type of publication** Full paper (final analysis) **Funding** Warner Lambert/Parke Davis **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** During a 3-month baseline period, seizure frequency was recorded. After the baseline period, participants were randomly	**Number of participants** 45 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 39 years (SD not stated); total: 16–59 years **Gender** Total: men = 20, women = 23 **Age at onset of seizures** Duration of epilepsy: median = 23 years (range: 1–43 years) **Pretrial medication** CBZ (n = 39), CZP (n = 14), VPA (n = 8), and PHT (n = 3) **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Total: not stated; GBP 900 mg/day: median = 26.0 (in 3-month baseline period); GBP 1200 mg/day: median = 23.0 (in 3-month baseline period); placebo: median = 36.0 (in 3-month baseline period) **Other characteristics** Not stated	**Intervention 1** GBP; 900 mg/day; 3 months No. randomised: 16 No. completed: 16 **Intervention 2** GBP; 1200 mg/day; 3 months No. randomised: 9 No. completed: 9 **Comparator** Placebo; NA; 3 months No. randomised: 18 No. completed: 18	**Withdrawals prerandomisation** Two participants were lost prior to randomisation for reasons not stated **Withdrawals postrandomisation** None stated **Adverse events** **Intervention 1** GBP 900 mg/day (n = 16): drowsiness 2 (13%), blurred vision 2 (13%), headache 1 (6%), slight tremor 1 (6%), manic behaviour 1 (6%), nystagmus 1 (6%), gastric irritability 1 (6%), eczema 1 (6%) **Intervention 2** GBP 1200 mg/day (n = 9): drowsiness 4 (44%), blurred vision 1 (11%), dizziness 2 (22%), slight tremor 1 (11%), nystagmus 1 (11%), gastric irritability 1 (11%), eczema 1 (11%), miscellaneous 2 (22%) **Comparator** Placebo (n = 18): drowsiness 2 (11%), blurred vision 1 (6%), headache 2 (11%), dizziness 1 (6%), slight tremor 1 (6%), depressive behaviour 1 (6%), gastric irritability 1 (6%), eczema 1 (6%), miscellaneous 1 (6%)	**Authors' conclusions** GBP had a clear dosage-related antiepileptic effect on patients experiencing severe AED-resistant epilepsy with partial and secondarily generalised seizures and was also associated with a low frequency of side-effects **Comments** None

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
allocated to groups receiving one of two doses of GBP or of placebo for 3 months **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** The Wilcoxon signed ranks test was used to compare seizure frequency between the baseline and treatment periods in the different treatment groups. Comparison of the changes in seizure frequency between the placebo group and individual doses was made with Kruskal–Wallis one-way ANOVA **Length of trial/frequency of follow-up** 3 months; monthly	**Inclusion/exclusion criteria** Inclusion: severe epilepsy and were experiencing 4 or more seizures per month despite appropriate modification of their therapy with one or two conventional AEDs. The dosage of the current AED therapy had been stable for 3 months before screening			

Results

Outcome 1	Outcome 2
Outcome Change in seizure frequency; median change in seizure frequency during baseline period (3 months) compared with treatment period (3 months) **Intervention 1** GBP 900 mg/day (n = 16): baseline median = 26.0; treatment median = 19.5; change median = –6.5, p = 0.008; Wilcoxon's test 0.42 **Intervention 2** GBP 1200 mg/day (n = 9): baseline median = 23.0; treatment median = 10.0; change median = –13.0, p-value not stated; Wilcoxon's test 0.01 **Comparator** Placebo (n = 18): baseline median = 36.0; treatment median = 30.0; change median = –6.0, p-value not stated; Wilcoxon's test 0.26	**Outcome** Proportion of responders; responders were defined as having at least a 50% reduction in seizure frequency **Intervention 1** GBP 900 mg/day (n = 16): 2 (12%) **Intervention 2** GBP 1200 mg/day (n = 9): 3 (33%) **Comparator** Placebo (n = 18): 3 (17%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
UK Gabapentin Study Group, 1990[73] **Related publications** Abstract of preliminary analysis[335] **Country** Not stated **Source** Literature search **Aim** To assess the efficacy of 1200 mg/day GBP in a multicentre, double-blind, placebo-controlled, parallel-group study **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** Participants were screened for 3 months to establish a baseline seizure frequency and drug plasma concentrations were measured	**Number of participants** 127 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** GBP (n = 61): 30 years; placebo (n = 66): 31 years; GBP (n = 61): 15–62 years; placebo (n = 66): 14–73 years **Gender** GBP: men = 39%, women = 61%; Placebo: men = 44%, women = 56% **Age at onset of seizures** Median duration of epilepsy: GBP (n = 61): 17 years (range 2–47 years); placebo (n = 66): 19 years (range 4–38 years) **Pretrial medication** None stated **Ongoing concurrent medication** GBP (n = 61): 0 AEDs = 1, 1 AED = 20, 2 AEDs = 38, 3 AEDs = 2; placebo (n = 66): 0 AED = 0, 1 AED = 21, 2 AEDs = 43, 3 AEDs = 2 **Co-morbidities** Not stated	**Intervention 1** GBP; 1200 mg/day; 14 weeks No. randomised: 61 No. completed: 45 **Comparator** Placebo; 14 weeks No. randomised: 66 No. completed: 57	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** GBP (n = 61): lost to follow-up (n = 9), AEs (n = 7). Placebo (n = 66): lost to follow-up (n = 5), AEs (n = 4) **Adverse events** **Intervention 1** GBP (n = 61): number of patients reporting AEs = 38 (62%). Most frequent reports: somnolence (14.8%), fatigue (13.1%), dizziness (6.6%), increased weight (4.9%) **Comparator** Placebo (n = 66): number of patients reporting AEs = 27 (41%). Most frequent reports: headache (9.1%), dizziness (4.5%), somnolence (4.5%)	**Authors' conclusions** GBP is an effective additional treatment for patients, with partial epilepsy refractory to standard therapy, is fairly well tolerated and appears to have a favourable efficacy to toxicity ratio **Comments** ANOVA showed no overall centre effect, but treatment–centre interaction did occur because one centre found placebo to be superior to GBP. However, there was no indication from residual variables that the ANOVA model was inappropriate There were no significant changes in plasma concentrations of other anticonvulsants during the study. Mean and median plasma GBP concentrations were higher in responders than non-responders. When response ratio was plotted against GBP plasma concentration, results indicated increased efficacy with increased GBP plasma concentrations

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
at 12, 8 and 4 weeks prior to the treatment period. Participants then entered a 14-week treatment phase. For the first 2 weeks participants received either 1 capsule of GBP (200 mg), or a placebo capsule, 3 times daily. For the next 12 weeks this intake was doubled (i.e. GBP 1200 mg/day) **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** A sample size of 120 participants was considered sufficient to provide 80% likelihood to observe a significant difference between treatment groups, assuming a responder rate of 15% with placebo, 45% with GBP, a Type I error of 5% and a drop-out rate of 20% **Analysis methods** Distribution of baseline variables between treatment groups was compared by means of the Wilcoxon test or Fisher's exact test. Fisher's exact test (2-sided) was used to compare responder rates between treatment groups. A supplementary analysis used logistic regression with factors for treatment and centre to explore if there was a centre effect on response or an interaction between treatment and centre. The response ratio was analysed by an ANOVA model that took account of treatment, centre and treatment-by-centre interactions. The primary analysis was an ITT analysis, including all participants who received at least one dose of study medication.	**Baseline seizure frequency** Seizure frequency per 28 days: all seizures: GBP (n = 61): 13 (range 3–368); placebo (n = 66): 13 (range 1–216); secondary tonic–clonic seizures: GBP (n = 61): 5 (range 0.3–47); placebo (n = 66): 4 (range 0.3–32) **Other characteristics** 19 had simple partial seizures, 88 had complex partial seizures and 76 had SGTC seizures at screening; some patients had more than one seizure type **Inclusion/exclusion criteria** Inclusion: participants with partial epilepsy resistant to treatment with with 1 or 2 standard AEDs; 1 partial seizure per week, with or without secondary generalisation, despite adequate medication with 1 or 2 standard AEDs			

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
In reviewing participant clinical data and seizure descriptions, the authors found that a number of participants had been enrolled who had a high probability of having partial epilepsy or symptomatic generalised epilepsy. A second analysis was then conducted, excluding data for participants who had any of the following: partial seizures, localised cerebral pathology on imaging or an identified aetiology consistent with partial epilepsy. This evaluable-participant analysis thus included only patients with probable idiopathic generalised epilepsy **Length of trial/frequency of follow-up** 14 weeks; seizure frequency, AEs, routine biochemical and haematological investigations and plasma concentrations of GBP and other AEDs monitored at 0, 2, 6, 10 and 14 weeks. Participants underwent a full clinical and neurological examination and EEG at weeks 0 and 14				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**		
Outcome Change in seizure frequency; the median percentage change in partial seizure frequency from baseline **Intervention 1** GBP (n = 52): –29.2% In both GBP and placebo groups the median reduction in seizure frequency was greater for patients in whom partial seizures did not show any secondary generalisation **Comparator** Placebo (n = 61): –12.5%	**Outcome** Proportion of responders; the percentage of participants with at least a 50% reduction in the frequency of partial seizures during the treatment period as compared with baseline **Intervention 1** GBP vs placebo: GBP (n = 52): 23%, p = 0.049 **Comparator** Placebo (n = 61): 9%	**Outcome** Response ratio; mean adjusted response ratio **Intervention 1** GBP vs placebo: GBP (n = 52): –0.192, p = 0.0056 **Comparator** Placebo (n = 61): –0.060		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
US Gabapentin Study Group No.5, 1993[138] **Related publications** None **Country** USA **Source** Literature search **Aim** To define the safety, efficacy and dose–response characteristics of GBP administered as add-on therapy in 306 patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** During a 12-week baseline period, serum concentrations of AEDs were monitored for	**Number of participants** 306 **Type of epilepsy** Refractory **Type of seizures** Combination of partial **Mean age/age range** Total (n = 306): 35 years (SD not stated); GBP 600 mg/day (n = 53): 34; GBP 1200 mg/day (n = 101): 35; GBP 1800 mg/day (n = 54): 35; comparator (n = 98): 34; total (n = 306): 16–70 years; GBP 600 mg/day (n = 53): 16–67; GBP 1200 mg/day (n = 101): 19–65; GBP 1800 mg/day (n = 54): 18–70; comparator (n = 98): 17–66 **Gender** Total (n = 306): men = 202 (66%), women = 104 (34%); GBP 600 mg/day (n = 53): men = 36 (68%), women = 17 (32%); GBP 1200 mg/day (n = 101): men = 60 (59%), women = 41 (41%); GBP 1800 mg/day (n = 54): men = 37 (69%), women = 17 (31%); comparator (n = 98): men = 69 (70%), women = 29 (30%) **Age at onset of seizures** Duration of epilepsy (years): total (n = 306): 21 years (range 1–49 years); GBP 600 mg/day (n = 53): 20 years (range 3–36 years); GBP 1200 mg/day (n = 101): 21 years (range	**Intervention 1** GBP; 600 mg/day; 12 weeks No. randomised: 53 No. completed: 49 **Intervention 2** GBP; 1200 mg/day; 12 weeks No. randomised: 101 No. completed: 91 **Intervention 3** GBP; 1800 mg/day; 12 weeks No. randomised: 54 No. completed: 53 **Comparator** Placebo; 12 weeks No. randomised: 98 No. completed: 95	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Number excluded from analysis: 18. Participants who had a period of more than 14 consecutive days without study drug during the double-blind phase or who had inadequate recording of seizures. Seven (3%) of the 208 patients who received GBP and one (1%) of the 98 patients who received placebo withdrew owing to AEs. Three patients receiving GBP 600 mg/day withdrew: one due to myoclonic jerking, one due to tiredness, asthma and tinnitus and one due to urinary frequency. Two patients in the 1200 mg/day treatment group withdrew: one due to agitation, warm feeling, drunk feeling and slurred speech and the other with drowsiness and poor concentration. Two patients in the 1800 mg/day treatment group withdrew: one patient developed a left hemiparesis and CT subsequently revealed a new infarct in the right caudate lobe; the second patient withdrew following clinical laboratory abnormalities which returned to normal following a transurethral prostatectomy. One patient receiving placebo withdrew owing to dyspnea and numbness and tingling of the extremities	**Authors' conclusions** GBP'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 **Comments** The authors state that only participants likely to complete the study were enrolled Dosages of concurrent AEDs were to be maintained as administered in baseline; however, dosages could be decreased if required due to toxicity Intervention 1 at 600 mg/day is less than the usual range of 900–1200 mg/day Dosages were administered over 2 or 3 days from 300 or 600 mg/day on the first day up to 600, 1200 or 1800 mg/day in three divided doses

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
stability. Baseline seizure frequency was determined from a daily seizure diary kept by each patient. Double-blind phase (12 weeks): patients having a minimum of six partial seizures during the baseline period were randomly assigned to receive GBP at one of three doses (600, 1200 or 1800 mg/day) or placebo, in addition to their previously prescribed AEDs **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** A sample size of 180 patients, with 90 evaluable patients in both the GBP 1200 mg/day and placebo treatment groups, was estimated to have an 80% likelihood of having a 20% difference in responder rates detected (at $p < 0.05$, two-sided), assuming a placebo response of 15%. Sample sizes of 45 patients or more were considered sufficient to test statistical significance of dose–response data in the treatment groups receiving 600 and 1800 mg/day of GBP **Analysis methods** The protocol specified 1200 mg/day as the dosage to be compared with placebo in statistical testing of results for response ratio and responder rate. Supplementary statistical analyses not called for in the protocol were performed for the 600 and 1800 mg/day treatment groups. Response ratio was analysed by an ANOVA model that included effects due to treatment, centre and treatment × centre interaction. Responder rate was analysed	3–45 years); GBP 1800 mg/day ($n = 54$): 21 years (range 1–41 years); comparator ($n = 98$): 22 years (range 2–49 years) **Pretrial medication** Not stated **Ongoing concurrent medication** Number taking one concurrent AED = 113/306 (36.9%); number taking two concurrent AEDs = 192/306 (62.7%); number taking three concurrent AEDs: 1/306 (0.3%) **Co-morbidities** Not stated **Baseline seizure frequency** Total ($n = 306$): mean 36.3, median 10.8, range 2.0–1092.7; GBP 600 mg/day ($n = 53$): mean 21.7, median 10.0, range 2.0–271.7; GBP 1200 mg/day ($n = 101$): mean 51.7, median 11.0, range 2.3–1092.7; GBP 1800 mg/day ($n = 54$): mean 31.5, median 12.7, range 3.7–207.8; comparator ($n = 98$): mean 31.1, median 10.7, range 2.3–455.0 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: males and females, aged ≥ 16 years, with documented partial seizures refractory to treatment taking currently available AEDs. Participants had to have an average of		**Adverse events** **Intervention 1** Any AE with a frequency of at least 10% in any treatment group GBP 600 mg ($n = 53$): 46 (86.8%); somnolence 4 (7.5%), dizziness 13 (24.5%), ataxia 6 (11.3%), nystagmus 5 (9.4%), headache 10 (18.9%), tremor 4 (7.5%), fatigue 6 (11.3%), rhinitis 4 (7.5%), diplopia 5 (9.4%), nausea and/or vomiting 7 (13.2%) **Intervention 2** GBP 1200 mg ($n = 101$): 89 (88.1%); somnolence 36 (35.6%); dizziness 25 (24.8%); ataxia 26 (25.7%); nystagmus 17 (16.8%); headache 9 (8.9%); tremor 15 (14.9%); fatigue 11 (10.9%); rhinitis 11 (10.9%); diplopia 11 (10.9%); nausea and/or vomiting 6 (5.9%) **Intervention 3** GBP 1800 mg ($n = 54$): 49 (90.7%); somnolence 11 (20.4%); dizziness 10 (18.5%); ataxia 10 (18.5%); nystagmus 9 (16.7%); headache 11 (20.4%); tremor 7 (13.0%); fatigue 7 (13.0%); rhinitis 7 (13.0%); diplopia 2 (3.7%); nausea and/or vomiting 5 (9.3%) **Comparator** Placebo ($n = 98$): 71 (72.4%); somnolence 12 (12.2%); dizziness 9 (9.2%); ataxia 11 (11.2%);	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
using results for response ratio and Jonckhere's non-parametric test for trend, assuming the null hypothesis (0 mg = 600 mg = 1200 mg = 1800 mg) against the alternative hypothesis (0 mg ≥ 600 mg ≥ 1200 mg ≥ 1800 mg), where at least one of the inequalities is strict. Subjective global evaluations were compared using a χ^2 test **Length of trial/frequency of follow-up** 12 weeks; in the 12-week double-blind phase, physical and neurological examinations, determination of AED serum concentrations and clinical laboratory tests were performed at weeks 0, 2, 4, 8, and 12	4 partial seizures per month for the 3 months prior to baseline, while taking 1 or 2 AEDs at stable dosages. Females were not pregnant or nursing, and those of child-bearing potential used a reliable method of birth control and were periodically tested for pregnancy Exclusion: participants with atypical absence seizures or non-epileptic seizures; progressive structural lesion in the CNS or a progressive encephalopathy; severe liver or kidney insufficiency, a WBC count below 3000/mm^3 and neutrophil count below 1500/mm^3; receipt of other investigational AEDs within the previous 3 months, or more than 1 dose of two investigational drugs in the previous year; chronic alcohol or drug abuse within the previous 3 years		nystagmus 13 (13.3%); headache 12 (12.2%); tremor 9 (9.2%); fatigue 7 (7.1%); rhinitis 10 (10.2%); diplopia 4 (4.1%); nausea and/or vomiting 9 (9.2%)	

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; the reduction in the number of seizures per 28 days **Intervention 1** Seizure reduction (adjusted mean response ratio): –0.151 (95% CI: –0.218 to –0.035), $p = 0.007$, median –0.138 **Intervention 2** Seizure reduction (adjusted mean response ratio): –0.118 (95% CI: –0.174 to –0.013), $p = 0.023$, median –0.111	**Outcome** Proportion of responders; responders were defined as having at least a 50% reduction in number of seizures from baseline to end of treatment. Percentage values and not absolute numbers were reported **Intervention 1** 18.4%, $p = 0.103$ **Intervention 2** 17.6%, $p = 0.080$	**Outcome** Change in seizure frequency; median percentage change in the number of seizures per 28 days **Intervention 1** –24.3% **Intervention 2** –20.0% **Intervention 3** –31.9%	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; independent assessment by participant and physician of participant's ability to perform activities of daily living at the end of double-blind treatment as compared with baseline **Intervention 1** Evaluations by patient ($n = 48$): better, 44%; same, 54%; worse, 2%; $p = 0.179$ Evaluations by physician ($n = 48$): better, 40%; same, 58%; worse, 2%; $p = 0.378$

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Intervention 3 Seizure reduction (adjusted mean response ratio): –0.233 (95% CI: –0.299 to –0.118), $p < 0.001$, median –0.190 **Comparator** Seizure reduction (adjusted mean response ratio): –0.025, median –0.030	**Intervention 3** 26.4%, $p = 0.007$ **Comparator** 8.4%	**Comparator** –5.9%	**Intervention 2** Evaluations by patient ($n = 90$): better, 42%; same, 50%; worse, 8%; $p = 0.179$ Evaluations by physician ($n = 90$): better, 36%; same, 61%; worse, 3%; $p = 0.378$ **Intervention 3** Evaluations by patient ($n = 52$): better, 46%; same, 52%; worse, 2%; $p = 0.179$ Evaluations by physician ($n = 52$): better, 37%; same, 62%; worse, 2%; $p = 0.378$ **Comparator** Evaluations by patient ($n = 93$): better, 33%; same, 65%; worse, 2%; $p = 0.179$ Evaluations by physician ($n = 95$): better, 24%; same, 75%; worse, 1%; $p = 0.378$

Gabapentin (unlicensed use)

Crossover studies (n = 0)
Parallel studies (n = 4)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Brodie, 2002[93] **Related publications** Abstract[330] **Country** Multinational **Source** Literature search **Aim** To prove non-inferiority of GBP compared to LTG with respect to time to exit **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** 945-212 **Study design** Monotherapy; new vs new; parallel trial; non-inferiority trial **Setting** Not stated **Method/timing of randomisation** Computerised (stratified by centre); after enrolment	**Number of participants** 315 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** [Data have been designated commercial-in-confidence and have been removed] **Gender** [Data have been designated commercial-in-confidence and have been removed] **Age at onset of seizures** [Data have been designated commercial-in-confidence and have been removed] **Pretrial medication** [Data have been designated commercial-in-confidence and have been removed] **Ongoing concurrent medication** [Data have been designated commercial-in-confidence and have been removed]	**Intervention 1** GBP; 1800–3600 mg/day; 30 weeks [Data have been designated commercial-in-confidence and have been removed] **Comparator** LTG; 100–300 mg/day; 30 weeks [Data have been designated commercial-in-confidence and have been removed]	**Withdrawals prerandomisation** [Data have been designated commercial-in-confidence and have been removed] **Withdrawals postrandomisation** [Data have been designated commercial-in-confidence and have been removed] **Adverse events** **Intervention 1** [Data have been designated commercial-in-confidence and have been removed] **Comparator** [Data have been designated commercial-in-confidence and have been removed]	**Authors' conclusions** [Data have been designated commercial-in-confidence and have been removed] **Comments** [Data have been designated commercial-in-confidence and have been removed]

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period [Data have been designated commercial-in-confidence and have been removed] **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** [Data have been designated commercial-in-confidence and have been removed] **Analysis methods** [Data have been designated commercial-in-confidence and have been removed] **Length of trial/frequency of follow-up** [Data have been designated commercial-in-confidence and have been removed]	**Co-morbidities** [Data have been designated commercial-in-confidence and have been removed] **Baseline seizure frequency** [Data have been designated commercial-in-confidence and have been removed] **Other characteristics** [Data have been designated commercial-in-confidence and have been removed] **Inclusion/exclusion criteria** [Data have been designated commercial-in-confidence and have been removed]			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome [Data have been designated commercial-in-confidence and have been removed]	**Outcome** [Data have been designated commercial-in-confidence and have been removed]	**Outcome** [Data have been designated commercial-in-confidence and have been removed]	**Outcome** [Data have been designated commercial-in-confidence and have been removed]
Intervention 1 [Data have been designated commercial-in-confidence and have been removed]	**Intervention 1** [Data have been designated commercial-in-confidence and have been removed]	**Intervention 1** [Data have been designated commercial-in-confidence and have been removed]	**Intervention 1** [Data have been designated commercial-in-confidence and have been removed]
Comparator [Data have been designated commercial-in-confidence and have been removed]	**Comparator** [Data have been designated commercial-in-confidence and have been removed]	**Comparator** [Data have been designated commercial-in-confidence and have been removed]	**Comparator** [Data have been designated commercial-in-confidence and have been removed]

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Chadwick, 1996[74] **Related publications** Abstract[331] **Country** Multinational **Source** Literature search **Aim** To assess the safety and efficacy of 1200 mg/day GBP as adjunctive therapy in patients with refractory generalised epilepsy **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after enrolment **Details of pretrial period** Participants were randomised at screening and entered a 12-week baseline observation phase during which they received their prescribed regimens of standard AEDs	**Number of participants** 129 **Type of epilepsy** Refractory **Type of seizures** Generalised onset **Mean age/age range** ITT population (n = 129): GBP 1200 mg/day (n = 58): 30 years; placebo (n = 71): 29 years. Evaluable population (n = 64): GBP 1200 mg/day (n = 28): 30 years; placebo (n = 36): 30 years. ITT population (n = 129): GBP (n = 58): 16–62 years; placebo (n = 71): 13–61 years. Evaluable population (n = 64): GBP 1200 mg/day (n = 28): 17–60; placebo (n = 36): 13–61 years **Gender** ITT population (n = 129): GBP (n = 58): men = 27 (46.6%), women = 31 (53.4%); placebo (n = 71): men = 28 (39.4%), women = 43 (60.6%). Evaluable population (n = 64): GBP (n = 28): men = 10 (35.7%), women = 18 (64.3%); placebo (n = 36): men = 14 (38.9%), women = 22 (61.1%) **Age at onset of seizures** Duration of epilepsy, ITT population (n = 129): GBP (n = 58): 22 years (range 2–57); placebo (n = 71): 20 years (range 3–42).	**Intervention 1** GBP; 1200 mg/day; 20–24 weeks No. randomised: 58 No. completed: 54 **Comparator** Placebo; NA; 20–24 weeks No. randomised: 71 No. completed: 65	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** ITT population: GBP (n = 58): lost to follow-up (n = 0), lack of efficacy (n = 1), AE (n = 1), death (n = 1), lack of compliance (n = 1); placebo (n = 71): lost to follow-up (n = 1), lack of efficacy (n = 0), AE (n = 5), death (n = 0), lack of compliance (n = 0) **Adverse events** **Intervention 1** ITT population: GBP (n = 58): number of patients with AEs = 39 (67.2%), number of total reports = 101, number of deaths = 1. Most frequent AEs (events reported for ≥3 patients in either treatment group): somnolence 7 (12.1%), fatigue 6 (10.3%), dizziness 6 (10.3%), convulsions 5 (8.6%), ataxia 4 (6.9%), weight increase 4 (6.9%), nausea and/or vomiting 4 (6.9%), emotional lability 4 (6.9%), amblyopia 3 (5.2%), rash 3 (5.2%), thrombocytopenia 3 (5.2%), headache 2 (3.4%) **Comparator** ITT population: placebo (n = 71): number of patients with AEs = 40 (56.3%), number of total reports = 95, number of deaths = 0.	**Authors' conclusions** The results of this study show a trend toward an effect of GBP in reducing the frequency of GTC seizures and suggest that further exploration of high-dose GBP in generalised epilepsy is warranted **Comments** This study uses GBP for primary generalised seizures, which is not licensed Information on funding and methods of randomisation was obtained from authors directly

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Study medication was added to existing therapies during a 14-week efficacy assessment phase, which comprised a 2-week drug titration period (600 mg/day GBP or placebo) and 12 weeks of treatment at full dose (1200 mg/day GBP or placebo) Following the efficacy assessment phase, blinded treatment was continued for a further 6–10 weeks during the interim phase, to allow collection of case report forms before the treatment code was broken for individual participants **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The planned sample size of 120 randomised patients was considered sufficient to provide 80% power to detect a difference between treatments, assuming a responder rate of 15% with placebo, 45% with GBP and a drop-out rate of 20% **Analysis methods** All statistical testing was 2-sided, and differences between treatment groups were considered significant if $p < 0.05$. Response ratio for GTC seizures was analysed by an ANOVA with treatment, centre and treatment-by-centre interaction in the model. Fisher's extract test (2-sided) was used to compare responder rates for GTC seizures between treatment groups. The primary analysis was an ITT analysis, including all participants who received at least one dose of study medication.	Duration of epilepsy, evaluable population ($n = 64$): GBP ($n = 28$): 17 years (range 4–57); placebo ($n = 36$): 20 years (range 3–36) **Pretrial medication** ITT population ($n = 129$): VPA (71%), CBZ (55%), PHT (33%). CBZ/VPA was the most frequently used combination, taken by 25% of participants. Benzodiazepines in combination with other drugs was taken by 24% of participants. Characteristics were similar in the evaluable population ($n = 64$) **Ongoing concurrent medication** ITT population ($n = 129$): GBP ($n = 58$): 0 AEDs = 0 (0.0%), 1 AED = 11 (19.0%), 2 AEDs = 36 (62.1%), 3 AEDs = 11 (19.0%), 4 AEDs = 0 (0.0%); placebo ($n = 71$): 0 AEDs = 1 (1.4%), 1 AED = 15 (21.1%), 2 AEDs = 37 (52.1%), 3 AEDs = 15 (21.1%), 4 AEDs = 3 (4.2%). Evaluable population ($n = 64$): GBP ($n = 28$): 0 AEDs = 0 (0.0%), 1 AED = 7 (25.0%), 2 AED = 19 (67.9%), 3 AEDs = 2 (7.1%), 4 AEDs = 0 (0.0%); placebo ($n = 36$): 0 AEDs = 1 (2.8%), 1 AED = 9 (25.0%), 2 AEDs = 18 (50.0%), 3 AEDs = 7 (19.4%), 4 AEDs = 1 (2.8%) **Co-morbidities** Not stated		Most frequent AEs (events reported for ≥3 patients in either treatment group): somnolence 3 (4.2%), fatigue 4 (5.6%), dizziness 3 (4.2%), convulsions 8 (11.3%), ataxia 5 (7.0%), weight increase 5 (7.0%), nausea and/or vomiting 4 (5.6%), emotional lability 3 (4.2%), amblyopia 2 (2.8%), rash 2 (2.8%), thrombocytopenia 0 (0.0%), headache 6 (8.5%)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
In reviewing participant clinical data and seizure descriptions, the authors found that a number of participants had been enrolled who had a high probability of having partial epilepsy or symptomatic generalised epilepsy. A second analysis was then conducted, excluding data for participants who had any of the following: partial seizures, localised cerebral pathology on imaging or an identified aetiology consistent with partial epilesy. This evaluable-participant analysis therefore included only patients with probable idiopathic generalised epilepsy **Length of trial/frequency of follow-up** 20–24 weeks; not stated	**Baseline seizure frequency** ITT baseline GTC seizure frequency per 28 days (n = 129): GBP (n = 58): n = 40, mean = 7.4, median = 3.9, range = 0–54.3; placebo (n = 71): n = 57, mean = 7.3, median = 3.3, range = 0–103.3. Evaluable baseline GTC seizure frequency per 28 days (n = 64): GBP (n = 28): n = 17, mean = 4.8, median = 3.7, range = 0–18.3; placebo (n = 36): n = 28, mean = 4.7, median = 2.2, range = 0–32.7 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: ≥ 12 years, with medically uncontrolled generalised seizures, with a min. of 1 generalised seizure per week despite treatment with 1 or 2 standard AEDs, not including benzodiazepines. Dosages of standard AEDs were held constant for 3 months prior to the baseline phase			

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Change in seizure frequency; median percentage change in the number of GTC seizures occurring per 28 days of observation, compared between the 12-week baseline and the 14-week treatment periods. (Negative values indicate a reduction and positive values indicate an increase in seizure frequency from baseline) **Intervention 1** ITT population: GBP (n = 39): median change –29.3% Evaluable population: GBP 1200 mg/day (n = 16): –41.9% **Comparator** ITT population: placebo (n = 53): –15.2% Evaluable population: placebo (n = 25): –15.2	**Outcome** Proportion of responders; responders were defined as having at least a 50% reduction in seizure frequency during the treatment period as compared with baseline **Intervention 1** ITT population: GBP (n = 40): 27.5% (11/40), p = 0.317 (GBP vs placebo) Evaluable population: GBP (n = 17): 41.2% (7/17), p = 0.072 (GBP vs placebo) **Comparator** ITT population: placebo (n = 57): 17.5% (10/57) Evaluable population: placebo (n = 28): 14.3% (4/28)	**Outcome** Response ratio; response ratio for GTC seizures. (Negative values indicate a reduction and positive values indicate an increase in seizure frequency from baseline) **Intervention 1** ITT population: GBP (n = 40): mean = –0.155 (SEM 0.066), adjusted mean (ANOVA with treatment-by-centre interaction) = –0.181, p = 0.169 (GBP vs placebo). Evaluable population: GBP (n = 17): mean = –0.182 (SEM 0.126), adjusted mean (ANOVA with treatment × centre interaction) = –0.182, p = 0.2496 (GBP vs placebo) **Comparator** ITT population: placebo (n = 57): mean = –0.057 (SEM 0.061), adjusted mean = –0.034 Evaluable population: placebo (n = 28): mean = 0.002 (SEM 0.096), adjusted mean = 0.002

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Chadwick, 1998[250] **Related publications** Abstract;[332] abstract[333] **Country** Multinational **Source** Literature search **Aim** GBP is widely approved as add-on therapy for epilepsy treatment for partial seizures with and without secondary generalisation. To investigate the efficacy of GBP administered as monotherapy in patients with newly diagnosed epilepsy, a randomised double-blind trial was performed **Type of publication** Full paper (final analysis) **Funding** Parke-Davis **Trial ID** Study Group 945-77 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Randomisation schedule using blocks of 4 and 8; after enrolment	**Number of participants** 292 **Type of epilepsy** Newly diagnosed **Type of seizures** Partial onset **Mean age/age range** GBP (300 mg) (n = 72): 37 years (SD 17.3); GBP (900 mg) (n = 72): 34 years (SD 16.0); GBP (1800 mg) (n = 74): 37 years (SD 16.9); CBZ (n = 74): 34 years (SD 16.4); GBP (300 mg) (n = 72): 12–83 years; GBP (600 mg) (n = 72): 15–73 years; GBP (1800 mg) (n = 74): 12–86 years; CBZ (n = 74): 13–72 years **Gender** GBP (300 mg) (n = 72): men = 40, women = 32; GBP (600 mg) (n = 72): men = 35, women = 37; GBP (1800 mg) (n = 74): men = 41, women = 33; CBZ (n = 74): men = 41, women = 33 **Age at onset of seizures** Duration of epilepsy GBP (300 mg) (n = 72): mean = 1.0 years (SD 2.2), range = 0.0–14.4 years; GBP (600 mg) (n = 72): mean = 0.6 years (SD 1.0), range = 0.0–4.5 years; GBP (1800 mg) (n = 74): mean = 1.5 years (SD 4.5), range = 0.0–28.2 years; CBZ (n = 74): mean = 1.3 years (SD 2.3), range = 0.0–13.5 years	**Intervention 1** GBP; 300 mg/day; 24 weeks No. randomised: 72 No. completed: 18 **Intervention 2** GBP; 900 mg/day; 24 weeks No. randomised: 72 No. completed: 28 **Intervention 3** GBP; 1800 mg/day; 24 weeks No. randomised: 74 No. completed: 28 **Comparator** CBZ; 600 mg/day; 24 weeks No. randomised: 74 No. completed: 27	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** GBP (300 mg): exit event (n = 45), non-compliance (n = 4), other/administrative (n = 5); GBP (900 mg): exit event (n = 29), AE (n = 3), non-compliance (n = 8), other/administrative (n = 4); GBP (1800 mg): exit event (n = 32), AE (n = 10), non-compliance (n = 4); CBZ: exit event (n = 22), AE (n = 18); non-compliance (n = 5), other/administrative (n = 2) **Adverse events** **Intervention 1** AEs occurring in at least 5 GBP patients GBP (300 mg) (n = 72): dizziness (n = 5), headache (n = 10), fatigue (n = 9), nausea/vomiting (n = 4), somnolence (n = 2), viral infection (n = 1), abdominal pain (n = 3), nervousness (n = 1), weight increase (n = 4), rhinitis (n = 2), bronchitis (n = 2), paraesthesia (n = 2), pharyngitis (n = 1) **Intervention 2** GBP (900 mg) (n = 72): dizziness (n = 11), headache (n = 10), fatigue (n = 9), nausea/vomiting (n = 5), somnolence (n = 5), viral infection (n = 5), abdominal pain	**Authors' conclusions** GBP at 900 or 1800 mg/day is effective and safe as monotherapy for patients with newly diagnosed partial epilepsy **Comments** Length of follow-up and treatment does not include the titration period The CBZ dose was slightly below the usual recommended dose, although the authors note that it was agreed by all the investigators as an appropriate dose for patients with newly diagnosed epilepsy. The authors note that GBP is a subtherapeutic dose, which they say was chosen as comparator rather than placebo Time to exit was longer for patients who received 1800 or 900 mg/day GBP than for patients who received 300 mg/day (p = 0.0395, 0.0175, respectively). Kaplain–Meier curves presented but no further data reported

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Patients were randomised to receive one of three masked doses of GBP (300, 900 or 1800 mg/day), which were titrated over 7 days, or open-label CBZ (600 mg/day), which was titrated over 21 days. The 300-mg dose of GBP was chosen as comparator rather than placebo for safety and ethical reasons. Titration was followed by a 24-week maintenance period. Participants were required to exit the study if they experienced any of the following events during the 24-week maintenance period: one GTC seizure; a total of 3 simple or complex partial seizures; status epilepticus; lack of efficacy, i.e. new seizure types that the investigator considered severe enough to warrant early withdrawal **ITT analysis performed/method** Authors state yes; censoring for time to event data **Sample size calculation** Sample size was based on the expectation that AED therapy may provide long-term remission in 60–70% of patients with newly diagnosed epilepsy and 26% using subtherapeutic doses. Therefore, it was estimated that the completion rate would be 30% for GBP 300 mg/day and 70% for GBP 1800 mg/day. Sixty evaluable participants per dosage group were considered sufficient to provide 95% power to detect a difference between these two dosage groups at the 0.05% level. Recruitment was aimed at 75 participants per group	**Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: newly diagnosed patients with partial epilepsy; AED therapy naive or received fewer than 2 weeks of AED therapy discontinued before study entry; history of epilepsy in remission for at least 2 years without AED treatment but experiencing a recurrence of seizures; at least 2 unprovoked reliably evaluated and classified partial seizures or GTC seizures in the previous 6 months; 12 years or older; weighing between 40 and 110 kg; for women of childbearing potential, not lactating, a negative pregnancy test at screening and use of a reliable contraceptive method. Exclusion criteria: idiopathic generalised epilepsy; status epilepticus; progressive encephalopathy or findings suggesting a progressive structural lesion in the CNS; investigational drug in the past		(*n* = 3), nervousness (*n* = 3), weight increase (*n* = 2), increased appetite (*n* = 4), rhinitis (*n* = 4), bronchitis (*n* = 2), paresthesia (*n* = 2), pharyngitis (*n* = 1) **Intervention 3** GBP (1800 mg) (*n* = 74): dizziness (*n* = 11), headache (*n* = 10), fatigue (*n* = 6), nausea/vomiting (*n* = 6), somnolence (*n* = 5), viral infection (*n* = 4), abdominal pain (*n* = 4), nervousness (*n* = 5), weight increase (*n* = 2), increased appetite (*n* = 4), rhinitis (*n* = 1), bronchitis (*n* = 2), paraesthesia (*n* = 1), pharyngitis (*n* = 3) **Comparator** CBZ (*n* = 74): dizziness (*n* = 10), headache (*n* = 10), fatigue (*n* = 22), nausea/vomiting (*n* = 9), somnolence (*n* = 10), viral infection (*n* = 4), abdominal pain (*n* = 1), weight increase (*n* = 1), increased appetite (*n* = 2), rhinitis (*n* = 3), paraesthesia (*n* = 1), pharyngitis (*n* = 2)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods The primary efficacy variable was time to exit event. This analysis used Kaplan–Meier product limit estimates with time to exit as the dependent variable by treatment group strata. Data from patients who completed the evaluation phase or withdrew for reasons other than an exit event were statistically censored. Homogeneity between the 3 GBP groups was evaluated using the Wilcoxon test followed by pairwise comparisons ($p = 0.0475$). Secondary efficacy analysis (completion rate, exit event rate, AE withdrawal rate, and exit plus AE withdrawal rate) used the Cochran–Mantel–Haenzel χ^2 test adjusting for centre. To compare CBZ and GBP treatment groups, time to exit was analysed using Kaplan–Meier survival estimates. In an *ad hoc* analysis the 95% CIs were calculated for each group for efficacy variables with a 20% difference between treatments used as the reference for equivalence **Length of trial/frequency of follow-up** 24 weeks; 24 weeks	3 months; contraindication for CBZ; a medical or psychiatric condition or disease that could affect study outcome			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of patients completing treatment; patients were defined as completing when they had attended the end of evaluation phase in week-24 of the evaluation phase **Intervention 1** GBP (300 mg) (n = 72): n = 18 % difference (CBZ vs GBP 300 mg): 11.5 (95% CI: –3.4 to 26.3) **Intervention 2** GBP (900 mg) (n = 72): n = 28 % difference (CBZ vs GBP 900 mg): –2.4 (95% CI: –18.1 to 13.3) **Intervention 3** GBP (1800 mg (n = 74): n = 28 % difference (CBZ vs GBP 1800 mg): –1.4 (95% CI: –16.9 to 14.2) **Comparator** CBZ (n = 74): n = 27	**Outcome** Exit/withdrawal rate; a patient was deemed to have exited a study if they had one of the following: one GTC seizure; a total of 3 SPSs or CPSs seizures; status epilepticus; or new seizure types considered severe enough to warrant withdrawal during maintenance period **Intervention 1** GBP (300 mg) (n = 72): n = 45 % difference (CBZ vs GBP 300 mg): –32.8 (95% CI: –48.1 to –17.5) **Intervention 2** GBP (900 mg) (n = 72): n = 29 % difference (CBZ vs GBP 900 mg): –10.5 (95% CI: –25.9 to 4.8) **Intervention 3** GBP (1800 mg (n = 74): n = 32 % difference (CBZ vs GBP 1800 mg): –13.5 (95% CI: –28.9 to 1.8) **Comparator** CBZ (n = 74): n = 22	**Outcome** Exit/withdrawal rate; due to AEs **Intervention 1** GBP (300 mg) (n = 72): n = 0 % difference (CBZ vs GBP 300 mg): 24.3 (95% CI: 14.5 to 34.1) **Intervention 2** GBP (900 mg) (n = 72): n = 3 % difference (CBZ vs GBP 900 mg): 20.2 (95% CI: 9.3 to 31.0) **Intervention 3** GBP (1800 mg (n = 74): n = 10 % difference (CBZ vs GBP 1800 mg): 10.8 (95% CI: –1.7 to 23.3) **Comparator** CBZ (n = 74): n = 18	**Outcome** Exit/withdrawal rate; due to AEs or exit criteria **Intervention 1** GBP (300 mg) (n = 72): n = 45 % difference (CBZ vs GBP 300 mg): –8.4 (95% CI: –24.4 to 7.5) **Intervention 2** GBP (900 mg) (n = 72): n = 32 % difference (CBZ vs GBP 900mg): 9.6 (95% CI: –6.5 to 25.8) **Intervention 3** GBP (1800 mg (n = 74): n = 42 % difference (CBZ vs GBP 1800 mg): –2.7 (95% CI: –18.7 to 13.3) **Comparator** CBZ (n = 74): n = 40

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Lopes-Lima, 1999[46] **Related publications** None **Country** Spain and Portugal **Source** Literature search **Aim** To evaluate the efficacy and safety of GBP versus VPA as add-on therapy and monotherapy in patients with partial epilepsy **Type of publication** Abstract (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** Participants had a 12-day titration period (until 1800–2400 mg/day of GBP or 1500 mg/day of VPA), followed by an	**Number of participants** 64 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 64): 37.8 years; not stated **Gender** Not stated **Age at onset of seizures** Mean duration of epilepsy: total (n = 64): 14.4 years **Pretrial medication** Not stated **Ongoing concurrent medication** CBZ during the add-on phase **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: patients with partial seizures, with or without secondary generalisation, inadequately controlled by CBZ therapy	**Intervention 1** GBP; 1800–2400 mg/day; 30 weeks No. randomised: not stated No. completed: not stated **Comparator** VPA; 1500 mg/day; 30 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** None stated **Comments** This is an abstract and lacks details regarding study methods, findings and quality. The numbers of participants randomised to each intervention are not stated. There are no details concerning patients completing the study or analyses used

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
8-week add-on evaluation period, 4–6 weeks of CBZ withdrawal, and 16 weeks of monotherapy evaluation. Patients exited the study if they experienced a protocol-defined exit event indicating lack of efficacy **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 30 weeks; not stated				
Results				
Outcome 1	**Outcome 2**			
Outcome Time to exit/withdrawal; no definition reported **Intervention 1** GBP add-on phase: non-significant differences were found in time to exit ($p = 0.064$) GBP monotherapy phase: % finishing the study without exit: 22% **Comparator** VPA add-on phase: not stated VPA monotherapy phase: % finishing the study without exit: 25%	**Outcome** Time to exit/withdrawal; time to withdrawal due to AEs **Intervention 1** GBP add-on phase: time to AE withdrawal with combination GBP–CBZ was significantly better ($p = 0.0054$) than the combination VPA–CBZ GBP monotherapy phase: % finishing the study without AE withdrawal: 22% **Comparator** VPA add-on phase: not stated VPA monotherapy phase: % finishing the study without AE withdrawal: 25%			

Lamotrigine (licensed use)

Crossover studies (*n* = 15)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Banks, 1991[88] **Related publications** Main report of seizure frequency data,[161] trial report[337] **Country** Australia **Source** Literature search **Aim** To assess the efficacy of LTG as adjunct therapy for patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** H34-035-C86 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 12 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (*n* = 10): 29.2 years (SD 9.73); Total (*n* = 10): 20–50 years **Gender** Total (*n* = 10): men = 4, women = 6 **Age at onset of seizures** Not stated **Pretrial medication** CBZ alone (*n* = 2); CBZ and VPA (*n* = 3); PHT and VPA (*n* = 1); CBZ and CLB (*n* = 3); VPA and PRM (*n* = 1) **Ongoing concurrent medication** See details of pretrial period **Co-morbidities** Not stated **Baseline seizure frequency** Not stated	**Intervention 1** LTG; 150 or 300 mg/day; 12 weeks No. randomised: not stated No. completed: 4 **Comparator** Placebo; NA; 18 weeks No. randomised: not stated No. completed: 6	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Two participants were lost to follow-up but it is not stated from which treatment group they came, why they left or at what stage they left the study **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** Clinically the results suggested that LTG did not affect mnestic function or specific cognitive abilities. From the data there were indications of reduced cerebral efficiency although it was unclear whether this was due to LTG alone or to presumed polypharmacy effects. It is imperative that a double-blind single-drug crossover study be undertaken to assess better the effect of LTG whilst removing the influence of multiple AEDs. At present LTG demonstrates effective seizure control with minimal cognitive impact **Comments** Additional information taken from trial report of whole study (*n* = 41 participants). The authors state that initially 12 participants were recruited for this part of the study; however only 10 completed all of the assessments and are discussed in the report. It is not possible to tell from which group the two participants who were lost to follow-up came or how many participants were originally randomised to the two groups

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period The study comprised a 3-month retrospective baseline period, requiring a minimum of 4/month partial seizures for inclusion in the study, and two active treatment periods (LTG or placebo) of 12 weeks punctuated by a 1-week reduction of medication and 3 weeks of placebo, with a similar washout phase at the end of the study **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The initial aim of the study was to recruit 30 participants with 20 completing; however, subsequent information suggested that the power of the study would be too low and that 40–50 participants (40 completing) were required to provide sufficient power to detect differences in seizure frequency. This study only looks at cognitive outcomes **Analysis methods** Seizure frequency was analysed using an ANOVA model which incorporated centre and crossover period terms. No further details are given about the analysis of the cognitive outcomes **Length of trial/frequency of follow-up** 32 weeks; baseline and end of each phase	**Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: 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 other than epilepsy; abnormal laboratory values; status epilepticus in previous 6 months; use of investigational drug in previous 6 months; taking more than two AEDs or taking VPA monotherapy; chronic medication; alcohol or other substance abuse; evidence of previous non-compliance (i.e. clinic attendance); pregnancy, lactation or current exposure to risk of pregnancy			Two patients did not complete all three assessments and their results have been discarded. It is not clear at what points in the study these patients were 'lost to follow-up'. Likewise, the reasons for non-completion are not specified Only a selection of the neurophysiological assessment results were reported. However, it is apparent that the baseline measures of mnestic function, concentration and attention, and general cerebral efficiency varied considerably between patients, in what is in any case a very small sample of patients The authors state that the different format of scores and incomplete data sets made it impossible to use parametric statistical methods

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; median number of seizures over a 12-week period and the % change associated with comparing LTG with placebo **Intervention 1** Median (range) number of seizures: total (*n* = 10): 28 (8–195) Median (range) % change vs placebo: total (*n* = 10): –27% (–67 to +22%) **Comparator** Median (range) number of seizures: total (*n* = 10): 46 (20–153)	**Outcome** Trail Making Test; in part A the patient connects numbered circles 1 to 25 in numerical order as quickly as possible. In part B 25 circles are connected as quickly as possible alternating between numbers and letters. The percentile is reported **Intervention 1** Patient no. 1 (LTG/placebo): Trail Making Test (part B) (%ile): baseline = 75, phase I = 75, phase II = 90 Patient no. 3 (LTG/placebo): Trail Making Test (part B) (%ile): baseline = 10, phase I = 10, phase II = 10 Patient no. 6 (LTG/placebo): Trail Making Test (part B) (%ile): baseline = 10, phase I = 10, phase II = 25 Patient no. 8 (LTG/placebo): Trail Making Test (part B) (%ile): baseline = 10, phase I = 10, phase II = 10 Patient no. 2 (placebo/LTG): Trail Making Test (part B) (%ile): baseline = 10, phase I = 10, phase II = 25 Patient no. 4 (placebo/LTG): Trail Making Test (part B) (%ile): baseline = 10, phase I = 10, phase II = 10 Patient no. 5 (placebo/LTG): Trail Making Test (part B) (%ile): baseline = 10, phase I = 10, phase II = 10 Patient no. 7 (placebo/LTG): Trail Making Test (part B) (%ile): baseline = 25, phase I = 25, phase II = 10 Patient no. 9 (placebo/LTG): Trail Making Test (part B) (%ile): baseline = 50, phase I = 25, phase II = 10	**Outcome** Digit Symbol Test; a subtest of the Wechsler intelligence scale that measures pyschomotor speed that measures the number of items completed in 90s. Speed receives greater credit than accuracy or power **Intervention 1** Patient no. 1 (LTG/placebo): Digit Symbol (scaled score): baseline = 6, phase I = 4, phase II = 9 Patient no. 3 (LTG/placebo): Digit Symbol (scaled score): baseline = 6, phase I = 7, phase II = 9 Patient no. 6 (LTG/placebo): Digit Symbol (scaled score): baseline = 5, phase I = 4, phase II = 5 Patient no. 8 (LTG/placebo): Digit Symbol (scaled score): baseline = 5, phase I = 4, phase II = 5 Patient no. 2 (placebo/LTG): Digit Symbol (scaled score): baseline = 4, phase I = 4, phase II = 3 Patient no. 4 (placebo/LTG): Digit Symbol (scaled score): baseline = 4, phase I = 4, phase II = 3 Patient no. 5 (placebo/LTG): Digit Symbol (scaled score): baseline = 5, phase I = 5, phase II = 4 Patient no. 7 (placebo/LTG): Digit Symbol (scaled score): baseline = 9, phase I = 8, phase II = 6 Patient no. 9 (placebo/LTG): Digit Symbol (scaled score): baseline = 5, phase I = 5, phase II = 4	**Outcome** Stroop Colour Word Test; a colour plate with colour names printed in incongruous colours is used. In the first part of the test the person reads the words and ignores the colours and then in the second part of the test they say the colour of the print and ignore the words. The number of words read in 45s is recorded **Intervention 1** Patient no. 1 (LTG/placebo): Stroop C/W (T score): baseline = 54, phase I = 48, phase II = 52 Patient no. 3 (LTG/placebo): Stroop C/W (T score): baseline = 32, phase I = 36, phase II = 36 Patient no. 6 (LTG/placebo): Stroop C/W (T score): baseline = 26, phase I = 24, phase II = 26 Patient no. 8 (LTG/placebo): Stroop C/W (T score): baseline = 44, phase I = 40, phase II = 42 Patient no. 2 (placebo/LTG): Stroop C/W (T score): baseline = 24, phase I = 22, phase II = 24 Patient no. 4 (placebo/LTG): Stroop C/W (T score): baseline = 36, phase I = 36, phase II = 34 Patient no. 5 (placebo/LTG): Stroop C/W (T score): baseline = 24, phase I = 30, phase II = 20 Patient no. 7 (placebo/LTG): Stroop C/W (T score): baseline = 32, phase I = 32, phase II = 26 Patient no. 9 (placebo/LTG): Stroop C/W (T score): baseline = 30, phase I = 32, phase II = 22

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Patient no. 10 (placebo/LTG): Trail Making Test (part B) (%ile): baseline = 90, phase I = 90, phase II = 90 **Comparator** See above	Patient no. 10 (placebo/LTG): Digit Symbol (scaled score): baseline = 11, phase I = 12, phase II = 11 The Stroop Colour/Word measure and the Digit Symbol subtest of the Wechsler scale were the most sensitive of the measures involved. Scores from these two measure appropriately reflected period changes on 7 out of the 10 patients **Comparator** See above	Patient no. 10 (placebo/LTG): Stroop Colour Word Test (T score): baseline = 54, phase I = 48, phase II = 50 The Stroop Colour/Word measure and the Digit Symbol subtest of the Wechsler scale were the most sensitive of the measures involved. Scores from these two measure appropriately reflected period changes on 7 out of the 10 patients **Comparator** See above

Outcome 5

Outcome
Rey Complex Figure Test Recall; investigates new learning, perceptual organisation and visual memory. Participants are asked to copy a complex figure and the accuracy of copy and of delayed recall drawing (30 minutes delay with distracting material between drawings), procedural method of drawing and embellishments to the drawing are scored

Intervention 1
Patient no. 1 (LTG/placebo): Complex Figure Test Recall (%ile): baseline = 30, phase I = 20, phase II = 30
Patient no. 3 (LTG/placebo): Complex Figure Test Recall (%ile): baseline = 10, phase I = 40, phase II = 90
Patient no. 6 (LTG/placebo): Complex Figure Test Recall (%ile): baseline = 10, phase I = 10, phase II = 10
Patient no. 8 (LTG/placebo): Complex Figure Test Recall (%ile): baseline = 10, phase I = 10, phase II = 20
Patient no. 2 (placebo/LTG): Complex Figure Test Recall (%ile): baseline = 50, phase I = 25, phase II = 50
Patient no. 4 (placebo/LTG): Complex Figure Test Recall (%ile): baseline = 10, phase I = 20, phase II = 10
Patient no. 5 (placebo/LTG): Complex Figure Test Recall (%ile): baseline = 10, phase I = 10, phase II = 10
Patient no. 7 (placebo/LTG): Complex Figure Test Recall (%ile): baseline = 60, phase I = 70, phase II = 50
Patient no. 9 (placebo/LTG): Complex Figure Test Recall (%ile): baseline = 20, phase I = 20, phase II = 10
Patient no. 10 (placebo/LTG): Complex Figure Test Recall (%ile): baseline = 10, phase I = 10, phase II = 10

The recall segment of the Complex Figure Test provided additional support for the prediction of treatment sequence of 6 of the patients

Comparator
See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Beran, 1998[134] **Related publications** Abstract of final analysis,[338] industry trial report[432] **Country** Australia **Source** Literature search **Aim** To carry out a double-blind, placebo-controlled, crossover trial of add-on LTG in patients with refractory generalised seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM40057 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was an 8-week baseline phase, followed by two treatment periods (LTG or placebo) of 8 weeks, each of which was followed by a 4-week	**Number of participants** 26 **Type of epilepsy** Refractory **Type of seizures** Generalised onset **Mean age/age range** Total (n = 26): 29 years (SD not stated); total (n = 26): 15–50 years **Gender** Total (n = 26): men = 11, women = 15 **Age at onset of seizures** Mean age at epilepsy onset: total (n = 26) 7.4 years (range 0.02–15 years) **Pretrial medication** See concurrent medications below **Ongoing concurrent medication** VPA (n = 26), CBZ (n = 10), CZP (n = 5), PHT (n = 3), ethosuximide (n = 2), PRM (n = 2) **Co-morbidities** Not stated	**Intervention 1** LTG/placebo; 75 mg/day; 8 weeks No. randomised: 13 No. completed: 10 **Comparator** Placebo/LTG; 150 mg/day; 8 weeks No. randomised: 13 No. completed: 12	**Withdrawals prerandomisation** Total: not eligible (n = 1) **Withdrawals postrandomisation** Total: rash (n = 2); withdrawal (n = 1) **Adverse events** **Intervention 1** AEs reported by more than two patients: LTG phase; rash (n = 7, 27%), ataxia (n = 3, 12%), diplopia (n = 3, 12%), dizziness (n = 2, 8%), headache (n = 2, 8%), tremor (n = 2, 8%), accidental injury (n = 2, 8%), drowsiness (n = 2, 8%), tiredness (n = 1, 4%) **Comparator** AEs reported by more than two patients: placebo phase; headache (n = 2, 8%), tremor (n = 1, 4%), accidental injury (n = 2, 8%), tiredness (n = 5, 19%)	**Authors' conclusions** This study shows that LTG is effective add-on therapy in patients with refractory generalised epilepsies. Statistically significant reduction in seizures in both absence and tonic–clonic seizure types was seen even with low doses of LTG **Comments** Additional data extracted from trial report. However, it was not possible to obtain further information on the compatibility of the two treatment groups at baseline as this table was missing from the trial report The 12-week length of treatment for each group includes the 2-week titration period, the 1-week taper phase and the 3-week washout period. Therefore, patients were not receiving the target dosages of LTG for the whole of this period The number of participants randomised or who completed the trial are not given separately for each treatment group. All that is stated is that a total of 23 patients were randomised and a total 21 patients completed the trial Results above are given for LTG as a whole, the two separate LTG groups (LTG target dose 75 and

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
taper/washout period. There were two target doses of LTG: 150 mg daily or patients taking VPA and an enzyme-inducing AED and 75 mg daily for patients taking VPA without an enzyme-inducing AED. The dose was increased over the first 3 weeks of the treatment periods: for LTG target dose 150 mg daily LTG, daily doses started at 50 mg daily in week 1 and this was increased weekly by 50 mg until the target dose of 150 mg was reached. Patients were then maintained on this target dose for the rest of the treatment phase. For LTG target dose 75 mg daily LTG, daily doses started at 25 mg daily in week 1 and this was increased weekly by 25 mg until the target dose of 75 mg was reached. Patients were then maintained on this target dose for the rest of the treatment phase. There was a 1-week taper at the end of the treatment period (i.e. during the 1st week of the 4-week taper/washout period) in which daily doses for the LTG target dose 150 mg group, the daily dose was reduced by 50 mg to 100 mg daily, and for the LTG target dose 75 mg group, the daily dose was reduced by 25 mg to 50 mg **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** A seizure rate for each treatment period was calculated based on the number of days, during each treatment period, that a complete seizure record was available. The percentage change in seizure rate for individual seizure types between the LTG and placebo phases was calculated in terms of a percentage reduction with either LTG or placebo (the smaller rate calculated as a	**Baseline seizure frequency** Monthly seizure frequency: absence (n = 19): mean = 177 (range 1–1033); myoclonic (n = 3): mean = 57 (range 15–137); tonic–clonic (n = 17): mean = 4.7 (range 1–24) **Other characteristics** Seizure types: total (n = 26): absence only = 8, absence and tonic–clonic = 12, tonic–clonic only = 2, myoclonic only = 1, myoclonic and tonic–clonic = 1, absence, myoclonic and tonic clonic = 2 **Inclusion/exclusion criteria** Inclusion: generalised epilepsy as manifested by seizure patterns of absences, myoclonus or tonic–clonic seizures or a combination of these with generalised spike and wave discharges on the EEG at a frequency of 2.5 Hz or faster without any focal features Exclusion: Frank tonic attacks or a diagnosis of Lennox–Gastaut syndrome; confounding organic, psychiatric, or progressive neurological disease or significant laboratory abnormality			150 mg) were not analysed separately There were no significant differences between the LTG and placebo groups in AED plasma concentrations 20 patients continued on to open-label LTG after completion of the trial for a mean duration of 26 months (range 16–38 months). 80% of these patients had experienced ≥ 50% reduction in seizure frequency, with 25% becoming seizure-free

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
percentage of the larger rate) for each patient. Differences in seizure rates between active treatment and placebo for the two trial periods were analysed using the Mann–Whitney test for paired observations. Tests for period by treatment interaction were performed using the Wilcoxon rank-sum test. Tonic–clonic seizures and absence seizures were analysed separately. Statistical analysis of myclonic seizures was not possible because of small patient numbers **Length of trial/frequency of follow-up** 24 weeks; physical and neurological examination, biochemistry and haematology screens were carried out at the end of each of the treatment and taper/washout periods				

Results	
Outcome 1	**Outcome 2**
Outcome Proportion of responders; responders were defined as having at least a 50% reduction in seizure frequency	**Outcome** Proportion of responders; defined as number of patients showing a marked improvement (decrease 50–100% with LTG), mild improvement (decrease 26–49% with LTG), no change (decrease 1–25% with LTG or placebo), worse (decrease >26% with placebo)
Intervention 1 First-phase data: LTG (n = 13): 5/13 Paired data comparing LTG with placebo: Absence seizures: 33% Tonic–clonic seizures: 50% Myoclonic seizures: one patient was worse on LTG than placebo and the other showed no change Overall, the paired analysis found a significant effect for a reduction in seizure rate on LTG compared with placebo for tonic–clonic (p = 0.03) and absence seizures ($p < 0.001$)	**Intervention 1** Follow-up data (LTG vs placebo): LTG Absence seizures: marked improvement = 5, mild improvement = 7, no change = 1, worse = 2 Tonic–clonic seizures: marked improvement = 7, mild improvement = 1, no change = 5, worse = 1 Myoclonic seizures: marked improvement = 0, mild improvement = 0, no change = 1, worse = 1 Reduction in seizure rate with LTG (LTG vs placebo) was significant for both tonic–clonic (p = 0.03) and absence seizures ($p < 0.001$)
Comparator First-phase data: placebo (n = 13): 3/13	**Comparator** NA data presented are paired data comparing LTG with placebo

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Binnie, 1987[50] **Related publications** Industry trial report[339] **Country** European **Source** Literature search **Aim** To attempt a preliminary assessment of the efficacy and safety of LTG as add-on therapy in patients with poorly controlled epilepsy **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** H34-007 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Inpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a 7-day baseline observation period to familiarise patients with the trial procedures (Phase 0). This was followed by	**Number of participants** 10 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 10): mean = 31 years (SD 9). No further data. Total (n = 10): range 16–46 years. No further data **Gender** Total (n = 10): men (n = 6), women (n = 4). No further data **Age at onset of seizures** Not stated **Pretrial medication** See concurrent medications **Ongoing concurrent medication** Participants were taking 2–4 concomitant AEDs: CBZ (n = 10/10); CLB (n = 1/10); CZP (n = 1/10); flunarizine (FNR) (n = 1/10); PB (n = 2/10); PHT (n = 6/10); VPA (n = 5/10) **Co-morbidities** Not stated	**Intervention 1** LTG/placebo; 100–250 mg/day; 6 days No. randomised: 5 No. completed: 5 **Comparator** Placebo/LTG; 6 days No. randomised: 5 No. completed: 5	**Withdrawals prerandomisation** There were no withdrawals **Withdrawals postrandomisation** There were no withdrawals **Adverse events** **Intervention 1** Headache (n = 1), apathy (n = 1), ataxia (n = 2), ataxia and dizziness (n = 1) **Comparator** Not stated	**Authors' conclusions** Six patients showed a 50% seizure reduction on LTG and two an increase. Side-effects (ataxia, dizziness and apathy) occurred in 3 patients, but only at levels above 3 μg/ml and were rapidly relieved when the dose was reduced in two. EEG spike counts were significantly reduced on LTG. There was no evidence of interactions with co-medication **Comments** Demographic details are not specified for the two sequence groups. Full length of treatment period was 7 days with first day on reduced dose, therefore there were 6 days on full dose. The titration period was short compared with current manufacturers' information for health professionals. Although an inclusion criteria of at least 4 seizures/week is specified, there is no specification as to the length of the period over which this should take place. Owing to the lack of washout period the authors state that Phase III was regarded as the control placebo period for patients who received LTG in Phase I, and in the group who received LTG in Phase II, Phase I served as the placebo control period. The sign test was used. This is a test of the direction of differences between

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
the first 7-day treatment period (Phase I). There was no washout period prior to crossover. The second treatment period (Phase II) of 7 days was followed by a 7-day placebo phase for both sequence groups (Phase III) **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated. However, the authors state that the small sample size was chosen as the study was only exploratory **Analysis methods** The sign test was used to examine whether there was a significant reduction in seizures on LTG **Length of trial/frequency of follow-up** 7 days; neurological examination and vital signs checked at end of each treatment phase. Seizure frequency documented daily	**Baseline seizure frequency** Total (n = 10): range (all seizure types) 1–90 seizures/month. No further data **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: 16–46 years; confident diagnosis of epilepsy uncomplicated by psychogenic seizures; seizures classifiable by International Classification of Seizures (ICS) and easily recognisable by patient/staff; minimum seizure frequency of 4/week; AEDs unaltered over previous 6 weeks. Exclusion criteria: other serious illness; haematological or renal abnormalities on laboratory investigation; abnormalities of liver function other than those attributable to AEDs; use of other regular medication; pregnancy or risk of pregnancy			two measures rather than the extent of the difference Intervention1 dosage: dosage was based on half-life estimates for each individual patient. Minimum 100 and maximum 250 mg/day The authors also report data relating to plasma concentrations and LTG but these data have not been extracted. Although using a crossover design, the authors used an additional placebo phase against which to compare patients in the LTG/placebo sequence group Weekly seizure counts for individual patients according to seizure type were reported in the trial but are not reported in this table

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Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Proportion of seizure-free patients; number of participants who were seizure-free during the specified phase **Intervention 1** LTG: *n* = 1/10 **Comparator** Placebo: *n* = 1/10	**Outcome** Seizure frequency; median (and mean) seizure counts over the specified trial periods (each week in duration) **Intervention 1** Phase 0: median = 5.0 (mean = 6.2) LTG: median = 2.5 (mean = 2.1) Placebo vs LTG (p = 0.055) **Comparator** Placebo: median = 3.5 (mean = 7.3) Phase III placebo/washout: median = 5.0 (mean = 6.9)	**Outcome** Percentage responders; ≥ 50% reduction in seizure count **Intervention 1** First-phase data LTG (*n* = 5): 2/5 End-phase data: 6/10 **Comparator** First-phase data placebo (*n* = 5): 1/5

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Binnie, 1989[159] **Related publications** Industry trial report[340] **Country** European **Source** Literature search **Aim** To assess the efficacy of LTG as an add-on therapy in patients with poorly controlled partial seizures, to assess adverse reactions in these patients, to examine possible interactions between LTG and other AEDs, with reference to plasma AED concentrations, and to examine the effects of tapered withdrawal on seizure frequency (carryover or rebound effects) **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM 30029 (H34/C/85/AWP/55/16) (UK-016) **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient	**Number of participants** 34 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 30): 37.1 years (SD 10.26); LTG/placebo (n = 15): 36.0 years (SD 9.47); placebo/LTG (n = 15): 38.3 years (SD 11.21); total (n = 30): 16–51 years; LTG/placebo (n = 15): 21–51 years; placebo/LTG (n = 15): 16–50 years **Gender** Total (n = 30): men = 22, women = 8; LTG/placebo (n = 15): men = 11, women = 4; placebo/LTG (n = 15): men = 11, women = 4 **Age at onset of seizures** Mean duration of seizures Total (n = 30): 22.8 years (SD 11.0); LTG/placebo (n = 15): 23.8 years (SD 11.9); placebo/LTG (n = 15): 21.9 years (SD 10.3) n = mean age of onset of epilepsy; total (n = 30): 14.3 years (SD 10.7) **Pretrial medication** See concurrent medications **Ongoing concurrent medication** One concurrent AED (n = 2/30) Two concurrent AEDs (n = 13/30)	**Intervention 1** LTG/placebo; 75, 100 or 200 mg/day; 12 weeks No. randomised: 16 No. completed: 15 **Comparator** Placebo/LTG; NA; 12 weeks No. randomised: 18 No. completed: 15	**Withdrawals prerandomisation** Withdrawn during baseline (n = 1) **Withdrawals postrandomisation** Placebo/LTG sequence: error in dispensing (n = 1); LTG/placebo sequence: maculo-papular rash while on LTG (n = 1), admission to hospital for cholecystectomy during placebo (n = 1) **Adverse events** **Intervention 1** Asthenia (n = 6), diplopia (n = 7), tremor (n = 1), headache (n = 5), somnolence (n = 4), dizziness (n = 3), nausea (n = 1) Serious adverse reactions: vision abnormal (n = 1), depression (n = 1) **Comparator** Asthenia (n = 4), diplopia (n = 7), tremor (n = 3), headache (n = 2), somnolence (n = 6), dizziness (n = 5), nausea (n = 3) Serious adverse reactions: rash (n = 1), headache (n = 2), nausea (n = 1), asthenia (n = 1)	**Authors' conclusions** There was a modest statistically significant reduction in total and partial seizures on LTG compared with placebo treatment. There was no difference in AEs or abnormal biochemical or haematological findings between the LTG and placebo periods. The plasma concentrations of concomitantly administered AEDs were not affected by LTG treatment. It is concluded that LTG shows promise as an AED with low toxicity **Comments** Additional data have been extracted from the industry trial report Although the treatment period was 12 weeks, dosage of LTG was still being adjusted up until week 8 if necessary Group 1: minimum dose received was 50mg and maximum was 400 mg/day Group 2: minimum dose received was 50mg and maximum was 400 mg/day There was a significant period effect with total seizure counts tending to be higher in treatment period 1 (p <0.05). There was not a significant treatment × period interaction. The authors

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Method/timing of randomisation Not stated; after enrolment **Details of pretrial period** There was a baseline period of 8 weeks to familiarise patients with trial procedures and to provide a seizure frequency reference point in the instance of an order effect. This was followed by 12-week treatment period during which titration occurred. The intended dose for patients on enzyme-inducing concomitant AEDs only was 200 mg/day (Group 1), patients on enzyme-inducing concomitant AEDs (Group 2) and VPA received 100 mg/day and patients on VPA monotherapy 75 mg/day. At the beginning of week 1 of treatment half the intended LTG dose was provided. At the end of week 1 the dose was doubled. Based on trough plasma levels at end of week 2 a dose was prescribed for week 3. Based on plasma LTG estimations at end of weeks 2, 3, 4 and 8, further adjustments were made to dose as necessary. The treatment phase was followed by a 6-week washout period. Dosage was tapered over the first 2 weeks of washout with placebo received for the remaining 4 weeks. Treatment phase 2 and washout 2 followed the same procedure. Time of randomisation was not clear **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The trial aimed at obtaining a minimum of 20 completed patients, as this is considered the minimum number required to demonstrate a treatment effect using a crossover design	Three concurrent AEDs (n = 13/30) Four concurrent AEDs (n = 2/30) Concurrent AEDs: CBZ, VPA, AZM, CLB, ethosuximide, OXC, PB, PHT, PRM Other concurrent chronic medications: clorazepate, dipotassium, haloperidol, pericyazine, DZP **Co-morbidities** Not stated **Baseline seizure frequency** Mean baseline seizure counts: total (n = 30): 34.6 (SD 85.7); LTG/placebo (n = 15): 23.7 (SD 27.7); placebo/LTG (n = 15): 45.5 (SD 119.1) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: 16–65 years; confident diagnosis of epilepsy uncomplicated by pseudoseizures; seizures easily recognisable by patients or relatives and classifiable by ICS; must have partial seizures possibly with other types; at least 4 seizures/month and a seizure diary for at least the previous 3 months; epilepsy resistant to drugs of first choice, appropriate to the type of epilepsy; unchanged AEDs for the previous 3 months Exclusion: severe organic or psychiatric disease; severe mental			also report data relating to the plasma concentrations of LTG and concurrent AEDs, but these data have not been extracted

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods Data were analysed using the Wilcoxon rank-sum test for a 2-period model. The model assumes treatment effects to be additive; however, treatment effect on seizure frequency is likely to be multiplicative. Log transformation of the raw data renders the effects additive on the transformed scale to conform to the model. Therefore, log transformation of the data was not performed to normalise the data but to satisfy the requirements of the statistical model **Length of trial/frequency of follow-up** 44 weeks; follow-up at weeks 1, 2, 4, 8 and 12 of treatment period and weeks 1, 2 and 6 of washout	subnormality; progressive neurological disorder; haematological, biochemical or renal abnormalities on laboratory screening considered to be of clinical significance and not attributable to AEDs; status epilepticus in the preceding 6 months or more than once in the previous 2 years; use of any investigative AED in preceding 6 months; use of more than 2 AEDs (this was relaxed as it was found too restrictive); use of other chronic medication; non-compliance or failure to document seizures or adverse experiences; pregnancy, lactation or risk of pregnancy			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; total seizure counts for each individual patient during 12-week treatment periods on LTG and placebo and percentage change (expressed relative to the larger of the total seizure counts in the two treatment periods) **Intervention 1** Patients with fewer seizures on LTG: LTG/placebo sequence group (total no. of seizures on LTG, % change): patient no. 1 (n = 29, 28%); no. 7 (n = 101, 30%); no. 9 (n = 44, 28%); no. 16 (n = 14, 22%); no. 17 (n = 17, 6%); no. 20 (n = 42, 5%); no. 27 (n = 14, 18%); no. 34 (n = 4, 67%) Placebo/LTG sequence group (total no. of seizures on LTG, % change): patient no. 3 (n = 31, 38%); no. 6 (n = 10, 41%); no. 11 (n = 26, 16%); no. 13 (n = 14, 59%); no. 14 (n = 4, 20%); no. 18 (n = 63, 34%); no. 19 (n = 20, 9%); no. 21 (n = 6, 45%); no. 22 (n = 10, 41%); no. 28 (n = 37, 43%); no. 32 (n = 444, 36%)	**Outcome** Proportion of responders; number of patients showing improvement in each of the specified categories **Intervention 1** Total seizures: 1–25% improvement (n = 7/30) 26–50% improvement (n = 10/30) 51–100% improvement (n = 2/30) No change (n = 2/30)	**Outcome** Seizure days; the total number of days on which seizures occurred **Intervention 1** Seizure days: 1–25% improvement (n = 10/30) 26–50% improvement (n = 6/30) 51–100% improvement (n = 2/30) No change (n = 4/30)	**Outcome** Percentage responders; number of patients showing a ≥ 50% reduction in seizures **Intervention 1** First-phase data LTG (n = 16): 1/16 End-phase data: 12/30 **Comparator** First-phase data placebo (n = 18): 1/18 End-phase data: not reported

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Patients with fewer seizures on placebo: LTG/placebo sequence group (total no. of seizures on LTG, % change): patient no. 4 (*n* = 18, 28%); no. 12 (*n* = 89, 29%); no. 15 (*n* = 25, 32%); no. 25 (*n* = 19, 16%); no. 30 (*n* = 18, 17%); no. 33 (*n* = 20, 50%) Placebo/LTG sequence group (total no. of seizures on LTG, % change): patient no. 5 (*n* = 68, 9%); no. 10 (*n* = 10, 10%); no. 29 (*n* = 20, 10%) Patients showing no change: LTG/placebo sequence group (total no. of seizures on LTG, % change): patient no. 23 (*n* = 17, 0%) Placebo/LTG sequence group (total no. of seizures on LTG, % change): patient no. 31 (*n* = 8, 0%) **Comparator** Patients with fewer seizures on LTG: LTG/placebo sequence group (total no. of seizures on placebo): Patient no. 1 (*n* = 40); no. 7 (*n* = 145); no. 9 (*n* = 61); no. 16 (*n* = 18); no. 17 (*n* = 18); no. 20 (*n* = 44); no. 27 (*n* = 17); no. 34 (*n* = 12) Placebo/LTG sequence group (total no. of seizures on placebo): patient no. 3 (*n* = 50); no. 6 (*n* = 17); no. 11 (*n* = 31); no. 13 (*n* = 34); no. 14 (*n* = 5); no. 18 (*n* = 95); no. 19 (*n* = 22); no. 21 (*n* = 11); no. 22 (*n* = 17); no. 28 (*n* = 65); no. 32 (*n* = 697) Patients with fewer seizures on placebo: LTG/placebo sequence group (total no. of seizures on placebo): patient no. 4 (*n* = 13); no. 12 (*n* = 63); no. 15 (*n* = 17); no. 25 (*n* = 16); no. 30 (*n* = 15); no. 33 (*n* = 10) Placebo/LTG sequence group (total no. of seizures on placebo): patient no. 5 (*n* = 62); no. 10 (*n* = 9); no. 29 (*n* = 18) Patients showing no change: LTG/placebo sequence group (total no. of seizures on placebo): patient no. 23 (*n* = 17) Placebo/LTG sequence group (total no. of seizures on placebo): patient no. 31 (*n* = 8)	The median percentage reduction in seizure count attributable to LTG was 17% (95% CI: 0 to 30) Partial seizures: 1–25% improvement (*n* = 8/30) 26–50% improvement (*n* = 10/30) 51–100% improvement (*n* = 2/30) No change (*n* = 2/30) **Comparator** Total seizures: 1–25% improvement (*n* = 5/30) 26–50% improvement (*n* = 4/30) 51–100% improvement (*n* = 0/30) Partial seizures: 1–25% improvement (*n* = 4/30) 26–50% improvement (*n* = 4/30) 51–100% improvement (*n* = 0/30)	The analysis of total seizure days showed a reduction during LTG treatment period ($p = 0.06$) **Comparator** Seizure days: 1–25% improvement (*n* = 7/30) 26–50% improvement (*n* = 1/30) 51–100% improvement (*n* = 0/30)	

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Boas, 1996[136] **Related publications** Industry submission,[346] abstract[347] **Country** Denmark **Source** Literature search **Aim** The antiepileptic effect of LTG was assessed in a double-blind, placebo-controlled, crossover trial in adult patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30022 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** There was a 12-week baseline period to establish baseline seizure frequency. This was followed by a 12-week treatment	**Number of participants** 56 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 56): 40.4 years (SD 13.1); placebo/LTG (n = 26): 41.5 years (SD 13.2); LTG/Placebo (n = 30): 39.5 years (SD 13.2); total (n = 56): 18–67 years; placebo/LTG (n = 26): 19–67 years; LTG/placebo (n = 30): 18–66 years **Gender** Total (n = 56): male = 27, female = 29; placebo/LTG (n = 26): male = 12, female = 14; LTG/placebo (n = 30): male = 15, female = 15 **Age at onset of seizures** Age at onset of seizures: total (n = 56): 0–59 years; placebo/LTG (n = 26): 0–59 years; LTG/placebo (n = 30): 0–58 years **Pretrial medication** Not stated **Ongoing concurrent medication** No concurrent AED: total: (1/56); placebo/LTG: (1/26); LTG/placebo: (0/30) One concurrent AED: total: (5/56); placebo/LTG: (7/26); LTG/placebo: (8/30)	**Intervention 1** LTG/placebo; 75–400 mg/day; 12 weeks No. randomised: 30 No. completed: 20 **Comparator** Placebo/LTG; 100–400 mg/day; 12 weeks No. randomised: 26 No. completed: 18	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** 18 participants did not complete study: placebo/LTG (n = 8), LTG/placebo (n = 10) Reasons for withdrawal: LTG/placebo (n = 30): refused treatment (n = 3), adverse experience (n = 4), death (n = 0), intercurrent illness (n = 0), ineffective treatment (n = 3); placebo/LTG (n = 26): refused treatment (n = 1), adverse experience (n = 3), death (n = 1), intercurrent illness (n = 1), ineffective treatment (n = 3) **Adverse events** **Intervention 1** LTG/placebo (n = 30): dizziness 36%, headache 24%, asthenia 12%, unevaluable reaction 5%, vomiting 10%, eczema 2%, nausea 10% **Comparator** Placebo/LTG (n = 26): dizziness 19%, headache 29%, asthenia 17%, unevaluable reaction 10%, vomiting 5%, eczema 10%, nausea 2%, 2 deaths: 1 sudden death in epilepsy, 1 kidney tumour	**Authors' conclusions** The results of this study show that LTG is effective in the treatment of partial and secondary generalised seizures in patients with refractory epilepsy. LTG was well tolerated and did not affect the plasma concentrations of concomitant AEDs **Comments** Additional information taken from the trial report (LAM30022) Although there was a 12-week treatment, week 1 of treatment was reduced dose with weeks 2–12 on full treatment dose. The titration period was short compared with current manufacturers' information for health professionals Although inclusion criterion was 16–65 years, demographic data indicate that maximum age was 67 years. Authors refer to amended seizure inclusion criteria (reduced from 4 seizures/month over 3 months to 3 seizures/month over 1 month. It is not indicated at what stage during the study this was implemented and why. LTG dosage for the balanced group was also amended during the study, although the authors do not indicate why and at what stage this occurred. The authors

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
period, the first week of which participants were on a reduced dose of LTG which was increased in week 2. There were 3 different dosing groups for LTG. The dosing groups were as follows: induced group (patients taking enzyme-inducing AEDs without VPA): 200 mg/day LTG in week 1 of treatment period and 400 mg/day for weeks 2–12; Balanced group (patients taking enzyme inducing AEDs with VPA): 75 mg/day in week 1 of treatment period and 150 mg/day for weeks 2–12 (this was later amended to 11 mg/day week 1 and 200 mg/day weeks 2–12), inhibited group (patients taking VPA without enzyme-inducing AEDs): 50 mg/day in week 1 and 75 mg/day for weeks 2–12. This was followed by a 4-week washout period during which LTG was tapered out over the first week of washout and all patients then received placebo. The second phase of the study followed the same procedure **ITT analysis performed/method** Authors state no; not stated **Sample size calculation** Not stated **Analysis methods** The authors used total seizure count from each of the phases of the study. Comparison between the two treatment groups (for total seizure count, each seizure type and number of seizure days)was carried out using an analysis of variance of log transformed seizure data in order to test for treatment effect, period effect and time × period interaction. A treatment effect estimate was obtained and converted	Two concurrent AEDs: total: (39/56); placebo/LTG: (18/26); LTG/placebo: (21/30) Three concurrent AEDs: total: 1/56); placebo/LTG: (0/26); LTG/placebo: (1/30) **Co-morbidities** Not stated **Baseline seizure frequency** Total (n = 56): 88; placebo/LTG (n = 26): 39; LTG/placebo (n = 30): 49 (includes simple partial, complex partial, secondary generalised and primary generalised; data also available by seizure type) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: 16–65 years; confident diagnosis of epilepsy uncomplicated by pseudoseizures; partial seizures (with or without secondary generalisation) easily recognisable by patients/relatives and classifiable by ICS; at least 4 POSs/month for previous 3 months (amended to 3 seizures of partial onset/month over 1-month baseline seizure diary if they had a very stable seizure frequency); seizures resistant to first choice AED and medication appropriate to type of epilepsy and administered at therapeutic plasma concentrations; concomitant medication unchanged for previous 3 months; patients unresponsive to any established drug			indicate that dosage could be reduced if there was concern about side-effects. Although there is no reference to increasing dosage, some patients were receiving doses beyond the predetermined limits. Dosage in the balanced group should have been 200 mg/day weeks 2–12, but in the placebo/LTG group the dose range was 100–400 mg/day whereas in the LTG/placebo group it was 75–200 mg/day. In the inhibited group the dosage should have been 75 mg/day weeks 2–12 but was 150 g in the placebo/LTG group and 75 g in the LTG/placebo group The data reported for number of concurrent AEDs appear to be incorrect. Although it is indicated that 7 from the placebo/LTG sequence group and 8 from the LTG/placebo sequence group were using two concurrent AEDs, only five patients for the total group are reported to be using two concurrent AEDs. This should probably read 15 For outcome 1, percentage responders, the numbers used in this extraction are taken from Table 16 of the trial report and these numbers are slightly different from those reported in the paper and summary of the trial report

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
to an estimate of the percentage seizure reduction on LTG from placebo with 95% CI **Length of trial/frequency of follow-up** 11 months; end of each 12-week treatment period	and no longer on any AED were eligible. Exclusion: severe organic or psychiatric disease; severe mental subnormalities; progressive neurological disease; abnormal values of laboratory screen considered to be of clinical significance and not attributable to enzyme induction; status epilepticus in previous 6 months or more than once in previous 2 years; use of other investigational drugs in previous 6 months; more than 2 AEDs; other chronic medication; alcohol or other substances abuse; inability to fulfil protocol requirements; pregnancy, lactation, or current risk of pregnancy			ANOVA of seizure counts between the 2 treatment groups excluding the first 2 weeks of each treatment period (dose escalation phase) gave similar results to using the full 12-week treatment period. There was no evidence of treatment × period interaction but there was a significant period effect with patients responding better in the second treatment period ($p = 0.014$). Although the study was multicentre, this was not included as a variable in the analysis

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Percentage responders; ≥ 50% reduction in total seizure count **Intervention 1** First-phase data: ($n = 30$): 6/30 Final data ($n = 56$): 9/56 **Comparator** First-phase data: ($n = 26$): 3/26	**Outcome** Change in seizure-free interval; mean % (95% CI) reduction in seizure days on LTG relative to placebo **Intervention 1** All seizures ($n = 38$): mean = 27.5% (95% CI: 9.2 to 42.2), $p = 0.008$ SPSs ($n = 14$): mean = –37.9 (95% CI: –128.3 to 16.7), $p = 0.235$ CPSs ($n = 32$): mean = 28.7% (95% CI: 7.1 to 45.3), $p = 0.018$ Secondary generalised ($n = 13$): mean = 34.1% (95% CI: 14.5 to 49.3), $p = 0.010$ Primary generalised ($n = 6$): mean = 43.9% (95% CI: –9.1 to 71.1), $p = 0.164$.	**Outcome** Physician global evaluation of improvement/efficacy; investigator global evaluation of patient progress **Intervention 1** Placebo/LTG sequence group: 63% of patients showed improvement (mild or moderate) LTG/placebo sequence group: 36% of patients showed improvement **Comparator** Placebo/LTG sequence group: 36% of patients showed improvement (mild or moderate)	**Outcome** Change in seizure severity; classified according to marked improvement: 50–100% fewer seizures; moderate improvement: 25–49% fewer seizures; slight improvement: 11–24% fewer seizures; no change ± 10% change; worse: >10% more seizures **Intervention 1** All seizures ($n = 38$): 24% marked improvement; 32% moderate improvement; 16% slight improvement; 5% no change; 24% worse

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Comparator See above	LTG/placebo sequence group: 45% of patients showed an improvement	SPSs (n = 14): 21% marked improvement; 14% moderate improvement; 0% slight improvement; 14% no change; 50% worse CPSs (n = 32): 22% marked improvement; 28% moderate improvement; 9% slight improvement; 6 % no change; 34% worse Secondary generalised (n = 13): 69% marked improvement; 8% moderate improvement; 0% slight improvement; 0 % no change; 23% worse Primary generalised (n = 6): 50% marked improvement; 0% moderate improvement; 0% slight improvement; 50% no change; 0% worse **Comparator** See above

Outcome 5
Outcome Change in seizure frequency Reported as mean % (95% CI) reduction in total seizure count on LTG relative to placebo **Intervention 1** All seizures (n = 38): mean = 30.3% (95% CI: 8.4 to 47.0) (p = 0.014) SPSs (n = 14): mean = –19.4% (95% CI: –138.2 to 40.2) (p = 0.625) CPSs (n = 32): mean = 29.2% (95% CI: 3.8 to 47.9) (p = 0.035) Secondary generalised (n = 13): mean = 37.9% (95% CI: 18.9 to 52.4) (p = 0.005) Primary generalised (n = 6): mean = 48.6% (95% CI: –9.2 to 75) (p = 0.158) **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Cordova, 1995[40] **Related publications** None **Country** Mexico **Source** Literature search **Aim** An evaluation of the efficacy/safety of LTG in partial seizures as add-on to AEDs **Type of publication** Abstract (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** There was a 12-week baseline period to verify seizure frequency and stable dose/serum levels of concurrent AEDs. This was followed by a 12-week treatment period. The procedure for titration is not	**Number of participants** 29 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Other AEDs **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Not stated	**Intervention 1** LTG/placebo; 150 or 300 mg/day; 12 weeks No. randomised: not stated No. completed: not stated **Comparator** Placebo/LTG; NA; 12 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: mild rash ($n = 4$); surgery ($n = 1$); protocol violation ($n = 1$) **Adverse events** **Intervention 1** The authors report that no major AEs were observed. There were 4 withdrawals due to mild rash although it was not specified whether this was during placebo or LTG **Comparator** See Intervention 1	**Authors' conclusions** This trial was designed before the gradual introduction of LTG was devised; it confirms the efficacy/safety of LTG in high or low dose according to the type of concomitant AED. When added to VPA, the LTG dose apparently need not be reduced by 50%, but this issue should be further investigated to settle interindividual variations in lengthening of the drug's half-life **Comments** The paper is an abstract and therefore has limited information regarding study design, quality and outcome data

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
described. Patients currently using inducing AEDs only were given 300 mg/day LTG and those taking VPA with or without inducers were given 150 mg/day. The washout period was 4 weeks in length **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 12 weeks				
Results				
Outcome 1	**Outcome 2**			
Outcome Proportion of responders; percentage of participants experiencing specified reductions in seizure frequency **Intervention 1** LTG: >50% reduction (37.5%); 25–50% reduction (25%); <25% reduction (37.5%) (equally distributed in both dose groups). Reduction in total seizure count in both dose groups pooled was 59.5% ($p < 0.00001$); reduction in the high-dose group was 68.5% and in the low dose group was 44.6% ($p < 0.004$) **Comparator** Not stated	**Outcome** Change in seizure-free interval; the percentage change in seizure-free days **Intervention 1** The increase in seizure-free days was 57.6% **Comparator** Not stated			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Jawad, 1989[160] **Related publications** Industry trial report[360] **Country** UK **Source** Literature search **Aim** The antiepileptic effect of LTG was assessed in a double-blind, placebo-controlled crossover trial in adult patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30024 (H34/C/85/AWP/57) (UK-021) **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** There was an 8-week baseline period to establish baseline seizure counts. This was followed by a 12-week treatment period	**Number of participants** 24 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 21): 37.3 years (SD 13.2); LTG/placebo (n = 10): 38.9 years (SD 12.81); placebo/LTG (n = 11): 35.9 years (SD 13.94); total (n = 21): 19–65 years; LTG/placebo (n = 10): 23–64 years; placebo/LTG (n = 11): 19–65 years **Gender** Total (n = 21): men = 12, women = 9; LTG/placebo (n = 10): men = 5, women = 5; placebo/LTG (n = 11): men = 7, women = 8 **Age at onset of seizures** Mean age at onset: total (n = 21): 9.7 years (SD 7.6); LTG/placebo (n = 10): 12.6 years (SD 9.6); placebo/LTG (n = 11): 7.2 years (SD 4.3) Mean duration of seizures: Total (n = 21): 27.6 years (SD 15.2); LTG/placebo (n = 10): 26.3 years (SD 16.0); placebo/LTG (n = 11): 28.7 years (SD 15.2) **Pretrial medication** Not stated	**Intervention 1** LTG/placebo; 75–400 mg/day; 12 weeks No. randomised: 12 No. completed: 10 **Comparator** Placebo/LTG; NA; 12 weeks No. randomised: 12 No. completed: 11	**Withdrawals prerandomisation** None stated **Withdrawals postrandomisation** LTG/placebo sequence: received LTG in both treatment periods therefore excluded from the analysis (n = 1), serious illness not thought attributable to LTG (n = 1); placebo/LTG sequence: breach of eligibility criteria (n = 1) **Adverse events** **Intervention 1** LTG: tiredness (n = 9) 43%, drowsiness (n = 5) 24%, headache (n = 5) 24%, ataxia (n = 4) 19%, diplopia (n = 4) 19%, tremor (n = 2) 10%, nausea (n = 2) 10%, hostility (n = 2) 10%, confusion (n = 1) 5%, irritability (n = 1) 5%, slurred speech (n = 1) 5%, vomiting (n = 1) 5%, skin rash (n = 1) 5%, chills (n = 1) 5%, accommodation abnormality (n = 1) 5%, CNS depression (n = 1) 5%, back pain (n = 1) 5%, haematuria (n = 1) 5% Reported at least one AE: n = 21. All but seven of the 119 reports of AEs were classified as 'non-serious'; none was classified as 'life-threatening'. Five of the seven reports occurred during LTG treatment; four of these were	**Authors' conclusions** The results of this trial indicate that LTG has significant antiepileptic activity when added to the standard therapy of patients with resistant complex partial seizures, appears not to interact with these drugs and has an acceptable therapeutic ratio. Further trials of the drug, preferably as monotherapy, are fully justified **Comments** Additional data extracted from the industry trial report. Although the full treatment period was 12 weeks, treatment on full dose was for 11 weeks although dose could be altered up to week 4 of treatment period. The titration period was short compared with current manufacturers' information for health professionals. Group 1: the proposed dose was 100 or 200 mg/day depending on concomitant AEDs. Minimum dose received was 75 mg/day and maximum was 400 mg/day Group 2: the proposed dose was 100 or 200 mg/day depending on concomitant AEDs. Minimum dose received was 100 mg/day and maximum was 300 mg/day. Data in the trial report differ slightly from data in the published

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
with full dose of LTG being achieved by week 2. Patients on enzyme-inducing concomitant AEDs only received 200 mg/day (Group 1), patients on enzyme-inducing concomitant AEDs and VPA received 100 mg/day (Group 2). Trough plasma LTG concentrations were measured at the end of weeks 1, 2 and 4 and the dose of LTG was adjusted, assuming linear kinetics to achieve trough concentrations of 1.5–2 mg/l. The washout period was 6 weeks with dosage being reduced over the first 2 weeks and placebo administered for the rest of the period. Treatment period 2 was also 12 weeks, followed by another 6-week washout period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Power calculations were performed assuming a mean number of 5 seizures/month and a between-subject variance of twice the mean (i.e. 10/month. Assuming that the within-subject variance for a crossover study would be 6.3, the power to show a 25% seizure reduction in a group of 20 subjects was ~0.7. **Analysis methods** Seizure counts were accumulated to give total for each phase of the trial. The data were analysed using the Wilcoxon rank-sum test for a two-period model. The model assumes treatment effects to be additive; however, treatment effect on seizure frequency is likely to be multiplicative. Log transformation of the raw data renders the effects additive on the transformed scale to	**Ongoing concurrent medication** One concurrent AED: total: (5/21); placebo/LTG: (1/11); LTG/placebo (4/10) Two concurrent AEDs: total: (16/21); placebo/LTG: (10/11); LTG/placebo (6/10) Concurrent AEDs were: CBZ (n = 18); PHT (n = 7); PRM (n = 11); PB (n = 1) **Co-morbidities** Not stated **Baseline seizure frequency** Mean total baseline seizure counts: total (n = 21): 31.7 (SD 23.0); LTG/placebo (n = 10): 36.3 years (SD 29.7); placebo/LTG (n = 11): 27.5 years (SD 14.8) **Other characteristics** Not stated **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		reported from one patient who was withdrawn from the study **Comparator** Placebo: tiredness (n = 8) 38%, drowsiness (n = 1) 5%, headache (n = 1) 5%, diplopia (n = 2) 10%, hostility (n = 1) 5%, irritability (n = 1) 5%, skin rash (n = 1) 5%, CNS depression (n = 1) 5%, shortness of breath; n = 1) 5%, amnesia (n = 1) 5%, hallucination (n = 1) 5%, pain (n = 1) 5%	paper with respect to AEs and number of concurrent AEDs Statistical analysis showed there was no treatment × period interaction or period effect. The authors also report data relating to the plasma concentrations of LTG and concurrent AEDs but these data have not been extracted

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
conform to the model. Therefore, log transformation of the data was not performed to normalise the data. A 95% CI based on the Wilcoxon rank-sum test was also computed for the median difference in drug effects **Length of trial/frequency of follow-up** 44 weeks; patients were seen at screen and at the end of baseline. Patients were seen weekly for the first 2 weeks of each treatment period, again after 2 weeks and then at 4-weekly intervals. During the washout period, patients were seen after the first 2 weeks, and again after 4 weeks	seizures and AEs; women not at risk of pregnancy. Exclusion: suffering from severe organic or psychiatric illness; progressive neurological disease; tests revealing possible abnormality of bone marrow, liver or renal function other than those attributable to concomitant AEDs; chronic drugs other than AEDs or oral contraceptives; alcohol abuse; mental retardation; evidence of previous serious non-compliance			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; median (range) number of seizures with LTG vs placebo grouped according to % improvement with LTG **Intervention 1** *n* = 21 All seizures: 0–25% improvement with LTG (*n* = 1): median = 25 26–50% improvement with LTG (*n* = 3): LTG median = 19 (12–48) 51–100% improvement with LTG (*n* = 14): median 11 (2–37) No change (*n* = 2): median = 29 (14–44) Increase (*n* = 1): median = 21	**Outcome** Proportion of responders (at least 50% or other specified criteria); number of patients who ≥51% improvement in total seizure count between the two treatment periods (the % improvement is expressed relative to the larger of the two treatment period seizure totals) **Intervention 1** First-phase data LTG (*n* = 12): 6/12 End-phase data: LTG: 14/24 **Comparator** First-phase data LTG (*n* = 12): 1/12 End-phase data: not reported	**Outcome** Seizure days; number of patients in each category for % change with LTG for days with seizures **Intervention 1** Days with seizures: 1–25% decrease (*n* = 2) 26–50% decrease (*n* = 3) 51–100% decrease (*n* = 12) No change (*n* = 1) Increase (*n* = 3) The analysis of total seizure days showed a significant reduction during LTG treatment period ($p < 0.002$) **Comparator** Not reported	**Outcome** Seizure frequency; total seizure counts for each individual patient during the 12-week treatment periods on LTG and placebo **Intervention 1** Placebo/LTG sequence group (for each patient): Patient no. 2 (*n* = 6); no. 4 (*n* = 2); no. 6 (*n* = 11); no. 7 (*n* = 13); no. 9 (*n* = 15); no. 10 (*n* = 21); no. 14 (*n* = 10); no. 15 (*n* = 48); no. 20 (*n* = 14); no. 21 (*n* = 25); no. 22 (*n* = 10) LTG/placebo sequence group: Patient no. 1 (*n* = 22); no. 3 (*n* = 37); no. 5 (*n* = 24); no. 11 (*n* = 36); no. 12 (*n* = 11); no. 13 (*n* = 4); no. 16 (*n* = 7); no. 17 (*n* = 44); no. 19 (*n* = 12); no. 24 (*n* = 19)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Partial seizures: 1–25% decrease (n = 1) 26–50% decrease (n = 3) 51–100% decrease (n = 12) No change (n = 0) Increase (n = 1) Secondarily generalised seizures: 1–25% decrease (n = 0) 26–50% decrease (n = 1) 51–100% decrease (n = 7) No change (n = 5) Increase (n = 2) The median reduction in seizure frequency with LTG was 59% (95% CI: 34 to 76%) The analysis of seizure counts over the whole 12-week treatment period on LTG showed a statistically significant reduction in seizures compared with placebo for total seizures ($p < 0.002$), simple and complex partial seizure counts ($p < 0.002$) and SGTC seizure counts ($p < 0.05$) **Comparator** 0–25% improvement with placebo (n = 1): median = 31 26–50% improvement with placebo (n = 3): median = 29 (17–30) 51–100% improvement with placebo (n = 14): median = 43.5 (16–175) No change (n = 2): median = 29 (14–44) Increase (n = 1): median = 16			**Comparator** Placebo/LTG sequence group (for each patient): Patient no. 2 (n = 22); no. 4 (n = 78); no. 6 (n = 27); no. 7 (n = 32); no. 9 (n = 68); no. 10 (n = 16); no. 14 (n = 22); no. 15 (n = 73); no. 20 (n = 14); no. 21 (n = 31); no. 22 (n = 21) LTG/placebo sequence group: Patient no. 1 (n = 55); no. 3 (n = 157); no. 5 (n = 85); no. 11 (n = 175); no. 12 (n = 101); no. 13 (n = 21); no. 16 (n = 16); no. 17 (n = 44); no. 19 (n = 17); no. 24 (n = 29)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Loiseau, 1990[89] **Related publications** Industry trial report[361] **Country** European **Source** Literature search **Aim** To assess the efficacy and safety of LTG as an add-on therapy in a randomised double-blind placebo-controlled trial of the drug in 23 adult patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30009 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Central randomisation centre; after pretrial period	**Number of participants** 25 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 23): 34.2 years (SD 12.41); LTG/placebo (n = 10): 38.1 years (SD 12.91); placebo/LTG (n = 13): 31.2 years (SD 11.62); 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 **Age at onset of seizures** Duration of seizures: 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) **Pretrial 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	**Intervention 1** LTG/placebo; 150 or 300 mg/day; 8 weeks No. randomised: 11 No. completed: 10 No. analysed: 0 **Intervention 2** NA No. randomised: 0 No. completed: 0 No. analysed: 0 **Intervention 3** NA No. randomised: 0 No. completed: 0 No. analysed: 0 **Comparator** Placebo/LTG; NA; 8 weeks No. randomised: 14 No. completed: 13 No. analysed: 0	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Placebo/LTG group: withdrawn owing to breach of admission criteria (n = 1) LTG/placebo group: withdrew consent (n = 1) **Adverse events** **Intervention 1** Vertigo (n = 3/23) 13%, nervousness (n = 2/23) 9%, anomaly vascular (n = 1/23) 4%, acne (n = 1/23) 4%, oedema peripheral (n = 1/23) 4%, pain (n = 1/23) 4%, conjunctivitis (n = 1/23) 4%, asthenia (n = 1/23) 4%, dizziness (n = 1/23) 4% All events were classified as not serious and there were no withdrawals because of AEs **Comparator** Nervousness (n = 1/23) 4%, somnolence (n = 1/23) 4%, stupor (n = 1/23) 4%, dry mouth (n = 1/23) 4%, headache (n = 1/23) 4% All events were classified as not serious and there were no withdrawals because of AEs	**Authors' conclusions** LTG has demonstrated unequivocal efficacy as an add-on therapy in patients with poorly controlled simple and complex seizures. The drug was well tolerated over the 2-month treatment period. There were no changes in laboratory safety measures considered to be attributable to LTG. It did not affect the plasma concentrations of concomitant AEDs **Comments** Additional data taken from trial report Although there was an 8-week treatment period in total, the first week was not full dose, therefore there were only 7 weeks at full treatment The authors provide data only on patients who completed the trial (n = 23). Although the text indicates that the minimum dose of LTG received was 75 mg/day, the corresponding table indicates that it was 150 mg/day. Three of the patients included in the trial had fewer than 4 seizures/month in the baseline period as specified by the inclusion criteria The authors used a balanced randomisation code which was generated for 40 patients (block size 4) to ensure an equal number

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 4-week baseline period (with constant AED dosage). This was followed by an 8-week treatment period with full dose of LTG achieved by week 2. Patients on enzyme-inducing concomitant AEDs only received 300 mg/day; patients on enzyme-inducing concomitant AEDs and VPA received 150 mg/day. In the event of an adverse experience attributable to trial medication, the dose could be reduced by 25% or 50%. This was followed by a 4-week washout period with tapering dose in the first week and placebo for the subsequent 3 weeks. Participants were then crossed over for another 8 weeks of treatment followed by another 4-week washout period, similar to the first **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The trial aimed to recruit 20 completed patients to comply with recommendations from the ILAE. Twenty patients were considered the minimum number required to demonstrate a treatment effect using a crossover design. No further details are given **Analysis methods** The seizure total for each phase was log transformed to conform to the Koch model. Data were then analysed using the Wilcoxon rank-sum test. Percentage reduction in seizure count totals was derived from the LTG/placebo ratio. Approximate 95% CIs were derived using	**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 **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: 16–65 years; confident diagnosis of epilepsy uncomplicated by suspected psychogenic attacks; partial seizures easily recognisable by patient/carer and classifiable by ICS; minimum of 4 partial seizures/month in each of previous 3 months and baseline period; AED unchanged for previous 3 months; seizures resistant to first-choice AEDs to therapeutic plasma concentrations. Exclusion: severe organic or psychiatric disease; severe mental subnormalities; progressive neurological disease; abnormal values of laboratory screen considered to be of clinical significance and not attributable to enzyme induction; status epilepticus in previous			of patients received placebo and LTG. This depended upon patient numbers being consecutive. The authors state that complex numbering arrangements between the two centres used in the study created an imbalance in the number of patients in the two groups The statistical analysis found there was no significant treatment × period interaction or period effect. The authors also report data relating to the plasma concentrations of LTG and concurrent AEDs but these data have not been extracted. The authors do not appear to have conducted a paired analysis, which is the appropriate analysis for crossover studies

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
the binomial theorem applied to the LTG/placebo seizure count ratio statistics **Length of trial/frequency of follow-up** 28 weeks; total seizure count over whole treatment period. For vital signs, adverse experiences and laboratory tests weekly for the first 2 weeks of treatment period, then after 2 and 4 weeks. Seen during the first week of washout and then after 3 weeks	6 months or more than once in previous 2 years; use of other investigational drugs in previous 6 months; more than 2 AEDs; other chronic medication; abuse of alcohol or other substances; inability to fulfil protocol requirements; pregnancy, lactation or current risk of pregnancy			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure frequency; reported as individual patient data relating to the total seizure counts during the 8-week treatment periods on LTG and placebo **Intervention 1** LTG/placebo sequence group (seizures whilst on LTG): Patient no. 1 ($n = 256$); no. 3 ($n = 14$); no. 6 ($n = 33$); no. 7 ($n = 16$); no. 10 ($n = 10$); no. 11 ($n = 16$); no. 18 ($n = 10$); no. 20 ($n = 17$); no. 23 ($n = 3$); no. 34 ($n = 0$) Placebo/LTG sequence group (seizures whilst on LTG): Patient no. 2 ($n = 50$); no. 4 ($n = 18$); no. 5 ($n = 25$); no. 8 ($n = 35$); no. 9 ($n = 0$); no. 12 ($n = 7$); no. 15 ($n = 15$); no. 16 ($n = 5$); no. 17 ($n = 34$); no. 19 ($n = 6$); no. 21 ($n = 7$); no. 22 ($n = 3$); no. 33 ($n = 25$) Placebo vs LTG ($p < 0.05$)	**Outcome** 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 1** 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 ($p < 0.05$)	**Outcome** Seizure days; Reported as the total number of seizure days **Intervention 1** 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	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; Physician reported global evaluation of improvement **Intervention 1** Number of patients considered better on LTG than placebo (10/23) Number of patients where there was no change from baseline for either treatment (8/23) **Comparator** Number of patients considered better on placebo than LTG (5/23)

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Comparator Placebo/LTG sequence group (seizures whilst on placebo): Patient no. 2 (n = 77); no. 4 (n = 22); no. 5 (n = 31); no. 8 (n = 21); no. 9 (n = 5); no. 12 (n = 16); no. 15 (n = 48); no. 16 (n = 4); no. 17 (n = 28); no. 19 (n = 10); no. 21 (n = 19); no. 22 (n = 8); no. 33 (n = 17) LTG/placebo sequence group (seizures whilst on placebo): Patient no. 1 (n = 333); no. 3 (n = 22); no. 6 (n = 28); no. 7 (n = 20); no. 10 (n = 21); no. 11 (n = 22); no. 18 (n = 9); no. 20 (n = 7); no. 23 (n = 9); no. 34 (n = 0)	**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)		
Outcome 5			
Outcome Percentage responders; ≥ 50% reduction in seizures **Intervention 1** First-phase data LTG (n = 11): 2/11 End-phase data (n = 25): 8/25 **Comparator** First-phase data placebo (n = 14): 1/14 End-phase data not reported			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Messenheimer, 1994[158] **Related publications** Industry trial report[367] **Country** USA **Source** Literature search **Aim** To evaluate add-on LTG therapy in patients receiving a stable regimen of AEDs that did not control their partial seizures adequately **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** P42/06/W7(1) **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was an 8-week baseline period followed by a 14-week treatment phase during which titration occurred. The starting dose was 100 mg/day for 3 days,	**Number of participants** 108 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 88): 35 years; LTG/placebo (n = 44): 35 years; placebo/LTG (n = 44): 35 years (SD not stated); total (n = 88): 18–64 years; LTG/placebo (n = 44): 18–58 years; placebo/LTG (n = 44): 18–64 years **Gender** Total (n = 88): men = 41, women = 47; LTG/placebo (n = 44): men = 21, women = 23; placebo/LTG (n = 44): men = 20, women = 24 **Age at onset of seizures** Mean duration of epilepsy total (n = 88): 23.1 years; LTG/placebo (n = 44): 22.3 years; placebo/LTG (n = 44): 24.0 years Mean age at onset: total (n = 88): 12.0 years; LTG/placebo (n = 44): 13.1 years; placebo/LTG (n = 44): 10.8 years **Pretrial medication** Not stated **Ongoing concurrent medication** One concurrent AED: total (n = 88): 41%; LTG/placebo (n = 44): 45%;	**Intervention 1** LTG/placebo; 400 mg/day max.; 14 weeks No. randomised: 46 No. completed: 44 **Comparator** Placebo/LTG; NA; 14 weeks No. randomised: 52 No. completed: 44	**Withdrawals prerandomisation** Total: n = 10, reasons not stated **Withdrawals postrandomisation** LTG: clinically significant adverse experience (n = 4), intercurrent illness (n = 1), withdrew consent (n = 1); placebo: exacerbation of seizure activity (n = 2), clinically significant adverse experience (n = 1), intercurrent illness (n = 1) **Adverse events** **Intervention 1** AEs occurring in ≥ 10% of participants (n = 94): ataxia (32%), headache (17%), dizziness (31%), diplopia (18%), somnolence (16%), rash (15%), rhinitis (13%), nausea (17%), accidental injury (14%). Five AEs (ataxia, dizziness, diplopia, somnolence and rash) occurred more frequently ($p \leq 0.05$) with add-on LTG treatment than with placebo. Blurred vision and other vision abnormalities, most of them mild and not considered serious, occurred significantly more often with LTG treatment than with placebo, but the frequency of these was <10% in both groups **Comparator** AEs occurring in ≥ 10% of participants (n = 96): ataxia (6%), headache (15%), dizziness (10%),	**Authors' conclusions** The addition of twice-daily LTG to an existing AED regimen was safe, effective and well tolerated in these medically refractory partial seizure patients **Comments** Additional data is extracted from the industry trial report The actual maintenance dose for 76% of patients averaged 377 mg/day. An additional 14% of patients received an actual mean maintenance dose of 317 mg/day The 14-week treatment period included a minimum of 3 weeks titration at the beginning and a 2-week tapering period at the end, therefore the treatment period at full dose of LTG was 9 weeks. Demographic data are provided only for the 88 patients included in the efficacy analysis Statistical analysis found no evidence of a significant treatment × period interaction. One of the 7 study centres had patients with a considerably greater range for baseline seizure frequency than the other centres. This group showed a 17% increase in seizure frequency. The median percentage reduction in the other 6 centres ranges from 0 to 36%. Data from the 7 centres were pooled for the main efficacy analysis

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
then 200 mg/day for 4 days, then 100 mg increments at weekly intervals until a maximum of 400 mg/day. The final 2 weeks of treatment had a blinded tapering regimen of LTG. This was followed by a 4-week washout period with no medication followed by a second 14-week treatment period. This was followed by a 3-week treatment-free period at the end of the study during which patients were observed. If the patient experienced a clinically significant adverse experience, the investigator could return the patient to the previous dosage for 1 week before attempting a further increase. The minimum dosage permitted in the study was 100 mg/day. When the maximum tolerated dosage of study medication was reached, the patient was maintained at this dosage until week 12 of the 14-week treatment period The required baseline seizure frequency was at least four seizures in each 4-week interval of the baseline period **ITT analysis performed/method** Authors state no; NA **Sample size calculation** Not stated **Analysis methods** Because the distribution of total seizure counts and changes in seizure days were highly skewed, data were therefore log transformed prior to ANOVA. The proportion of patients with a change in the investigator global evaluation scores was compared between treatments by the	placebo/LTG (n = 44): 36% Two concurrent AEDs: total (n = 88): 57%, LTG/placebo (n = 44): 52%; placebo/LTG: 61% Three concurrent AEDs: total (n = 88): 2%; LTG/placebo (n = 44): 2%; placebo/LTG (n = 44) 2% Total (n = 88): CBZ: 76%, PHT: 45% LTG/placebo (n = 44): CBZ 76%, PHT 45% Placebo/LTG: CBZ 76%, PHT 45% Additional concurrent AEDs taken: bromides, clorazepate, mephenytoin, methsuximide, PB, PRM **Co-morbidities** Not stated **Baseline seizure frequency** Median seizure frequency/month (simple partial, complex partial or secondarily generalised seizures): total (n = 88): 12.5; LTG/placebo (n = 44): 13.3; placebo/LTG (n = 44): 12.3 Median seizure frequency/month (simple partial or complex partial seizures): total (n = 88): 12.5; LTG/placebo (n = 44): 12.5; placebo/LTG (n = 44): 12.3 Median seizure frequency/month (secondarily generalised seizures): total (n = 88): 1.5; LTG/placebo (n = 44): 2.5; placebo/LTG (n = 44): 1.0 **Other characteristics** Not stated		diplopia (3%), somnolence (4%), rash (6%), rhinitis (6%), nausea (11%), accidental injury (7%)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Mantel–Haenszel statistic; $p \leq 0.05$ was considered statistically significant. All statistical tests and CIs were 2-sided. The efficacy analysis consisted of 88 patients who completed at least 12 weeks of the second leg of the crossover **Length of trial/frequency of follow-up** 43 weeks; at end of each treatment period and at the end of the follow-up period	**Inclusion/exclusion criteria** Inclusion: 18–65 years; simple or complex partial seizures with or without becoming secondarily generalised classified according to the ICSs; seizures not adequately controlled by currently marketed AEDs. Exclusion: Epilepsy duration <32 weeks; exhibiting pseudo-seizures or primary generalised seizures; seizures secondary to drugs, alcohol, infection, neoplasia, demyelination, metabolic illness or progressive degenerative disease; status epilepticus within 24 weeks of baseline; concomitant treatment with valproate within 2 weeks of baseline; abuse of drugs or alcohol; current psychoactive medication; 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; pregnancy or risk of pregnancy			

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Proportion of responders; reported as percentage number of patients (range) experiencing the defined categories of seizure reduction, compared with placebo during the LTG maintenance period **Intervention 1** First-phase data LTG (n = 46): 4/46 End-phase data: ≥ 50% decrease: 20% (13–27%) 26–49% decrease: 24% (13–42%) 25% no change: 38% (17–60%) 26–49% increase: 7% (0–14%) ≥ 50% increase: 11% (0–29%) Placebo vs LTG ($p < 0.001$) **Comparator** First-phase data placebo (n = 52): 4/52 End-phase data: not reported	**Outcome** Proportion of seizure-free patients; reported as percentage number of patients (range) experiencing the defined categories of reduction in seizure-free days, compared with placebo during the LTG maintenance period **Intervention 1** ≥ 50% decrease: 16% (0–29%) 26–49% decrease: 18% (0–40%) 25% no change: 49% (14–60%) 26–49% increase: 6% (0–14%) ≥ 50% increase: 11% (0–29%) Placebo vs LTG ($p < 0.01$) **Comparator** See above	**Outcome** Physician/patient global evaluation of improvement/efficacy; investigators' global evaluation of patient progress using a subjective assessment of overall clinical status. The rating scale ranged from 1 (marked deterioration) to 7 (marked improvement) **Intervention 1** Better response to LTG than to placebo: 47% No change in status: 31% Better response to placebo than LTG: 22% Placebo vs LTG ($p = 0.013$) **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sander, 1990[135] **Related publications** Industry submission[433] **Country** UK **Source** Literature search **Aim** The efficacy of LTG, a new AED chemically unrelated to drugs in current use, was evaluated in inpatients with severe refractory epilepsy **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** H34/C/85/AWP/1(UK-)022 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Inpatient **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** There was an 8-week baseline period where seizure frequencies were established. LTG was commenced in the	**Number of participants** 26 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 21): 34.6 years; total (n = 21): 23–42 years **Gender** Total: men = 18, women = 3; LTG/placebo (n = 10): men = 8, women = 2; placebo/LTG (n = 11): men = 10, women = 1 **Age at onset of seizures** Mean duration of epilepsy (n = 21): total: 25 years (range 8–40 years) **Pretrial medication** See concurrent medications **Ongoing concurrent medication** One AED (n = 3/21); two AEDs (n = 7/21); three AEDs (n = 11/21). Concurrent AEDs included CBZ (n = 19/21); PHT (n = 8/21); VPA (n = 13/21); PB (n = 3/21); CLB (n = 4/21); nitrazepam (n = 1/21) Other concurrent drugs: haloperidol, DZP, paracetamol, amoxycillin, aspirin, temazepam, ampicillin, folic acid, norimin (norethisterone ethinyloestradiol), normacol	**Intervention 1** LTG/placebo; 150–300 mg/day; 12 weeks No. randomised: 10 No. completed: 8 **Comparator** Placebo/LTG; NA; 14 weeks No. randomised: 11 No. completed: 10	**Withdrawals prerandomisation** Total: insufficient seizures (n = 4); rash (n = 1) **Withdrawals postrandomisation** LTG: overdose of CBZ (n = 1), AEs (n = 1); placebo: hospitalisation due to burns received during seizure (n = 1) **Adverse events** **Intervention 1** Ataxia (n = 4), diplopia (n = 3), dizziness (n = 3), drowsiness (n = 3), headache (n = 3), depression (n = 0), nausea (n = 2), vomiting (n = 2) **Comparator** Ataxia (n = 3), diplopia (n = 2), dizziness (n = 2), drowsiness (n = 3), headache (n = 2), depression (n = 1), nausea (n = 1), vomiting (n = 0)	**Authors' conclusions** Although there was no significant reduction in total seizure count during the LTG treatment period compared with placebo, there appears to be a drug effect as there was a marked reduction in GTC seizures in favour of LTG in the last 4 weeks of the treatment period. There was no significant difference in volunteered adverse experiences during active and placebo treatment. Concomitant serum AED concentrations, biochemical and haematological parameters were unaffected by LTG treatment **Comments** Additional data are extracted from the industry trial report. Although there was a 12-week treatment phase (14 weeks in the second phase), maximum dose of LTG was not achieved until week 2 of the treatment phase. The titration period was short compared with current manufacturers' information for health professionals The planned dose was 100 or 200 mg/day depending on concomitant AEDs. Minimum dose received was 150 mg/day and maximum 300 mg/day The statistical analysis found there was no significant treatment × period interaction or period

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
12-week treatment phase with maximum dose by week 2. For those not taking VPA the final dose of LTG was 200 mg and for those taking VPA the final dose was 100 mg. For patients without AEs who had <50% reduction in seizures the protocol permitted a 50% increase in dose. After the 12-week treatment period there was a 6-week washout period with LTG treatment tapered in the first 2 weeks and replaced with placebo. The second 12-week treatment period was extended by an extra 2 weeks so that treatment was not tapered while patients were away from the centre on holiday. This was followed by a similar washout period to that at crossover. Patients were required to experience at least 4 seizures per month during baseline **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** This trial aimed at obtaining a minimum of 20 completed patients, the minimum number required to demonstrate a treatment effect using a crossover design **Analysis methods** Statistical comparisons of seizure frequencies were made using non-parametric methods for a 2-period crossover model **Length of trial/frequency of follow-up** 46 weeks; physical, neurological and ECG at beginning and end of each study phase. All other assessments were at 2-week intervals in first month of each treatment period and monthly thereafter	**Co-morbidities** Not stated **Baseline seizure frequency** See Outcome 1 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: age 16–60 years; confident diagnosis of epilepsy uncomplicated by suspected psychogenic attacks; any seizure type but not absence seizures alone; seizures recognisable by patient or relative; at least four seizures per month through each of the previous 3 months; no abnormal laboratory values of clinical significance; not taking more than 3 standard AEDs; patient compliant and able to record seizures and AEs; females of childbearing potential using contraceptive methods Exclusion: any severe organic or psychiatric illness or progressive neurological disease; tests revealing possible abnormality of bone marrow, liver or renal function, other than those attributable to enzyme induction by concomitant AEDs; taking VPA as monotherapy; taking any chronic drug other than AEDs, oral contraceptives or long-term psychotropic drugs; abuse of alcohol or other drugs; pregnancy, lactation or current exposure to risk of pregnancy; evidence of previous serious non-compliance and psychogenic seizures			effect. The authors also report data relating to the plasma concentrations of LTG and concurrent AEDs but these data have not been extracted The authors report there was no significant difference between the AEs volunteered during the placebo and active treatment phases Data reported in the industry trial report differ slightly from data reported in the published paper with respect to AEs, length of treatment period 1 and the number of patients completing the study. Where differences are apparent, the data have been extracted from the published paper

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Seizure frequency; the total number of all seizures and the total number of generalised seizures experienced by the patients as a whole **Intervention 1** All seizures (n = 18): Baseline (n = 371) Weeks 0–4 (n = 450) Weeks 5–8 (n = 291) Weeks 9–12 (n = 288) Generalised seizures (n = 18): Baseline (n = 76) Weeks 0–4 (n = 72) Weeks 5–8 (n = 48) Weeks 9–12 (n = 33) Seizure frequencies over the last 8 weeks of the two treatment periods showed a statistically significant reduction in GTC seizures on LTG compared with placebo ($p < 0.05$) **Comparator** Total seizures (n = 18): Weeks 0–4 (n = 344) Weeks 5–8 (n = 298) Weeks 9–12 (n = 338) Generalised seizures (n = 18): Weeks 0–4 (n = 66) Weeks 5–8 (n = 53) Weeks 9–12 (n = 64)	**Outcome** Seizure-free days **Intervention 1** LTG (n = 18): 72 **Comparator** Placebo (n = 18): 64	**Outcome** Percentage responders; number of patients who showed ≥ 51% improvement in total seizure count (the % improvement is expressed relative to the larger of the two treatment period totals) **Intervention 1** End-phase data LTG: 2/21 **Comparator** Placebo: not reported

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Schapel, 1993[161] **Related publications** Full trial report,[337] cognitive outcomes for 10 patients[88] **Country** Australia **Source** Literature search **Aim** To assess the efficacy and safety of LTG in patients with partial seizures uncontrolled with established AEDs **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** H34-035-C86 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a 3-month retrospective baseline period to establish seizure frequency. Patients were given full dose of LTG by	**Number of participants** 41 **Type of epilepsy** Refractory **Type of seizures** Partial **Mean age/age range** Total (n = 41): mean 31.0 years (11.9); LTG/placebo (n = 20): 30.0 years (SD 11.4); placebo/LTG (n = 21): 32.0 years (SD 12.6); total (n = 41): 17–63 years; LTG/placebo (n = 20): 17–63 years; placebo/LTG (n = 21): 17–60 years **Gender** Total (n = 41): men = 21, women = 20; LTG/placebo (n = 20): men = 12, women = 8; placebo/LTG (n = 21): men = 9, women = 12 **Age at onset of seizures** Mean Age at onset of seizures: total (n = 41): 10.4 years (SD 9.6); LTG/placebo (n = 20): 10.5 years (SD 9.5); placebo/LTG (n = 21): 10.4 years (SD 10.0) **Pretrial medication** See concurrent medications **Ongoing concurrent medication** Total: CBZ (n = 30/41), PHT (n = 16/41), VPA (n = 13/41)	**Intervention 1** LTG/placebo; 150 or 300 mg/day; 12 weeks No. randomised: 20 No. completed: 20 **Comparator** Placebo/LTG; NA; 12 weeks No. randomised: 21 No. completed: 21	**Withdrawals prerandomisation** There were no withdrawals **Withdrawals postrandomisation** There were no withdrawals **Adverse events** **Intervention 1** AEDs reported by at least 3 patients during study; ataxia (n = 7), dizziness (n = 7), nausea (n = 7), headache (n = 6), vomiting (n = 6), rash (n = 6), asthenia (n = 4), diplopia (n = 4), pain (n = 4), vision abnormality (n = 4), rhinitis (n = 3), somnolence (n = 3) **Comparator** Ataxia (n = 2), nausea (n = 3); headache (n = 2), vomiting (n = 3), rash (n = 4), asthenia (n = 9), pain (n = 1), somnolence (n = 6)	**Authors' conclusions** The addition of LTG was associated with a significant reduction in the number of seizures experienced by patients with epilepsy refractory to established AEDs. It is well tolerated when given in addition to up to 2 other established AEDs **Comments** Additional information was taken from the industry trial report Although there was a 12-week treatment period, full dose was not received until week 2. One study participant was receiving 3 concurrent AEDs despite inclusion criterion of a maximum of 2 concomitant AEDs. The titration period was short compared with current manufacturers' information for health professionals The authors also report data relating to the plasma concentrations of LTG and concurrent AEDs but these data have not been extracted

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
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 **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The initial aim of the study was to recruit 30 participants with 20 completing; however, subsequent information suggested that the power of the study would be too low and that 40–50 participants (40 completing) were required to provide sufficient power to detect differences in seizure frequency **Analysis methods** Seizure counts were accumulated to give totals for each treatment phase. Log transformation of seizure counts was carried out prior to analysis. ANOVA was used to test for treatment effect, centre effect, period effect or treatment × period interaction. Centre and its interactions were not statistically significant in the initial model and were then dropped to give reduced models which were used to compute an estimate of the drug effect and 95% CIs	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) **Co-morbidities** Not stated **Baseline seizure frequency** Total baseline seizure frequency (3 months pretrial): 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) **Other characteristics** Not stated **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 other than			

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Length of trial/frequency of follow-up 12 weeks; baseline and at the end of each phase	epilepsy; abnormal laboratory values; status epilepticus in previous 6 months; use of investigational drug in previous 6 months; taking more than two AEDs or taking VPA monotherapy; chronic medication; alcohol or other substance abuse; evidence of previous non-compliance (i.e clinic attendance); pregnancy, lactation or current exposure to risk of pregnancy			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; number of participants experiencing specified percentage reductions in total seizure counts **Intervention 1** First-phase data: ≥50% reduction: 5/20 All phases data: all seizure types (n = 41): 50–100% decrease (n = 9); 26–49% decrease (n = 12); 1–25% decrease (n = 5); no change (n = 1). Placebo vs LTG ($p < 0.001$) SPSs and CPSs: 50–100% decrease (n = 8); 26–49% decrease (n = 12); 1–25% decrease (n = 3); no change (n = 1). Placebo vs LTG ($p < 0.05$) Secondarily generalised seizures: 50–100% decrease (n = 9); 26–49% decrease (n = 1); 1–25% decrease (n = 0); no change (n = 2) **Comparator** First-phase data: ≥50% reduction: 1/21 All phases data: all seizure types: 50–100% decrease (n = 0); 26–49% decrease (n = 4); 1–25% decrease (n = 10) SPSs and CPSs: 50–100% decrease (n = 1); 26–49% decrease (n = 6); 1–25% decrease (n = 8) Secondarily generalised seizures: 50–100% decrease (LTG n = 9) (placebo n = 3); 26–49% decrease (LTG n = 1) (placebo n = 1); 1–25% decrease (LTG n = 0) (placebo = 1)	**Outcome** Seizure days; number of participants experiencing specified percentage reductions in total number of seizure days **Intervention 1** 50–100% decrease (n = 9); 26–49% decrease (n = 7); 1–25% decrease (n = 11) Placebo vs LTG ($p < 0.001$) **Comparator** 50–100% decrease (n = 0); 26–49% decrease (n = 2); 1–25% decrease (n = 8)	**Outcome** Change in seizure frequency; median percentage reduction in seizure frequency for the different seizure types and median percentage reduction in seizure days **Intervention 1** All seizure types: median = 23.9% (95% CI: 11.5 to 34.6); SPSs and CPSs: median = 20.4% (95% CI: 5.5 to 33.0); secondarily generalised seizures: 45.8% (95% CI: –0.01 to 71.1); seizure days: 21.8% (95% CI: 10.7 to 31.5) **Comparator** Not reported	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; ratings are as follows: 1 = marked deterioration, 2 = moderate deterioration, 3 = mild deterioration, 4 = no change, 5 = mild improvement, 6 = moderate improvement **Intervention 1** LTG/placebo sequence: score 1 < 2 (n = 4), score 1 > 2 (n = 11) 12 patients showed no change in assessment between LTG and placebo treatment phases **Comparator** Placebo/LTG sequence: score 1 < 2 (n = 3), score 1 > 2 (n = 5)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Schmidt, 1993[91] **Related publications** Abstract of final results[375] **Country** Germany **Source** Industry submission **Aim** To assess the efficacy and safety of LTG as add-on therapy in patients with refractory partial seizures and to examine possible interactions between LTG and concomitant AEDs with reference to plasma concentrations **Type of publication** Industry trial report **Funding** GlaxoSmithKline **Trial ID** H34-18/C/85/WCY/34 (UK-018) **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 23 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 23): 30.3 years (SD 11.68); LTG/placebo: 31.2 years (SD 9.95); placebo/LTG: 29.5 years (SD 13.47); total (n = 23): 16–62 years; LTG/placebo: 19–46 years; placebo/LTG: 16–62 years **Gender** Total (n = 23): men = 11, women = 12; LTG/placebo: men = 5, women = 6; placebo/LTG: men = 6, women = 6 **Age at onset of seizures** Mean duration of epilepsy: total: 14.7 years (SD 0.84) Mean age at 1st seizure: total: 15.4 years (SD 12.82); LTG/placebo: 15.3 years (SD 11.39); placebo/LTG: 15.6 years (SD 14.51) Median age at 1st seizure: total: 12 years (range 1–50); LTG/placebo: 10 years (range 2–41); placebo/LTG: 13 years (range 1–50) **Pretrial medication** None stated, but the authors state that any previous AEDs were allowed to be continued during the study **Ongoing concurrent medication** LTG/placebo sequence (n = 11): CBZ (n = 9), PHT (n = 3), PB (n = 1), PRM	**Intervention 1** LTG/placebo; 400 mg/day mean dose; 24 weeks No. randomised: 11 No. completed: 9 **Comparator** Placebo/LTG; NA; 24 weeks No. randomised: 12 No. completed: 12	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG/placebo sequence: consent withdrawn (n = 2) **Adverse events** **Intervention 1** Incidence of AEs (reported by ≥ 10% of patients in either treatment group) LTG: headache (48%), dizziness (38%), asthenia (38%), diplopia (33%), nausea (29%), thinking abnormal (19%), insomnia (10%), back pain (10%), weight decrease (10%), abnormal vision (10%) **Comparator** Incidence of AEs (reported by ≥ 10% of patients in either treatment group) Placebo: headache (71%), dizziness (33%), asthenia (38%), diplopia (14%), nausea (10%), thinking abnormal (19%), weight decrease (0%), abnormal vision (5%)	**Authors' conclusions** LTG is efficacious in the treatment of partial seizures in patients with refractory epilepsy. LTG was safe and well tolerated. The majority of patients completing the study (86%) decided to continue in a long-term trial of LTG therapy **Comments** Sample size calculations are not reported, and the number of participants enrolled is less than required by the authors' *a priori* estimates, hence it is probable that the study is not sufficiently large enough to demonstrate effectiveness Equal numbers of patients in the LTG/placebo treatment group showed an improvement on both treatments, whereas 8 of 12 patients showed an improvement on LTG compared with 5 patients on placebo in the placebo/LTG group There were no ECG abnormalities emergent on LTG treatment and very few physical and neurological abnormalities reported during the study. Assessment of vital signs, weight, visual acuity and clinical laboratory tests did not show any abnormal changes attributable to LTG. LTG had no effect on the plasma concentration of concomitant AEDs. There was an indication

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period The study consisted of 12 weeks of treatment with LTG and placebo, in each case followed by a 4-week washout period (2 weeks taper, 2 weeks placebo). Total daily dose of LTG ranged from 50 to 540 mg. The daily dose of LTG was escalated over the first 3 weeks of the LTG treatment period depending on the patient's concomitant AEDs. LTG dosage could be decreased or not increased any further if the patient experienced side-effects. The LTG dosing regimen was as follows: (a) induced group (patients taking CBZ, PHT, PB or other liver enzyme-inducing AEDs, either alone or in combination): week 1, 100 mg/day, week 2, 200 mg/day; weeks 3–12, 400 mg/day; (b) balanced group (patients taking CBZ, PHT or PB in addition to VPA): week 1, 50 mg/day; week 2, 100 mg/day; weeks 3–12, 200 mg/day; (c) inhibited group (patients taking VPA alone): week 1, 25 mg/day; week 2, 50 mg/day; weeks 3–12, 100 mg/day. During the first 2 weeks of washout following treatment with LTG, each patient was tapered by decreasing the LTG dose to 50% of the maintenance dose in the first week and 25% in the second week. Placebo was then prescribed for the remaining 2 weeks of the washout period **ITT analysis performed/method** Authors state yes; not stated	(*n* = 1), aluminium hydroxide (*n* = 1), alprazolam (*n* = 1), amiloride (*n* = 1), hydrochlorothiazide (*n* = 1), DZP (*n* = 1) Placebo/LTG sequence (*n* = 12): CBZ (*n* = 9), PHT (*n* = 3), PB (*n* = 1), metoprolol (*n* = 1), metoclopramide (*n* = 1), oxilofirin (*n* = 1), thyroxine (*n* = 1), tizanidine (*n* = 1), acetylsalicylate (*n* = 1), DZP (*n* = 2) **Co-morbidities** None stated **Baseline seizure frequency** Mean number of seizures per month: total: 13.5 (SD 11.84); LTG/placebo: 13.9 (SD 14.18); placebo/LTG: 13.0 (SD 9.63) Median number of seizures per month: total: 10.5 (range 1–52); LTG/placebo: 10 (range 1–52); placebo/LTG: 12 (range 4–37) **Other characteristics** 65% patients had symptomatic epilepsy and 35% had multiple partial seizure types **Inclusion/exclusion criteria** Inclusion: age 16–65 years; confident diagnosis of epilepsy uncomplicated by suspected pseudoseizures; at least 4 partial seizures per month in previous 3 months; daily seizure diary for previous 3 months; easily recognisable seizures resistant to drugs of first choice; no more than two concomitant AEDs unchanged for previous 3 months or patients on no medication; no investigational drug in previous 6 months or chronic use of other non-AED medication except for oral contraceptives; no severe organic or psychiatric disease, mental subnormality or progressive neurological			that higher plasma LTG concentrations were associated with a beneficial response to LTG Any daily seizure count of ≥ 30 was classified as a serial seizure. Serial seizures were excluded from the main efficacy analyses

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sample size calculation The aim of the study was to recruit up to 30 patients with refractory partial seizures, with at least 20 patients completing the study **Analysis methods** Median percentage change in seizure counts between LTG and placebo was calculated with 95% CIs. ANOVA was carried out for various categories of seizures and seizure days to compare LTG and placebo treatments during the treatment and washout phases, respectively. ANOVA was also performed for the first treatment period alone for various categories of seizure type **Length of trial/frequency of follow-up** 32 weeks; assessments took place at the end of weeks 1, 2, 4, 8, 12 (treatment period 1), 17, 18, 20, 24 and 25 (treatment period 2)	disease; no abnormal laboratory values of clinical significance and negative for hepatitis B antigen; not experienced status epilepticus in previous 6 months or more than once in past 2 years; not pregnant, lactating or exposed to risk of pregnancy; no previous history of serious non-compliance, non-attendance at clinics or failure to document seizures and adverse experiences; written informed consent from parent, guardian or competent patient Exclusion: severe organic or psychiatric disease (other than epilepsy), severe mental subnormality, and/or progressive neurological disease; positive for hepatitis B antigen and any abnormal laboratory values at screen considered to be clinically significant; status epilepticus in the past 6 months or more than once in the past 2 years; use of any investigative drug in the past 6 months, or taking more than 2 AEDs; chronic medication other than AEDs and oral contraceptives; abuse of alcohol or other substances; inability to fulfil protocol requirement, evidence of serious non-compliance; pregnancy, lactation or current exposure to risk of pregnancy			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; at least a 50% reduction in total seizure counts **Intervention 1** First-phase data: LTG: 1/11 End-phase data: LTG: 6/21 (28.6%)	**Outcome** Change in seizure frequency; median decrease in total seizure counts between LTG and placebo **Intervention 1** LTG: 27% (95% CI: –4% to 57%), $p = 0.027$	**Outcome** Median decrease in total seizure days; median percentage change in seizure days between LTG and placebo **Intervention 1** LTG: 21% (95% CI: 0% to 57%), $p = 0.011$	**Outcome** Reduction in total seizure days by at least 50%; at least a 50% reduction in total seizure days **Intervention 1** LTG: 7/21 (33.3%)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Comparator First-phase data: LTG: 1/12	**Comparator** See above	**Comparator** See above	**Comparator** Not reported
Outcome 5			
Outcome Investigator global evaluation; ratings are as follows: 3 = mild deterioration, 4 = no change, 5 = mild improvement, 6 = moderate improvement **Intervention 1** Placebo/LTG sequence: LTG: score 3 (*n* = 1), score 4 (*n* = 3), score 5 (*n* = 3), score 6 (*n* = 5) LTG/placebo sequence: LTG: score 3 (*n* = 0), score 4 (*n* = 6), score 5 (*n* = 3), score 6 (*n* = 0) **Comparator** Placebo/LTG sequence: placebo: score 3 (*n* = 0), score 4 (*n* = 7), score 5 (*n* = 5), score 6 (*n* = 0) LTG/placebo sequence: placebo: score 3 (*n* = 1), score 4 (*n* = 5), score 5 (*n* = 2), score 6 (*n* = 1)			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Smith, 1993[55] **Related publications** Industry trial report[378] and abstracts[376,377] **Country** UK **Source** Literature search **Aim** This study was designed to evaluate the efficacy and safety of LTG, a potential new AED, and to develop and test new outcome measures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** H34-086-C88 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; not stated **Details of pretrial period** There was a 4-week baseline period followed by two 18-week treatment periods during which patients received LTG	**Number of participants** 81 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 33.7 years; total: 15–67 years **Gender** Total: 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) **Pretrial medication** See concurrent medication **Ongoing concurrent medication** Concurrent chronic medications other than AEDs: vitamin C, azapropazone, ibuprofen, atenolol, hydralazine, ethynodiol diacetate, ferrous gluconate, folic acid, pyridoxine, thyroxine, terfenadine, mianserin, indipamide, nifedipine, beclomethasone, salbutamol, trazodone hydrochloride, haloperidol, procyclidine, temazepam, cimetidine, piroxicam, eugynon, pyridixine, magnesium trisilicate, folic acid Concurrent AEDs: DZP	**Intervention 1** LTG/placebo; 200 or 400 mg/day; 18 weeks No. randomised: 41 No. completed: 32 **Comparator** Placebo/LTG; NA; 18 weeks No. randomised: 40 No. completed: 30	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** 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) **Adverse events** **Intervention 1** Ataxia (36%), diplopia (33%), dizziness (29%), nausea (29%), respiratory disorder (23%), vomiting (17%), headache (16%), somnolence (16%), blurred vision (14%), pain (13%), pharyngitis (11%), asthenia (10%), accommodation abnormality (9%), insomnia (9%), rash (9%), depression (7%), paraesthesia (7%), non-specific symptoms (7%), agitation (6%), amnesia (6%), fever (6%), tremor (6%), emotional lability (4%), menstrual disorder (4%), abdominal pain (4%), backpain (4%), bronchitis (3%), constipation (3%), convulsion (3%), cough (3%)	**Authors' 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 **Comments** Additional information was obtained from the authors and from the trial report Intervention 1 dosage: 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 Non-parametric analyses indicated significant treatment effects of LTG on total seizure count (p < 0.0000), CPSs (p = 0.0004) and SGTC seizures (p = 0.02). Parametric analysis indicated reductions in seizure frequency with LTG relative to placebo for all seizure types except simple partial seizures

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
or placebo separated by a 6-week washout period. The second treatment period was followed by a 4-week washout period. Patients receiving concurrent enzyme-inducing AEDs received a daily LTG dosage of 400 mg and those receiving a combination of an enzyme-inducing drug and VPA received 200 mg of LTG (for 16 of the 18 weeks). If the full dosage was not tolerated, it could be reduced to a minimum of 50% of the intended maximum dosage **ITT analysis performed/method** Authors state no; NA **Sample size calculation** The aim of the study was to recruit 80 patients with at least 60 patients completing the study. In previous studies, the mean difference in seizure counts between LTG and placebo treatment periods has been equal to approximately one-third of the within-patient standard deviation of that difference. To detect such an effect as statistically significant, at the level of 0.05 with power 70% (80%), would require approximately 50 (65) patients to complete the study **Analysis methods** The primary efficacy measure was seizure frequency during LTG treatment compared with placebo. The seizure totals for each patient in each of the two treatments were log transformed. Both parametric (ANOVA testing for a treatment effect, a period effect and a treatment × period interaction) and non-parametric analyses (Wilcoxon rank sum test) were carried out on the log	**Co-morbidities** Not stated **Baseline seizure frequency** Mean monthly seizure frequency: Simple partial (n = 15): 25.9 (range 2–70) Complex partial (n = 72): 25.2 (range 1–760) SGTC (n = 36): 5.3 (range 1–27) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: age 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 drug(s) 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		**Comparator** Ataxia (9%), diplopia (6%), dizziness (19%), nausea (11%), respiratory disorder (23%), vomiting (3%), headache (13%), somnolence (10%), blurred vision (4%), pain (9%), pharyngitis (1%), asthenia (17%), insomnia (1%), rash (7%), depression (7%), paraesthesia (1%), non-specific symptoms (7%), agitation (1%), amnesia (7%), tremor (3%), emotional lability (4%), menstrual disorder (3%), abdominal pain (3%), backpain (4%), bronchitis (1%), constipation (1%), convulsion (1%), cough (7%)	Data comparing seizure severity at placebo compared with baseline are also reported but have not been extracted. Data on the correlations between outcome measures have not been extracted Eight of the AEs had a significantly higher incidence with LTG: ataxia, diplopia, nausea, vomiting, blurred vision, pharyngitis, accommodation abnormality and insomnia There are some small discrepancies between the rates for AEs in this paper and Smith, 1993[376], which seems to report from the same data. Also in Smith, 1993[376] there was a category for severe rash and there was a significant difference between LTG and placebo. A statistically significant difference was also reported for fever. However, data have been extracted from Smith, 1993[55] as these are the most complete data Adjustment for multiple simultaneous comparisons by the Bonferroni method did not alter the significant results for the psychological dimensions of HRQoL

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
transformed data. Seizure severity scores, the HRQoL measures and the neuropsychological measures at baseline and at the end of each treatment phase were compared using paired *t*-tests Changes occurring with LTG relative to placebo were correlated for each physical and psychological parameter. When significant associations between changes in outcome variables were identified, multiple regression analysis was used to determine whether these associations were coincidental or independently significant **Length of trial/frequency of follow-up** 46 weeks; at the end of each treatment period				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; reported as number of patients in the given response categories with LTG compared with placebo **Intervention 1** First-phase data LTG (n = 41): 4/41 End-phase data: Total seizures (n = 62): Worse (>26% increase): n = 7 No change (±25%): n = 26 Mild improvement (26–49% decrease): n = 18 Marked improvement (≥50% decrease): n = 11	**Outcome** Change in seizure frequency; percentage seizure reduction comparing LTG with placebo **Intervention 1** (n = 62) Total seizures: 29.7% (95% CI: 17.8 to 39.9) Total partial seizures: 25.2% (95% CI: 10.7 to 37.4) Secondarily generalised seizures: 20.3% (95% CI: 0.3 to 36.2) CPSs: 33.4 (95% CI: 14.8 to 47.9) **Comparator** See above	**Outcome** Change in seizure severity; assessed by patient using a 16-item questionnaire divided into two subscales [perception and control (PERCEPT) and ictal and postictal (ICTAL)], and by the carer using an 8-item questionnaire. Mean scores are reported **Intervention 1** LTG (n = 53) PERCEPT: mean = 25.19 ICTAL: mean = 19.47 Carer view: mean = 20.35 Difference between means for LTG and placebo (95% CI) PERCEPT: –0.28 (95% CI: –1.00 to 0.43)	**Outcome** 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)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Partial seizures (n = 62): Worse (>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 (>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		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	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

Outcome 5	Outcome 6
Outcome 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	**Outcome** 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

continued

Outcome 5	Outcome 6
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	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

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Stolarek, 1994[162] **Related publications** None **Country** UK **Source** Literature search **Aim** Patients with refractory epilepsy, treated with an anticonvulsant regimen containing VGB, entered a balanced double-blind, placebo controlled, crossover trial of additional LTG **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Coin tossing; not stated **Details of pretrial period** There was a 4-week run-in period followed by two 12-week treatment periods during	**Number of participants** 22 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; total: 18–65 years **Gender** Total: men = 8, women = 12 (information available only for those who completed the trial) **Age at onset of seizures** Not stated **Pretrial medication** See concurrent medications **Ongoing concurrent medication** Total (n = 20): VGB (n = 20), CBZ (n = 15), CBZ 10, 11-epoxide (n = 15), VPA (n = 5), PHT (n = 3) **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: complex partial seizures with or without secondary	**Intervention 1** LTG/placebo; 200 mg/day; 12 weeks No. randomised: 11 No. completed: not stated **Comparator** Placebo/LTG; NA; 12 weeks No. randomised: 11 No. completed: 9	**Withdrawals prerandomisation** LTG: no withdrawals; placebo: no transport to attend study (n = 1), AEs (n = 1) **Withdrawals postrandomisation** Total: withdrew consent (n = 1); side-effects while taking placebo (n = 1) **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** This study suggests a substantial efficacy for a regimen containing VGB and LTG. Combinations of drugs with complementary modes of action may provide a rational pharmacological approach to the management of refractory epilepsy **Comments** Additional information was obtained directly from the authors The inclusion/exclusion criteria are limited, therefore it is possible that participants may have had concomitant conditions which may have had a confounding effect on the findings Although specific AEs are not reported, the authors report that there was no significant difference between LTG and placebo in the numbers of spontaneous or requested side-effects reported. Mean visual analogue scores for sedation, concentration, memory and depression did not differ significantly after 1 month's treatment (LTG 200 mg) and matched placebo

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
which patients received LTG or placebo separated by a 4-week washout period. The dose of LTG received was 50 mg/day weeks 1–4, 100 mg/day weeks 5–8 and 200 mg/day weeks 9–12 and matched placebo **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Statistical analysis of seizure data, AEs and AED concentrations was performed with the Wilcoxon rank test for matched pairs. The 95% CIs for the differences were calculated around median values. Mann–Whitney analysis for an order effect was carried out for total, partial and generalised seizures **Length of trial/frequency of follow-up** 36 weeks; weeks 0, 4, 8 and 12 during both treatment periods	generalisation; a minimum of 3 seizures/month for the previous 3 months despite a stable regimen of anticonvulsant treatment; an anticonvulsant regimen containing VGB Exclusion: criteria not stated			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure frequency; median numbers of seizures **Intervention 1** LTG (n = 20) Total seizures: Phase 1 (50 mg): median = 8.5 (range, 0–41) Phase 2 (100 mg): median = 6.5 (range, 0–36) Phase 3 (200 mg): median = 5.0 (range, 0–60) Overall: median = 18.5 (range, 0–137)	**Outcome** Change in seizure frequency; median reduction in seizure frequency experienced whilst on LTG vs placebo **Intervention 1** LTG (n = 20) Total seizures: Phase 1: median = 1.3 (95% CI: –1.5 to 4.0) Phase 2: median = 2.5 (95% CI: –6.5 to 0.5)	**Outcome** Change in seizure frequency; reduction in mean seizure counts comparing LTG and placebo **Intervention 1** (n = 20) Phase 1 mean seizure reduction: –6% Phase 2 mean seizure reduction: 32%	**Outcome** Proportion of responders; numbers of responders according to defined categories of seizure reduction comparing LTG and placebo

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 48
Partial seizures: Phase 1 (50 mg): median = 4.0 (range, 0–41) Phase 2 (100 mg): median = 5.5 (range, 0–36) Phase 3 (200 mg): median = 4.5 (range, 0–60) Overall: median = 18.0 (range, 0–137) Secondary generalised: Phase 1 (50 mg): median = 1.5 (range, 0–10) Phase 2 (100 mg): median = 1.0 (range, 0–9) Phase 3 (200 mg): median = 0 (range, 0–5) Overall: median = 2.5 (range, 0–16) **Comparator** Placebo (n = 20) Total seizures: Phase 1: median = 8.0 (range, 0–50) Phase 2: median = 9.5 (range, 1–66) Phase 3: median = 8.0 (range, 0–72) Overall: median = 24.0 (range, 0–188) Partial seizures: Phase 1: median = 7.0 (range, 0–50) Phase 2: median = 6.5 (range, 0–66) Phase 3: median = 6.5 (range, 0–72) Overall: median = 17.5 (range, 0–186) Secondary generalised: Phase 1: median = 1.0 (range, 0–9) Phase 2: median = 1.0 (range, 0–11) Phase 3: median = 1.0 (range, 0–8) Overall: median = 5.0 (range, 0–23)	Phase 3: median = 3.0 (95% CI: –7.5 to –0.5) ($p < 0.05$) Overall: median = 6.2 (95% CI: –15.5 to –2.0) ($p < 0.005$) Partial seizures: Phase 1: median = 1.5 (95% CI: –4.0 to 1.0) Phase 2: median = 2.0 (95% CI: –5.5 to 1.5) Phase 3: median = 2.0 (95% CI: –7.0 to 1.0) Overall: median = 3.0 (95% CI: –13.0 to –0.5) ($p < 0.02$) Secondary generalised: Phase 1: median = 0 (95% CI: –1.0 to 1.0) Phase 2: median = 0 (95% CI: –2.0 to 0.5) Phase 3: median = 0.5 (95% CI: –2.0 to 0) ($p < 0.05$) Overall: median = 1.5 (95% CI: –3.5 to 0.5) **Comparator** See above	Phase 3 mean seizure reduction: 37% Overall mean seizure reduction: 23% **Comparator** See above	**Intervention 1** (n = 20) Phase 1: >25% reduction (n = 5) >50% reduction (n = 3) Phase 2: >25% reduction (n = 4) >50% reduction (n = 7) Phase 3: >25% reduction (n = 3) >50% reduction (n = 9) Overall: >25% reduction (n = 6) >50% reduction (n = 4) **Comparator** See above

Outcome 5
Outcome Patient preference **Intervention 1** Preferred LTG (n = 16) ($p < 0.001$) **Comparator** Preferred placebo (n = 4)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Yaqub, 1995[82] **Related publications** None **Country** Saudi Arabia **Source** Literature search **Aim** To assess the efficacy and safety of LTG in a randomised double-blind, placebo-controlled, add-on, crossover study of 43 patients with severe epilepsy **Type of publication** Abstract (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** After randomisation, patients received LTG or placebo for 10 weeks. Patients were titrated to LTG maintenance dose of	**Number of participants** 43 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 43): 29 years (SD not stated); total (n = 43): 12–51 years **Gender** Total (n = 43): men = 23, women = 13 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Total (n = 43): 3.7 seizures/week **Other characteristics** Seizure types for included participants were: primarily generalised = 6, partial = 24 and secondarily generalised = 6	**Intervention 1** LTG/placebo; max. 400 mg/day; 10 weeks No. randomised: 43 No. completed: 36 **Comparator** Placebo/LTG; 10 weeks No. randomised: 43 No. completed: 36	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Overall (n = 36): poor compliance (n = 4) LTG (n = 36): dose-related CNS AEs (n = 2) Placebo (n = 36): AEs (n = 1) **Adverse events** **Intervention 1** Dose-related CNS AEs (n = 4) **Comparator** Placebo: AEs but not specified (n = 1)	**Authors' conclusions** LTG is efficacious and well tolerated as add-on treatment in patients with drug-resistant partial seizures receiving CBZ, PHT, or PB **Comments** These data are taken from an abstract rather than a full study report. It is lacking in detail therefore the quality of the study cannot be adequately assessed Sample size calculations are not reported so it is not possible to determine whether an adequate number of participants were enrolled in this study The response was almost the same in both types of seizure: 50% in generalised epilepsies and 53.3% in partial epilepsies

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
400 mg/day except those receiving VPA, who had half the dose **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 20 weeks; not stated	**Inclusion/exclusion criteria** Inclusion: patients with severe epilepsy (no further criteria reported)			
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Proportion of responders; responders were defined as having at least a 50% reduction in seizure frequency **Intervention 1** LTG: 52.7% (n = 19/36). The comparison with placebo showed a decrease in total seizure count of 44% during treatment with LTG compared with placebo **Comparator** Not stated				

Parallel studies (*n* = 20)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Biton, 2001[116] **Related publications** GSK trial report[345] and papers[126,341,343,344] **Country** USA **Source** Literature search **Aim** To compare the incidence and magnitude of change in body weight associated with LTG or VPA monotherapy in patients with epilepsy Depressive symptoms are highly prevalant in patients with epilepsy. The AED LTG has been shown to be an effective treatment for the depressive phase of bipolar disorder and to enhance mood and well-being in epilepsy patients. A recently completed double-blind epilepsy trial comparing the effects of LTG monotherapy and VPA monotherapy on weight change incorporated a battery of standard mood assessments Edwards, 2001[344] **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** SCAA4001	**Number of participants** 141 **Type of epilepsy** Combination of newly diagnosed/refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** LTG (*n* = 65): 34.5 years (SD 16); VPA (*n* = 68): 30.1 years (SD 14); LTG (*n* = 65): 12–68 years; VPA (*n* = 68): 12–76 years **Gender** LTG (*n* = 65): men = 27, women = 38; VPA (*n* = 68): men = 31, women = 37 **Age at onset of seizures** Age at onset was only provided for onset of GTC seizures (LTG *n* = 50; VPA *n* = 55) LTG: 28 years (SD 16); VPA: 26 years (SD 13) **Pretrial medication** Current or past AEDs reported at screening in previously diagnosed patients: PHT: LTG (*n* = 31); VPA (*n* = 33) CBZ: LTG (*n* = 10); VPA (*n* = 18) PB (*n* = 8); VPA (*n* = 4) Others: LTG (*n* = 19); VPA (*n* = 12)	**Intervention 1** LTG; 200 mg/day; 32 weeks No. randomised: 65 No. completed: 46 **Comparator** VPA; 20 mg/kg/d; 32 weeks No. randomised: 68 No. completed: 38	**Withdrawals prerandomisation** Lost prior to randomisation (reason not stated): *n* = 8 **Withdrawals postrandomisation** LTG: AEs (*n* = 6), withdrew consent (*n* = 7), protocol violations (*n* = 2), lost to follow-up (*n* = 2), other (*n* = 2); VPA: AEs (*n* = 9), withdrew consent (*n* = 7), protocol violations (*n* = 2), lost to follow-up (*n* = 7), other (*n* = 5) **Adverse events** **Intervention 1** Most common (≥ 10%) spontaneously reported AEs: Nausea (*n* = 8), asthenia (*n* = 13), somnolence (*n* = 5), tremor (*n* = 2), dizziness (*n* = 7); headache (*n* = 9); vomiting (*n* = 4), emotional disorder (*n* = 5), hair loss (*n* = 2), weight increase (*n* = 2), appetite increase (*n* = 1) At least one AE (*n* = 39) **Comparator** Nausea (*n* = 16), asthenia (*n* = 11), somnolence (*n* = 16), tremor (*n* = 19), dizziness (*n* = 6), headache (*n* = 4), vomiting (*n* = 9), emotional disorder (*n* = 7), hair loss	**Authors' conclusions** VPA monotherapy was associated with significantly greater weight gain than LTG monotherapy. Weight gain associated with VPA was significant within 10 weeks after initiating therapy and continued throughout the study. Efficacy of LTG was comparable to that of VPA; LTG tended to be better tolerated Considered in the context of other data showing LTG's antidepressant efficacy in bipolar depression, these results suggest that LTG improves mood in mildly depressed patients with epilepsy. LTG may be particularly useful in treating epilepsy patients with co-morbid depression, the most common psychiatric illness in epilepsy Edwards, 2001[344] **Comments** This data extraction form contains additional information from the related publications. Unless otherwise specified the information has been extracted from Bilton, 2001[116] It is not clear from the information provided how many of the previously diagnosed patients were not using AEDs on entry to the study and why

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Study design Monotherapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** There was a 2-week screening phase followed by an 8-week dose-escalation period and 24-week maintenance period. LTG was started at a dosage of 25 mg/day with a target dose of 200 mg/day. Investigators were then permitted to alter dosage based on clinical efficacy within 100–500 mg/day. VPA was started at 10–15 mg/kg/day with a target dose of 20 mg/kg/day. Adjustments were then permitted within the range 10–60 mg/kg/day. Double dummy dosing was used **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The sample size was calculated to detect differences in weight change but not efficacy. Based on an SD for weight gain of 8.8 lb, Type 1 error set at 0.05 and Type 2 at 0.8, 50 participants were considered sufficient to detect a mean difference of 4.4–6.6 lb **Analysis methods** ANCOVA was used with change in body weight as the dependent variable and	**Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Newly diagnosed patients: LTG: n = 22/65; VPA: n = 33/68 **Inclusion/exclusion criteria** Inclusion: age ≥ 12 years, with any epilepsy seizure type. Female patients had to have a negative urine or serum pregnancy test at screening and agree to use acceptable contraceptive methods during the study or be incapable of bearing children. Exclusion: previous use for more than 90 days of LTG, divalproex sodium, valproic acid or GBP; current use of an AED unless the drug could be withdrawn safely prior to randomisation; use of any investigational drug within the previous 12 weeks; chronic use of any medication that could influence seizure control; any acute or progressive neurological or severe psychiatric disease; any medical condition associated with significant changes in body weight; adherence to the ketogenic diet; participation in a weight-change programme; or current or planned use of vagal stimulation to control seizures		(n = 7), weight increase (n = 7), appetite increase (n = 7) At least one AE (n = 47)	The authors do not specify how data on seizure frequency was gathered. The 32-week follow-up period includes a titration phase of 8 weeks Intervention1 dose: mean 254 mg/day, SD 69 mg/day Comparator dose: mean dose 1822 mg/day (SD 633) This was not a homogeneous epilepsy group (there are newly diagnosed and previously diagnosed patients) and this is not taken into account in the analysis The authors also reported that mean time to withdrawal due to an AE was LTG mean = 103 (SD 70); VPA: mean = 79 (SD 48). For mean weight change over time ($p \leq 0.002$)

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
treatment group, age and gender as predictor variables. Baseline weight was defined as the average of the two weight readings before treatment. Change was defined as weight at week 32 minus weight at baseline. Spearman correlation analyses were used to identify possible predictors of change **Length of trial/frequency of follow-up** 32 weeks; weeks 3, 10, 14, 20, 26 and 32				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Clinically relevant weight gain; the number of participants with clinically relevant weight gain at week 32 (i.e. ≥ 8.8 lb or 10% greater than baseline) **Intervention 1** 6/50 (12%) **Comparator** 28/45 (62%)	**Outcome** Weight change; the mean weight change at weeks 10, 14, 20, 26, 32 **Intervention 1** Week 10 (0.6 kg), week 14 (0.7 kg), week 20 (0.3 kg), week 26 (0.4 kg), week 32 (0.6 kg) ($p \leq 0.002$ for all weeks) **Comparator** Week 10 (2.7 kg), week 14 (3.5 kg), week 20 (3.9 kg), week 26 (4.9 kg), week 32 (5.8 kg)	**Outcome** Change in body mass index (BMI); the mean change in BMI **Intervention 1** Mean change = 0.06 (SD 1.6) **Comparator** Mean change = 2.06 (SD 1.6)	**Outcome** Proportion of seizure-free patients; the proportion of patients remaining seizure-free during the titration and maintenance period **Intervention 1** ITT: *n* = 19/65 (29%) **Comparator** ITT: *n* = 18/68 (26%)	

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome Beck Depression Inventory (BDI); (mean change from baseline)[344]	**Outcome** Cornell Dysthymia Rating Scale; mean change from baseline	**Outcome** Profile of Mood States; mean change from baseline scores to week 32	**Outcome** ITT: responder rate: percentage of subjects with 50% reduction in seizures during the maintenance phase
Intervention 1 Week 10 LTG (n = 52): mean change = 2.2 Week 32 LTG (n = 44): mean change = 2.6	**Intervention 1** Week 10 LTG (n = 52): mean change = 1.4 Week 32 LTG (n = 44): mean change = 3.6	**Intervention 1** Total mood disturbance LTG (n = 42): mean change = 13.8 Confusion/bewilderment LTG: mean change = 1.0 Fatigue/inertia LTG: mean change = 1.2 Vigour/activity LTG: mean change = 1.6 Anger/hostility LTG: mean change = 2.9 Depression/dejection LTG: mean change = 3.8 Tension/anxiety LTG: mean change = 3.3	**Intervention 1** LTG: 34/65 (52%)
Comparator Week 10 VPA (n = 40): mean change = –0.1 Week 32 VPA (n = 35): mean change = 0.7	**Comparator** Week 10 VPA (n = 41): mean change = –0.3 Week 32 VPA (n = 33): mean change = 0.5	**Comparator** Total mood disturbance VPA (n = 36): mean change = 0.4 Confusion/bewilderment VPA: mean change = 0.4 Fatigue/inertia VPA: mean change = –0.7 Vigor/activity VPA: mean change = –1.3 Anger/hostility VPA: mean change = 0.4 Depression/dejection VPA: mean change = –0.6 Tension/anxiety VPA: mean change = –1.9	**Comparator** VPA 35/68 (51%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Brodie, 1995[121] **Related publications** Letter to the Editor and correction,[348] Richen's later summary article,[349] industry trial report,[127] cognitive results,[47] QoL results[77] **Country** UK **Source** Literature search **Aim** To compare the efficacy and safety of LTG and CBZ as monotherapy in patients with newly diagnosed epilepsy **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30039; H34-049-C87/H34-089-C88 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Central randomisation centre; After enrolment	**Number of participants** 260 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 260): 31.56 years (SD 15.15 years); LTG (n = 131): 32.74 years (SD 16.00 years); CBZ (n = 129): 30.36 years (SD 14.20 years); total (n = 260): 13–81 years; LTG (n = 131): 14–70 years; CBZ (n = 129): 13–81 years **Gender** Total (n = 260): men = 112, women = 148; LTG (n = 131): men = 54, women = 77; CBZ (n = 129): men = 58, women = 71 **Age at onset of seizures** Mean age at 1st seizure: total (n = 260): 28.68 years (SD 15.51 years); LTG (n = 131): 29.55 years (SD 16.35 years); CBZ (n = 129): 27.80 years (SD 14.62 years) **Pretrial medication** Not stated **Ongoing concurrent medication** Total: 175 patients took concomitant medication	**Intervention 1** LTG; 150 mg/day; 48 weeks No. randomised: 131 No. completed: 85 **Comparator** CBZ; 600 mg/day; 48 weeks No. randomised: 129 No. completed: 66	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG (n = 131): AEs (n = 19), protocol violation (n = 12), withdrew consent (n = 7), inadequate response (n = 3), other (n = 5) VPA (n = 129): AEs (n = 35), protocol violation (n = 17), withdrew consent (n = 6), inadequate response (n = 3), other (n = 2) **Adverse events** **Intervention 1** LTG (n = 131): total number reporting AE (n = 112) 85%; drug-related AE (n = 73) 56%; serious AE (n = 9) 7% Events reported by at least 5% of patients in a group: headache (n = 39), asthenia (n = 28), rash (n = 25), nausea (n = 23), dizziness (n = 16), sleepiness (n = 16), flu-like symptoms (n = 15), pharyngitis (n = 12), vomiting (n = 12), rhinitis (n = 11), amnesia (n = 8), infection (n = 8), back pain (n = 7), depression (n = 6), ataxia (n = 4) **Comparator** CBZ (n = 129): total number reporting AE (n = 115) 89%;	**Authors' conclusions** LTG and CBZ showed similar efficacy against partial onset seizures and primary GTC seizures in newly diagnosed epilepsy. LTG, however, was better tolerated **Comments** Additional information extracted from GSK trial report LAM30039. The earlier published article has been extracted (rather than from Richens[349]) since the former publication contains greater detail. The secondary publication has been used for additional data where possible One patient in each group violated entry criteria, and were included with only 1 seizure at baseline The authors note two drawbacks in the analyses: (1) the LTG group had a higher baseline seizure rate than the CBZ group and (2) there were significantly more withdrawals in the CBZ group than in the LTG group. Both drawbacks could influence the reported outcomes Industry trial report: in all efficacy analyses, six patients were excluded, two LTG and four CBZ. Therefore, 129 patients on LTG and 125 on CBZ were included in the efficacy analyses. In addition,

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a baseline phase. After randomisation patients received increasing doses of identical 50 mg LTG or 200 mg CBZ (one dose in the morning for 1 week, one in the morning and evening for 1 week, one in the morning and two in the evening for 2 weeks). At the end of 4 weeks, all patients were taking 150 mg/day LTG or 600 mg/day CBZ. During weeks 6–24 the daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant AEs had been reported provided that the drug concentration was in the lower half of the target range or lower. A similar decision could be made for a patient who did not report seizures or AEs but whose drug concentration had fallen below the target range **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** With 50 patients in each treatment group and 80% remaining seizure-free on CBZ, the study had a power of 70% to show a maximum difference between the drugs of 20% in terms of seizure-free patients **Analysis methods** Cox's proportional hazards model was used to assess the effect of baseline seizures and treatment on time to first seizure (Kaplan–Meier) after 6 weeks of treatment. The HR or RR with 95% CI was calculated. Time to withdrawal, a composite measure of efficacy and safety, was analysed by the same method. The proportion of randomised patients remaining seizure free	**Co-morbidities** Not stated **Baseline seizure frequency** Median (range) number of seizures in last 6 months before baseline: total (n = 260): 4 (1–1020); LTG (n = 131): 4 (1–1020); CBZ (n = 129): 3 (1–960) **Other characteristics** Mean weight: total (n = 260): 65.26 kg (SD 12.36 kg); LTG (n = 131): 66.30 kg (SD 13.10 kg); CBZ (n = 129): 64.22 kg (SD 11.52 kg) Patients with partial seizures: LTG (n = 73); CBZ (n = 73) Patients with primary GTC seizures: LTG (n = 60); CBZ (n = 62) **Inclusion/exclusion criteria** Inclusion: patients aged ≥ 13 years with newly diagnosed partial seizures without secondary generalisation, or primary or secondary GTC seizures who had not previously received treatment with an AED; two or more seizures in the previous 6 months, at least one of which should have been in the 3 months before being entered into the study. Exclusion: the presence of severe organic or psychiatric disease; severe mental abnormality, acute or progressive neurological disease; abnormal laboratory results; previous treatment with any AED; use of any chronic medication other than oral		drug-related AE (n = 96) 74%; serious AE (n = 4) 3% Events reported by at least 5% of patients in a group: headache (n = 32), asthenia (n = 37), rash (n = 25), nausea (n = 16), dizziness (n = 22), sleepiness (n = 29), flu-like symptoms (n = 10), pharyngitis (n = 9), vomiting (n = 9), rhinitis (n = 6), amnesia (n = 4), infection (n = 6), back pain (n = 2), depression (n = 11), ataxia (n = 11)	eight patients were excluded from some efficacy analyses as complete trial seizure diaries for the appropriate time periods were not available. Even though the authors state that six patients were excluded from all efficacy analyses, in the results reported in the paper for each outcome they still report the total LTG participants to be 131 and CBZ participants to be 129

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
during the last 40 and 24 weeks of the trial was analysed to obtain 95% CI for differences between proportions. Analyses were done for three categories: total seizures; partial seizures with or without secondary generalisation; and primary GTC seizures. 95% CI for differences between the groups in percentages of patients who reported adverse experiences were also obtained **Length of trial/frequency of follow-up** 48 weeks; baseline, during treatment every 2 weeks for 12 weeks, then every 6 weeks	contraceptives (unless they had a clinically significant chronic medical disorder or severe mental subnormality); abuse of alcohol and/or other substances; pregnancy, lactation or exposed to risk of pregnancy			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of seizure-free patients; proportion of patients who remained seizure free during the last 40 weeks of treatment (some patients were recorded in both seizure categories) **Intervention 1** LTG (n = 131): all seizures (n = 131): 26%; partial (n = 73): 22%; GTCs seizures (n = 60): 37% ORs: LTG (n = 131): all seizures: 0.873 (95% CI: 0.500 to 1.524); partial: 0.619 (95% CI: 0.289 to 1.325); GTC seizures: 1.108 (95% CI: 0.517 to 2.378) **Comparator** CBZ (n = 129): all seizures (n = 129): 29%; partial (n = 73): 31%; GTC seizures (n = 62): 35%	**Outcome** Proportion of seizure-free patients; proportion of patients who remained seizure free during last 24 weeks of treatment (some patients were recorded in both seizure categories) **Intervention 1** LTG (n = 131): all seizures (n = 131): 39%; partial (n = 73): 35%; GTC seizures (n = 60): 47% ORs: LTG (n = 131): all seizures: 1.050 (95% CI: 0.632 to 1.745); partial: 0.923 (95% CI: 0.462 to 1.843); GTC seizures: 0.996 (95% CI: 0.481 to 2.066) **Comparator** CBZ (n = 129): all seizures (n = 129): 38%; partial (n = 73): 37%; GTC seizures (n = 62): 47%	**Outcome** Time to exit/withdrawal; time to exit/withdrawal for any reason **Intervention 1** HR 1.57 (95% CI: 1.07 to 2.31) More LTG than CBZ patients completed the study (65% versus 51%, p = 0.018) **Comparator** See above	**Outcome** Time to first seizure; time to first seizure after 6 weeks of treatment **Intervention 1** HR 0.8 (95% CI: 0.6 to 1.2). There was no significant difference between the two groups in time to first seizure either for the whole study population or for the subgroup with partial seizures with or without secondary generalisation or the subgroup with primary tonic–clonic seizures **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Brodie, 1999[117] **Related publications** Abstract,[350] NRR,[351] industry trial report[352] **Country** UK **Source** Literature search **Aim** To compare LTG and CBZ in adults aged ≥ 65 years with newly diagnosed epilepsy **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** Industry trial report: 105-124-C93 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after enrolment **Details of pretrial period** After randomisation, patients were titrated to 100 mg/day LTG or 400 mg/day CBZ. Upward adjustments in 50 mg/day LTG or 200 mg/day CBZ increments were made in response to further seizures. Reductions in	**Number of participants** 150 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** LTG (n = 102): 77 years; CBZ (n = 48): 76 years; LTG (n = 102): 65–94 years; CBZ (n = 48): 66–88 years **Gender** LTG (n = 102): men = 54%, women = 46%; CBZ (n = 48): men = 58%, women = 42% **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Median (range) number of seizures at baseline: LTG (n = 102): 4 (1–276); CBZ (n = 48): 5 (1–108) **Other characteristics** Included participants were classified by the investigators as having	**Intervention 1** LTG; 75–500 mg/day; 24 weeks No. randomised: 102 No. completed: 72 **Comparator** CBZ; 200–2000 mg/day; 24 weeks No. randomised: 48 No. completed: 20	**Withdrawals prerandomisation** No participants were lost prior to randomisation **Withdrawals postrandomisation** LTG (n = 102): AEs (n = 18), protocol violation (n = 7), consent withdrawn (n = 3), lost to follow-up (n = 2) CBZ (n = 48): AEs (n = 20), protocol violation (n = 3), consent withdrawn (n = 2), intercurrent death (n = 2), lost to follow-up (n = 1) **Adverse events** **Intervention 1** LTG (n = 102): AEs >6%: poor coordination (n = 13), somnolence (n = 12), dizziness (n = 10), rash (n = 9), headache (n = 9), constipation (n = 9), vomiting (n = 9), diarrhoea (n = 7) Industry trial report: 91 (89%) participants experienced AEs; 46 (45%); participants experienced drug-related AEs; 21 (21%) participants experienced serious AEs Industry trial report: serious AEs: abdominal pain, nausea, vomiting (n = 1), accidental injury (n = 1), convulsion grand mal (n = 1), paranoid reaction (n = 1), jaundice (n = 1)	**Authors' conclusions** LTG can be regarded as an acceptable choice as initial treatment for elderly patients with newly diagnosed epilepsy **Comments** Sample size calculations are not reported so it is not possible to determine whether an adequate number of participants were enrolled in this study 24-week follow-up period includes a 6-week titration period, therefore patients were not receiving target doses for the full follow-up period Intervention 1 dose: 200–2000 mg/day; median 400 mg/day (range 200–800) Comparator dose: 200–2000 mg/day; median 400 mg/day (range 200–800) Further study details, data and analyses are available in the industry trial report The number of participants included in the analyses was not stated

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
dosage (25 mg LTG or 100 mg CBZ decrements) were allowed on the emergence of side-effects. The dosing schedule was weeks 1–2, 25 mg/day LTG, 100 mg/day CBZ; weeks 3–4, 50 mg/day LTG, 200 mg/day CBZ; weeks 5–6, 100 mg/day LTG, 400 mg/day CBZ; weeks 7–24, 75–500 mg/day LTG, 200–2000 mg/day CBZ **ITT analysis performed/method** Industry trial report: authors state yes; not stated **Sample size calculation** The authors planned to enrol 100 patients on LTG for the study in keeping with the International Conference on Harmonisation (ICH) guidelines (1993) for studies in the elderly. Fifty additional patients were randomised to CBZ to provide the treatment comparison **Analysis methods** Industrial trial report: the ITT and safety populations comprised all participants who had received at least one dose of study drug, even if they were protocol violators or did not complete the study – this ITT population comprised 102 participants in the LTG group and 48 in the CBZ group. The sponsor's preferred population comprised 94 and 44 subjects, respectively. If a participant had no record of seizures during the study, he/she was assumed to have no seizures during the study for the purpose of the analysis The percentage of patients reporting an AE was tabulated with 95% CIs.	idiopathic (LTG 41%, CBZ 31%), symptomatic (LTG 38%, CBZ 44%) and cryptogenic (LTG 21%, CBZ 25%) epilepsy. 30% of the LTG and 38% of the CBZ had had a previous cerebrovascular accident. Weight was 68 kg in both groups **Inclusion/exclusion criteria** Inclusion: ≥ 65 years old; with newly diagnosed epilepsy; with two or more seizures of any type during the previous year, with at least one event during the past 6 months		**Comparator** CBZ (n = 48): AEs > 6%: poor coordination (n = 17), somnolence (n = 29), dizziness (n = 17), rash (n = 25), headache (n = 17), constipation (n = 6), vomiting (n = 6), diarrhoea (n = 8) Industry trial report: 41 (85%) participants experienced AEs; 33 (69%) participants experienced drug-related AEs; 15 (31%) participants experienced serious AEs Industry trial report: serious AEs: rash maculopapular (n = 1), rash (n = 2), diarrhoea, vomiting (n = 1)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Withdrawal from the study and the proportion of patients remaining seizure free after 6 weeks of dosing were compared using the proportional hazard survival method adjusting for the pretreatment seizure frequency. Kaplan–Meier curves were constructed for both. In the seizure freedom analysis, patients were censored upon withdrawal from the study. An additional measure of global effectiveness, the proportion of patients who were both seizure free in the last 16 weeks of the study and did not discontinue treatment, was compared using Fisher's exact test **Length of trial/frequency of follow-up** 24 weeks; baseline, and then 2, 4, 6, 12 and 24 weeks after starting treatment. Unscheduled visits were allowed as				

Results

Outcome 1	Outcome 2	Outcome 3
Outcome Proportion of patients completing treatment; the number of participants remaining on treatment for the duration of the study **Intervention 1** LTG: 71%, HR from withdrawal rates: 2.4 (95% CI: 1.4 to 4.0), $p < 0.001$ (LTG vs CBZ) **Comparator** CBZ: 42%	**Outcome** Proportion of seizure-free patients; number of seizure-free patients remaining during the last 16 weeks of treatment **Intervention 1** LTG: 40/102 (39%), $p = 0.027$ (LTG vs CBZ) **Comparator** CBZ: 10/48 (21%)	**Outcome** Time to first seizure; time to first seizure for patients who remained in the study **Intervention 1** No difference between the treatments **Comparator** NA

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Brodie, 1999[47] **Related publications** Industry trial report.[127] **Country** UK **Source** Literature search **Aim** To compare the effects of LTG and CBZ monotherapy on neuropsychological tests in newly diagnosed patients with epilepsy **Type of publication** Abstract (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30039; H34-049-C87/H34-089-C88 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Central randomisation centre; after enrolment **Details of pretrial period** After a baseline period, patients were randomised to receive increasing doses of	**Number of participants** 168 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** (Taken from LAM30039) Inclusion: age ≥ 13 years; with newly diagnosed partial onset or primarily generalised onset epilepsy who had not previously received treatment with	**Intervention 1** LTG; 150 mg/day; 48 weeks No. randomised: not stated No. completed: not stated **Comparator** CBZ; 600 mg/day; 48 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** When comparing LTG and CBZ monotherapy in patients with newly diagnosed epilepsy, a long-term differential effect on cognitive function was found in favour of LTG **Comments** Additional information was extracted from GSK trial report LAM30039. The number of patients included in this analysis is lower than the total recruited to LAM30039. It is not possible, therefore, to state the patient baseline characteristics for the subgroup used in this analysis. The number of patients randomised to each group is not stated for these tests. The number of patients included in each step assessment is shown in the outcomes section of the extraction table

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
identical 50 mg LTG or 200 mg CBZ (one in the morning for 1 week, one in the morning and evening for 1 week, one in the morning and two in the evening for 2 weeks). At the end of 4 weeks, all patients were taking 150 mg/day LTG or 600 mg/day CBZ. During weeks 6–24 the daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant AEs had been reported provided that the drug concentration was in the lower half of the target range or lower. A similar decision could be made for a patient who did not report seizures or AEs but whose drug concentration had fallen below the target range **ITT analysis performed/method** Authors state yes; last observation carried forward **Sample size calculation** With 50 patients in each treatment group and 80% remaining seizure free on CBZ, the study had a power of 70% to show a maximum difference between the drugs of 20% in terms of seizure-free patients **Analysis methods** The Wilcoxon rank sum test was performed on post-treatment changes for each of the outcome measures at each visit. In addition, principal component analysis (PCA) was used to generate a single index score measuring overall cognitive function, which was analysed similarly **Length of trial/frequency of follow-up** 48 weeks; baseline and weeks 4, 12, 24, 48	an AED; two or more seizures in the previous 6 months, at least one of which should have been in the 3 months before being entered into the study			

continued

Results

Outcome 1

Outcome
Change in functional capacity; measured using neuropsychological testing (semantic processing, verbal learning, delayed recall, trailmaking, logical reasoning, recognition and Stroop)

Intervention 1
LTG: of the 9 outcome measures studied, 6 had significant differences in favour of LTG on at least one visit.
The results of the PCA showed that the first principal component could be interpreted as a measure of overall cognitive function. Significance testing gave *p*-values of 0.1836, 0.0081, 0.0003 and 0.0062 at weeks 4, 12, 24 and 48, respectively, where the differences favour LTG
Stroop Test, time taken median: week 4 ($n = 61$), –8.00; week 12 ($n = 51$), –14.00; week 24 ($n = 48$), –16.00; week 48 ($n = 32$), –15.50
Stroop Test, number of errors median: week 4 ($n = 61$), 0.00; week 12 ($n = 51$), 0.00; week 24 ($n = 48$), 0.00; week 48 ($n = 32$), 0.00
Logical reasoning test, time taken median: week 4 ($n = 21$), –15.00; week 12 ($n = 20$), –3.50; week 24 ($n = 15$), 1.00; week 48 ($n = 0$), no data
Logical reasoning test, number of errors median: week 4 ($n = 21$), 0.00; week 12 ($n = 20$), 0.00; week 24 ($n = 15$), –1.00; week 48 ($n = 0$), no data
Verbal learning 1, total correct median: week 4 ($n = 36$), 0.00; week 12 ($n = 31$), 1.00; week 24 ($n = 27$), 1.00; week 48 ($n = 12$), 1.00
Recognition test, total correct median: week 4 ($n = 37$), 0.00; week 12 ($n = 31$), 0.00; week 24 ($n = 27$), 0.00; week 48 ($n = 12$), 0.00
Semantic processing test, number of errors median: week 4 ($n = 21$), –1.00; week 12 ($n = 19$), –1.00; week 24 ($n = 15$), 0.00; week 48 ($n = 0$), no data
Semantic processing test, time taken median: week 4 ($n = 21$), –17.50; week 12 ($n = 19$), –33.00; week 24 ($n = 15$), –33.50; week 48 ($n = 0$), no data
Trail-making test, total elapsed time median: week 4 ($n = 61$), –6.00; week 12 ($n = 50$), –13.00; week 24 ($n = 48$), –13.00; week 48 ($n = 32$), –17.00

Comparator
CBZ: There were no significant differences in favour of CBZ
Stroop Test, time taken median: week 4 ($n = 55$), –7.00; week 12 ($n = 45$), –10.00; week 24 ($n = 38$), –15.00; week 48 ($n = 26$), –17.00
Stroop Test, number of errors median: week 4 ($n = 55$), –1.00; week 12 ($n = 45$), –1.00; week 24 ($n = 38$), 0.00; week 48 ($n = 26$), 0.00
Logical reasoning test, time taken median: week 4 ($n = 22$), 16.50; week 12 ($n = 17$), 15.00; week 24 ($n = 12$), 8.79; week 48 ($n = 2$), 28.50
Logical reasoning test, number of errors median: week 4 ($n = 22$), 0.00; week 12 ($n = 17$), 0.00; week 24 ($n = 12$), 0.50; week 48 ($n = 2$), 0.00
Verbal learning 1, total correct median: week 4 ($n = 34$), 0.00; week 12 ($n = 28$), 0.00; week 24 ($n = 23$), 0.00; week 48 ($n = 10$), 0.00
Recognition test, total correct median: week 4 ($n = 35$), 0.00; week 12 ($n = 29$), 0.00; week 24 ($n = 23$), 0.00; week 48 ($n = 10$), 0.00
Semantic processing test, number of errors median: week 4 ($n = 22$), 0.00; week 12 ($n = 18$), 1.00; week 24 ($n = 13$), 0.00; week 48 ($n = 2$), –0.50
Semantic processing test, time taken median: week 4 ($n = 22$), –1.71; week 12 ($n = 18$), –7.25; week 24 ($n = 13$), –20.50; week 48 ($n = 2$), –16.00
Trail-making test, total elapsed time median: week 4 ($n = 55$), –5.80; week 12 ($n = 45$), –9.00; week 24 ($n = 38$), –17.50; week 48 ($n = 26$), –20.50

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Bryant-Comstock, 2002[113] **Related publications** Abstract,[353] abstract,[363] trial report[122] **Country** Multinational **Source** Industry submission **Aim** To investigate treatment outcomes (QoL and seizure severity) for patients whose seizures were uncontrolled with their current monotherapy, and for whom there may be some benefit in 'switching' to either VPA or LTG **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** SCAB3001 **Study design** Monotherapy after add-on titration; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 663 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; total (n = not stated): ≥ 16 years **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Baseline measured, but data not reported **Other characteristics** Not stated **Inclusion/exclusion criteria** Included participants were 16 years or older with uncontrolled epilepsy on a stable dose of a single AED, with at least two seizures during the 8-week screening period	**Intervention 1** LTG; 200–500 mg/day; 28 weeks No. randomised: 368 No. completed: 128 **Comparator** VPA; not stated; 28 weeks No. randomised: 295 No. completed: 115	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** This study shows a significant improvement in the QoL of patients with epilepsy who are switched to LTG monotherapy compared with patients who are switched to VPA. These results provide evidence that patients receiving LTG perceive better psychosocial functioning and medication effects than those receiving VPA **Comments** Participants from Belgium, Finland, Portugal and all patients aged < 16 years did not complete the QoL instruments. In addition, participants from the USA were also not included in this analysis. This study used only one of two treatment comparisons contained in the trial SCAB3001 (105–133). VPA was administered at a dose thought suitable by the investigator and in accordance with the data sheet recommendations n = 52 (LTG) and n = 34 (VPA) participants completed the monotherapy phase At baseline, 243 patients completed the QOLIE-31, 242 completed the SEALS and 361 completed the AEP and LSSS These data are taken from an unpublished paper. They are

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period A randomised open-label trial. Patients were screened for 8 weeks prior to study entry and had to maintain a seizure record during that period and must have experienced at least 2 seizures during the screening period to be eligible. Randomised participants received either LTG or VPA as add-on therapy for 12 weeks. Patients considered suitable (stabilised) for withdrawal to monotherapy with study drug were then given the option of entering an 8-week withdrawal period from other AEDs. Those patients who achieved study drug monotherapy with either LTG or VPA continued with this treatment until week 28 Adults randomised to LTG were dose escalated during the first 8 weeks of the study; 50 mg/day in weeks 1–2; 50 mg twice daily in weeks 3–4; increasing to 200–500 mg/day during week 8, and thereafter were maintained on 200–500 mg/day for the duration they remained within the study or until week 28. VPA was administered as considered appropriate by the investigator and in accordance with data sheet recommendations **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The study was powered to support testing a hypothesis regarding the primary efficacy end-point, change in seizure rate from baseline at 28 weeks (no further details)				lacking in detail for randomisation procedure and participant characteristics. The quality of the study cannot be adequately assessed Sample size calculations are not reported and the referenced prior study also does not contain these details, so it is not possible to determine whether an adequate number of participants were enrolled in this study The mean dosage of LTG during the monotherapy phase is within the highest doses allowed, but more than the usual 100–200 mg/day stated by the manufacturers

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods For HRQoL data from all 4 instruments, comparison of data between treatment groups was performed using ANCOVA allowing for the effects of treatment group and baseline scores. Results from SEALS, QOLIE-31, AEP and LSSS are presented for all patients, and also for those patients who completed 7 weeks of monotherapy treatment with study drug. Methods used in statistical analysis of monotherapy completers have been reported previously.[122] Statistical analysis was conducted using SAS software and all comparisons were conducted at the 5% level. Data are presented as mean ± SD **Length of trial/frequency of follow-up** 28 weeks; baseline and 28 weeks				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure severity; using the Liverpool Seizure Severity Scale (LSSS) **Intervention 1** Baseline: LTG (n = 188): 32.85; ±12.63 (no difference between treatment groups at baseline) Week 28: LTG = 8.54; p = 0.33, 95% CI: –2.84 to 0.96). LSSS scores were reduced at 28 weeks in both treatment groups compared with baseline, suggesting a reduction in seizure severity	**Outcome** Change in patient-related QoL; measured using QOLIE-31 **Intervention 1** All participants (n = 128) Baseline: Seizure worry 47.76; overall QoL 58.65; emotional well-being 64.11; energy/fatigue 52.41; cognitive functioning 59.49; medication side-effects 56.79; social functioning 58.66; total score 58.02 Change at follow-up (week 28): Seizure worry 12.42 (difference vs VPA = 5.47, p = 0.065, 95% CI: –0.33 to 11.37); Overall QoL 109.02 (difference vs VPA = 9.03, p = 0.001, 95% CI:	**Outcome** Change in patient-related QoL; measured using the SEALS. Reported as mean scores **Intervention 1** All participants (n = 126) Baseline: Cognition 20.52; dysphoria 8.24; tiredness 6.29; temper 4.67; worry 6.72; total score 46.45 Change at follow-up (week 28): Cognition –4.25 (difference vs VPA = –6.07, p = 0.004, 95% CI: –10.16 to –1.98); dysphoria –1.85 (difference vs VPA = –1.33, p = 0.130, 95% CI: –3.07 to	**Outcome** Change in patient-related QoL; measured using the Liverpool Adverse Experience Profile **Intervention 1** Baseline: the scores did not differ between treatment groups at baseline Follow-up (week 28): patients receiving LTG (n = 155) reported significantly lower total scores for AEP than patients receiving VPA (n = 146). At week 28, the mean scores after allowing for baseline measurements were 15.59 in patients receiving LTG and 18.45 in those receiving VPA (p = 0.01; 95% CI: –5.03 to –0.69).

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
compared with baseline. There was no significant difference between treatment groups. Similarly, there was no significant difference between treatments in patients who completed 7 weeks of monotherapy (LTG = 18.5, VPA = 17.1; 95% CI: –9.47 to 7.95) **Comparator** Baseline: VPA (n = 173): 33.56; ±12.58 Week 28: VPA = 9.48 Patients who completed 7 weeks of monotherapy (VPA = 17.1)	4.33 to 13.73); Emotional well-being 7.95 (difference vs VPA = 6.51, p = 0.006, 95% CI: 1.94 to 11.08); energy/fatigue 10.74 (difference vs VPA = 8.71, p < 0.001, 95% CI: 3.87 to 13.54); cognitive functioning 5.80 (difference vs VPA = 4.13, p = 0.17, 95% CI: –1.79 to 10.04); medication side-effects 11.11 (difference vs VPA = 12.37, p < 0.001, 95% CI: 5.31 to 19.43); social functioning 9.87 (difference vs VPA = 8.87, p = 0.002, 95% CI: 3.44 to 14.30); total score 8.82 (difference vs VPA = 7.01, p < 0.001, 95% CI: 3.06 to 10.96) Monotherapy completers only (n = 51) Baseline: Seizure worry 46.45; overall QoL 60.69; emotional well-being 65.14; energy/fatigue 52.75; cognitive functioning 61.91; medication side-effects 54.42; social functioning 62.36; total score 59.76 Change at follow-up (week-28): Seizure worry 16.46 (difference vs VPA = 11.07, p = 0.025, 95% CI: 1.44 to 20.70); overall QoL 11.98 (difference vs VPA = 8.30, p = 0.036, 95% CI: 0.56 to 16.03); emotional well-being 10.59 (difference vs VPA = 12.31, p = 0.003, 95% CI: 4.42 to 20.20); energy/fatigue 12.46 (difference vs VPA = 11.75, p = 0.005, 95% CI: 3.67 to 19.84); Cognitive functioning 9.50 (difference vs VPA = 6.18, p = 0.215, 95% CI: –3.66 to 16.02); medication side-effects 15.35 (difference vs VPA = 16.54, p = 0.002, 95% CI: 6.26 to 26.82); social functioning 12.33 (difference vs VPA = 10.50, p = 0.019, 95% CI: 1.76 to 19.25); total score 11.54 (difference vs VPA = 9.28, p = 0.008, 95% CI: 2.46 to 16.11) Overall at baseline scores were similar for each treatment group. At 28 weeks follow-up there was a highly significantly difference between treatment groups in favour of patients receiving LTG (p < 0.001). Five	0.40); tiredness –1.91 (difference vs VPA = –2.57, p = 0.001, 95% CI: –4.10 to –1.05); temper –1.00 (difference vs VPA = –1.05, p = 0.064, 95% CI: –2.17 to 0.06); worry –0.83 (difference vs VPA = –0.49, p = 412, 95% CI: –1.66 to 0.69); total score –13.3 (difference vs VPA = –11.37, p = 0.005, 95% CI: –19.11 to –3.63) Monotherapy completers only (n = 52) Baseline: Cognition 18.72; dysphoria 8.31; tiredness 6.35; temper 4.69; worry 6.56; total score 44.63 Change at follow-up (week 28): Cognition –5.83 (difference vs VPA = –3.36, p = 0.010, 95% CI: –5.92 to –0.81); dysphoria –1.72 (difference vs VPA = –3.36, p = 0.010, 95% CI: –5.92 to –0.81); tiredness –2.59 (difference vs VPA = –3.36, p = 0.010, 95% CI: –5.92 to –0.81); temper –1.82 (difference vs VPA = –3.36, p = 0.010, 95% CI: –5.92 to –0.81); worry –1.36 (difference vs VPA = –3.36, p = 0.010, 95% CI: –5.92 to –0.81); total score –13.3 (difference vs VPA = –3.36, p = 0.010, 95% CI: –5.92 to –0.81) Overall at baseline SEALS scores were similar for each treatment group. At 28 weeks follow-up the total SEALS score was significantly lower (p = 0.003) in patients receiving LTG than in patients receiving VPA. Domain scores for cognition, dysphoria and tiredness were significantly lower in patients receiving LTG than for those receiving VPA (p < 0.05 in each case). Scores for temper and worry	There was no significant difference between treatment groups when considering those patients who completed 7 weeks of monotherapy treatment (LTG = –5.42, VPA = –1.73, 95% CI: –7.77 to 0.39) **Comparator** See Intervention 1

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	out of seven domain scores in the QOLIE-31 (overall QoL, emotional well-being, energy/fatigue, medication side-effects and social functioning) were significantly lower (indicating improved QoL, $p < 0.05$) in patients receiving LTG than in those receiving VPA. Domain scores for seizure worry and cognitive functioning were similar between treatment groups **Comparator** All participants ($n = 115$) Baseline: Seizure worry 46.48; overall QoL 60.59; emotional well-being 61.15; energy/fatigue 53.02; cognitive functioning 56.03; medication side-effects 54.37; social functioning 61.19; total score 57.26 Change at follow-up (week 28): Seizure worry 6.95; overall QoL 0.99; emotional well-being 1.44; energy/fatigue 2.04; cognitive functioning 1.67; medication side-effects –1.27; social functioning 1.00; total score 1.81 Monotherapy completers only ($n = 34$) Baseline: seizure worry 37.22; overall QoL 58.31; emotional well-being 57.76; energy/fatigue 48.24; cognitive functioning 52.93; medication side-effects 46.39; social functioning 59.39; total score 53.75 Change at follow-up (week 28): seizure worry 5.39; overall QoL 3.69; emotional well-being –1.72; energy/fatigue 0.71; cognitive functioning 3.32; medication side-effects –1.19; social functioning 1.83; total score 2.26	domains were similar between treatment groups **Comparator** All participants ($n = 116$) Baseline: Cognition 21.91; dysphoria 7.92; tiredness 6.45; temper 5.08; worry 7.43; total score 48.78 Change at follow-up (week 28): Cognition –0.88; dysphoria –0.2; tiredness 0.03; temper –0.61; worry –0.92; total score –2.65 Monotherapy completers only ($n = 34$) Baseline: Cognition 23.96; dysphoria 8.01; tiredness 7.44; temper 5.71; worry 8.65; total score 53.76 Change at follow-up (week 28): Cognition –0.24; dysphoria –0.38; tiredness –0.02; temper –0.77; worry –0.87; total score –1.89	

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Chmielewska, 2001[133] **Related publications** None **Country** Poland **Source** Literature search **Aim** To assess the efficacy and tolerability of LTG or tiagabine TGB as add-on treatment in patients with refractory CPSs with or without generalisation physician-rated and patient-rated measures **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy; new vs new; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** There was a 12-week baseline period with stable doses of baseline medication	**Number of participants** 48 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 48): not stated; LTG (n = 22): 25 years (SD 6.7); TGB (n = 26): 27 years (SD 8.2); not stated **Gender** Total (n = 48): men = 27, women = 21; LTG (n = 22): men = 13, women = 9; TGB (n = 26): men = 14, women = 12 **Age at onset of seizures** Epilepsy duration: total (n = 48): not stated; LTG (n = 22): 10 years (SD 7.1); TGB (n = 26): 11 years (SD 8.2) **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Total (n = 48): not stated; LTG (n = 22): 7.18; TGB (n = 26): 6.89	**Intervention 1** LTG; 400 mg/day; 20 weeks No. randomised: 22 No. completed: not stated **Comparator** TGB; 60 mg/day; 20 weeks No. randomised: 26 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** No. of participants with at least one relevant AE: n = 5/22 Cumulative incidence >10% in either group: headache (n = 6/22), fatigue (n = 5/22), disturbed sleep (n = 4/22), dizziness (n = 4/22), nervousness (n = 5/22), paraesthesia (n = 3/22), nausea (n = 2/22), flu syndrome (n = 2/22), rash (n = 1/22) **Comparator** No. of participants with at least one relevant AE: n = 9/26 Cumulative incidence >10% in either group: headache (n = 8/26), fatigue (n = 9/26), disturbed sleep (n = 7/26), dizziness (n = 6/26), nervousness (n = 1/26), paresthesia (n = 3/26), nausea (n = 4/26), flu syndrome (n = 2/26), rash (n = 0/26)	**Authors' conclusions** LTG and TGB were similarly efficacious as add-on and short-term treatment in refractory partial epilepsy. Overall incidence of AEs was greater with TGB; somnolence and fatigue were most frequently reported. The positive impact on the QoL was more marked among LTG patients. Comparable reduction in seizure frequency and severity after LTG and TGB did not entirely coincide with the improvement of patient's self-esteem and QoL **Comments** The number of patients completing the study is not stated, so it is not clear whether an ITT analysis was performed and whether there were any withdrawals and for what reasons. The details for randomisation and study setting are poor. The first 8 weeks on drug treatment involved a titration period and the remaining 12 weeks were classed as the evaluation period where the patients received a full maintenance dose of drug

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
administered, followed by a 20-week treatment period (8-week titration and 12-week evaluation period). In titration, doses of LTG were increased from 25 to 400 mg/day maximum given in one or two doses and TGB was increased from 5 to 60 mg/day maximum given in three doses **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Differences at baseline in test response were compared with differences at follow-up using the Wilcoxon test. A *p*-value of 0.05 was considered statistically significant **Length of trial/frequency of follow-up** 20 weeks; at baseline and 20 weeks	**Other characteristics** Unknown aetiology of seizures: LTG (n = 22): n = 18; TGB (n = 26): n = 22 Mean (SD) dosage during evaluation: LTG (n = 22): 378 mg/day (SD 53); TGB (n = 26): 43 mg/day (SD 14) **Inclusion/exclusion criteria** Inclusion: age 16–60 years; with (1) CPS in accordance with ILAE classification; (2) refractory epilepsy during at least 1 year and at least 4 or more CPS per 4 weeks during the preceding 3 months; (3) a maximum intake of 2 concomitant AEDs; and (4) ability to record all seizures in a seizure diary throughout the study Exclusion: evidence of status epilepticus during the previous year; any signs of serious somatic or psychiatric pathologies; or evidence of non-compliance during previous treatment			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; responders were defined as experiencing at least 50% reduction in monthly seizure frequency from baseline to week 20 follow-up **Intervention 1** LTG: n = 9/22 (41%) **Comparator** TGB: 9/26 (35%)	**Outcome** Proportion of seizure-free patients; the percentage of patients remaining seizure-free at end of evaluation (add-on) phase (20 weeks) **Intervention 1** LTG: 2/22 (9%) **Comparator** TGB: 2/26 (7.7%)	**Outcome** Change in seizure frequency; the difference in median monthly seizure frequency (baseline minus end of evaluation phase) **Intervention 1** LTG (n = 22): Baseline: median = 7.18 Follow-up (20 weeks): median = 4.31 Change in seizure frequency (baseline to follow-up): not stated, $p < 0.05$	**Outcome** Change in patient-related QoL; measured using 100-mm visual analogue scale (VAS): 0 mm = worst, 100 mm = best, well-being assessed by patient **Intervention 1** LTG (n=22): 69 mm (baseline 27 mm) **Comparator** TGB (n = 26): some improvement, but not marked

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
		Comparator TGB (n = 26): Baseline: median = 6.89 Follow-up (20 weeks): median = 4.25 Change in seizure frequency (baseline to follow-up): not stated, $p < 0.05$	
Outcome 5			
Outcome Change in seizure severity; measured using descriptive terminology scale of illness severity (mild, moderate or severe). Reported as the % of participants experiencing each of the specified categories of seizure severity **Intervention 1** LTG (n = 22): Baseline: mild = 2%, moderate = 30%, severe = 68% Follow-up: mild = 20%, moderate = 36%, severe = 44% **Intervention 2** TGB (n = 26): Baseline mild = 5%, moderate = 22%, severe = 73% Follow-up: mild = 15%, moderate = 31%, severe = 54%			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Gillham, 2000[77] **Related publications** Industry submission,[127] abstract[354] **Country** UK **Source** Literature search **Aim** To compare the effect of treatment with LTG or CBZ on HRQoL and to demonstrate the use of the SEALS as a comparative tool in clinical trials **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30039; H34-049-C87/H34-089-C88 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Central randomisation centre; after enrolment **Details of pretrial period** Patients were stratified into two groups based on clinical history: partial seizures	**Number of participants** 260 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 260): 31.56 years (SD 15.15 years); LTG (n = 131): 32.74 years (SD 16.00 years); CBZ (n = 129): 30.36 years (SD 14.20 years); Total (n = 260): 13–81 years; LTG (n = 131): 14–70 years; CBZ (n = 129): 13–81 years **Gender** Total (n = 260): men = 112, women = 148; LTG (n = 131): men = 54, women = 77; CBZ (n = 129): men = 58, women = 71 **Age at onset of seizures** Mean age at onset of seizures: Total (n = 260): 28.68 years (SD 15.51 years), range 0–80 years; LTG (n = 131): 29.55 (SD 16.35 years), range 0–67 years; CBZ (n = 129): 27.80 (SD14.62 years), range 1–80 years **Pretrial medication** Not stated **Ongoing concurrent medication** Total: 175 patients took concomitant medication	**Intervention 1** LTG; 150 mg/day; 48 weeks No. randomised: 131 No. completed: 85 **Comparator** CBZ; 600 mg/day; 48 weeks No. randomised: 129 No. completed: 65	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG (n = 131): AEs (n = 19), protocol violation (n = 12), withdrew consent (n = 7), inadequate response (n = 3), other (n = 5) VPA (n = 129): AEs (n = 35), protocol violation (n = 17), withdrew consent (n = 6), inadequate response (n = 3), other (n = 2) **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** LTG offers the patient with newly diagnosed epilepsy significant benefits of greater tolerability and better HRQoL compared with CBZ. The SEALS is an effective tool for use in clinical trials of AEDs; it was a better predictor of trial completion than seizure counts, and used as a covariate enabled better detection of treatment effects. In general practice, the use of SEALS to assess HRQoL has the potential to improve quality of care for people with epilepsy **Comments** Additional data on patient characteristics and more detailed SEALS scores reporting, taken from trial report LAM30039

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
without secondary generalisation, and those with GTC seizures. After randomisation, patients received increasing doses of identical 50 mg LTG or 200 mg CBZ (one in the morning for 1 week, one in the morning and evening for 1 week, one in the morning and two in the evening for 2 weeks). At the end of 4 weeks, all patients were taking 150 mg/day LTG or 600 mg/day CBZ. During weeks 6–24 the daily dose could be increased by one tablet at each visit if seizures continued and no clinically relevant AEs had been reported provided that the drug concentration was in the lower half of the target range or lower. A similar decision could be made for a patient who did not report seizures or AEs but whose drug concentration had fallen below the target range **ITT analysis performed/method** Authors state yes; last observation carried forward **Sample size calculation** With 50 patients in each treatment group and 80% remaining seizure-free on CBZ, the study had a power of 70% to show a maximum difference between the drugs of 20% in terms of seizure-free patients **Analysis methods** Simple summary statistics were calculated by visit for patients who completed the study and by time of dropout for those who withdrew early. The data were analysed using a repeated measures approach that may be affected by drop-out rates	**Co-morbidities** Not stated **Baseline seizure frequency** Median (range) number of seizures in last 6 months before baseline: total (n = 260): 4 (1–1020); LTG (n = 131): 4 (1–1020); CBZ (n = 129): 3 (1–960) **Other characteristics** Mean weight: total (n = 260): 65.26 kg (SD 12.36 kg); LTG (n = 131): 66.30 kg (SD 13.10 kg); CBZ (n = 129): 64.22 kg (SD 11.52 kg) Patients with partial seizures: LTG (n = 73); CBZ (n = 73) Patients with primarily GTC seizures: LTG (n = 60); CBZ (n = 62) **Inclusion/exclusion criteria** Inclusion: patients ≥ 13 years old; with newly diagnosed partial onset or primarily generalised onset epilepsy who had not previously received treatment with an AED; two or more seizures in the previous 6 months, at least one of which should have been in the 3 months before being entered into the study Exclusion: the presence of severe organic or psychiatric disease; severe mental abnormality, acute or progressive neurological disease; abnormal laboratory results; previous treatment with any AED; use of any chronic medication other than oral contraceptives (unless they had a			

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
SEALS scores were the dependent variable with covariates of time, treatment and log baseline seizure count. Time was included as a categorical variable with five levels (weeks 0, 4, 12, 24 and 48) to provide dropout-adjusted estimates of SEALS scores. A maximum likelihood approach was used to estimate the treatment effect and other parameters of interest. For the SEALS subscales, mean scores were calculated for each treatment group at each visit, after using last observation carried forward as a crude method of accounting for the patients who withdrew from the trial To determine the effect of baseline SEALS scores on the interpretation of the main end-point in the trial, withdrawal from the study, a survival analysis using the proportional hazards model was carried out. This analysis in the main effectiveness study (LAM30039) was carried out using treatment and baseline seizure count as covariates. The analysis presented here uses the baseline SEALS score as a covariate, in addition to the other two variables **Length of trial/frequency of follow-up** 48 weeks; baseline, and at weeks 4, 12, 24, and 48	clinically significant chronic medical disorder or severe mental subnormality); abuse of alcohol and/or other substances; pregnancy, lactation or exposed to risk of pregnancy			

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Results	
Outcome 1	**Outcome 2**
Outcome Change in patient-related QoL; assessed by the SEALS. The five subscales of SEALS are Worry, Temper, Cognition, Dysphoria and Tiredness, scored as 0 = never, 1 = occasionally, 2 = sometimes, 3 = many times **Intervention 1** LTG (n = 131): significantly higher (worse) SEALS scores at baseline than patients in CBZ group (p = 0.021). Over the duration of the trial, SEALS scores in the LTG group improved significantly from baseline (p < 0.001), but with no significant change between any of the on-treatment visits (p = 0.88) Patients taking LTG showed improvement on all five subscales, over the 48-week trial. The biggest improvement appeared to be in the Cognition subscale SEALS I median total score: week 4 (n = 92): 0.08 (95% CI: 0.04 to 0.21); week 12 (n = 83): 0.12 (95% CI: –0.01 to 0.19); week 24 (n = 81): 0.10 (95% CI: –0.13 to 0.16); week 48 (n = 63): 0.02 (95% CI: –0.14 to 0.14) SEALS II median total score: week 4 (n = 92): 0.00 (95% CI: –0.08 to 0.04); week 12 (n = 83): 0.00 (95% CI: –0.05 to 0.05); week 24 (n = 81): 0.05 (95% CI: –0.05 to 0.05); week 48 (n = 64): 0.00 (95% CI: –0.11 to 0.03) SEALS III median total score: week 4 (n = 91): 0.00 (95% CI: –0.05 to 0.05); week 12 (n = 82): 0.00 (95% CI: –0.05 to 0.10); week 24 (n = 80): 0.05 (95% CI: –0.04 to 0.11); week 48 (n = 63): 0.05 (95% CI: –0.02 to 0.15) For SEALS I, the total score was higher in the LTG group than the CBZ group for the 4 assessments, with the difference at week 4 being statistically significant. No other SEALS assessment showed a statistically significant difference between the treatment groups, but it should be remembered that as the trial progressed, only 'survivors' were assessed. This selected patients who tolerated the treatments **Comparator** CBZ (n = 129): significantly worse SEALS scores at week 4 than at baseline (p = 0.038), but at subsequent assessments, no significant change from baseline was observed (p = 0.394) Overall, patients randomised to CBZ showed deterioration in the Cognition, Dysphoria and Tiredness subscales over the 48–week trial. SEALS I median total score: week 4 (n = 78): 0.01; week 12 (n = 77): 0.00; week 24 (n = 68): 0.06; week 48 (n = 55): 0.00 SEALS II median total score: week 4 (n = 79): 0.05; week 12 (n = 77): 0.05; week 24 (n = 68): 0.03; week 48 (n = 55): 0.05 SEALS III median total score: week 4 (n = 79): 0.00; week 12 (n = 77): 0.00; week 24 (n = 68): –0.01; week 48 (n = 55): 0.00	**Outcome** Risk factors for withdrawal; based on treatment assignment, baseline seizure rate, and baseline SEALS scores. The HR estimates the risk of early withdrawal, at any time, from the CBZ group compared with the LTG group **Intervention 1** Excluding SEALS data: treatment assignment HR 1.60, p = 0.018; baseline seizure rate HR 1.009, p = 0.017; baseline SEALS score HR not applicable, i.e. in the analysis ignoring the SEALS scores, it appeared that CBZ patients had a 60% greater risk than LTG patients of dropping out at any time LTG (n = 131) including SEALS data: treatment assignment HR 1.82, p = 0.0057; baseline seizure rate HR 1.007, p = 0.058; baseline SEALS score HR 1.014, p = 0.0067, i.e. in the analysis including the SEALS scores, it appeared that CBZ patients had a 82% greater risk than LTG patients of dropping out at any time **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Gilliam, 1998[112] **Related publications** Letter;[355] industry trial report[356] **Country** USA **Source** Literature search **Aim** To report the results of a double-blind, double-dummy, active control study designed to evaluate the efficacy and safety of LTG administered as monotherapy to adult outpatients with partial seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The study consisted of an 8-week baseline period during which patients continued	**Number of participants** 220 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** LTG (n = 76): 37 years; VPA (n = 80): 36 years (SD not stated); LTG (n = 76): 13–73 years; VPA (n = 80): 14–71 years **Gender** LTG (n = 76): men = 33, women = 43; VPA (n = 80): men = 32, women = 48 **Age at onset of seizures** Not stated **Pretrial medication** Mean number of previous AEDs (range): LTG (n = 76): 4.4 (1–13); VPA (n = 80): 4.6 (1–14) **Ongoing concurrent medication** Baseline AED CBZ: LTG (n = 76): 48/76; VPA (n = 80): 46/80 PHT: LTG (n = 76): 28/76; VPA (n = 80): 34/80 **Co-morbidities** Not stated	**Intervention 1** LTG; 400–500 mg/day; 12 weeks No. randomised: 76 No. completed: 28 **Comparator** VPA; 100 mg/day; 12 weeks No. randomised: 80 No. completed: 13	**Withdrawals prerandomisation** Of the 220 patients screened for eligibility, 64 did not meet the study criteria **Withdrawals postrandomisation** LTG: withdrew during titration period (n = 20), met escape criteria during titration period (n = 13), protocol violation during monotherapy phase (n = 2), withdrew during monotherapy phase (n = 6), met escape criteria during monotherapy phase (n = 7) VPA: withdrew during titration phase (n = 9), met escape criteria during titration phase (n = 27), protocol violation during monotherapy phase (n = 3), withdrew during monotherapy phase (n = 7), met escape criteria during monotherapy phase (n = 21) **Adverse events** **Intervention 1** AEs reported by ≥ 10% of participants in either group Titration period Patients with ≥ 1 AE (n = 57/76); dizziness (n = 15/76), nausea (n = 12/76), headache (n = 10/76), dyspepsia (n = 0/76), somnolence (n = 6/76), asthenia (n = 9/76), coordination abnormalities (n = 9/76), vomiting (n = 8/76),	**Authors' conclusions** LTG is effective and well tolerated when administered as monotherapy in adult patients with partial seizures **Comments** The daily LTG dose received was calculated for the 57 participants who were treated for at least 5 weeks allowing time to complete dose escalation. 55 were treated with the target dose of 500 mg/day and the remaining two were treated with 400 mg/day Dose reductions were allowed for LTG but not VPA where there was an intolerance to drug treatment The exclusion criteria in this study were more limited than in other similar studies, therefore the generalisability of the findings may be limited Escape criteria included: doubling of average monthly seizure rate, doubling of highest consecutive 2-day seizure rate, emergence of new, more severe seizure type; clinically significant prolongation of GTC seizures relative to baseline Note: participants defined as escaped in the ITT population also included those who had ≥ 1 week of missing data or were

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
their baseline AED (CBZ or PHT monotherapy), those who met the inclusion criteria were then randomised to receive increasing doses of LTG (target 250 mg/b.d.) or VPA (target 500 mg/b.d.) during the first 4 weeks of an 8-week titration period. During the second 4-week period CBZ and PHT were withdrawn and patients meeting the inclusion criteria were entered into a 12-week monotherapy period. Drug treatment at any stage was discontinued if patients met certain 'escape' criteria signifying the worsening of seizures **ITT analysis performed/method** Authors state yes; see details of statistical analysis **Sample size calculation** The manufacturer's trial report states that a maximum of 150 patients were to be entered into each study to obtain at least 100 patients (n = 50 per group). Sample size calculation was based on a two-tailed χ^2 test on proportions. A difference of 50% between the two treatment group was assumed. A sample size of 42 per study group would allow detection of this difference with a power of 80% (0.05 significance level). The proportion of participants completing the 12 weeks of monotherapy was assumed to be 0.60 (LTG) and 0.30 (VPA) **Analysis methods** The primary efficacy variable was the proportion of patients in each treatment group meeting escape criteria any time after initiation of concomitant AED withdrawal. A secondary end-point was the comparison	**Baseline seizure frequency** Seizure frequency: LTG (n = 76): median/28 days = 9 (range, 1–737); VPA (n = 80): median/28 days = 10 (range, 3–226) Seizure type: LTG (n = 76): SPSs (n = 31), CPSs (n = 64), secondarily generalised (n = 38); VPA (n = 80): SPSs (n = 35), CPSs (n = 71), secondarily generalised seizures (n = 27) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion (screening phase): age ≥ 13 years; partial seizures with or without SGTC seizures considered unresponsive to at least one AED; at least 4 seizures every 4 weeks during the 12 weeks before screening; being treated with either CBZ or PHT Inclusion (randomisation): at least 4 seizures (simple, partial, complex partial or secondarily generalised, as classified by the ICSs) every 4 weeks during the baseline phase; no more than 20 consecutive seizure-free days during baseline; receiving CBZ or PHT monotherapy; judged otherwise healthy or to have stable chronic medical conditions Exclusion: recent diagnosis of epilepsy; pseudoseizures; generalised seizures; status epilepticus in previous 12 months; non-compliance; seizures due to metabolic illness, alcohol or drug abuse; surgery to		rash (n = 8/76), tremor (n = 5/76) Monotherapy period Patients with ≥ 1 AE (n = 26/43); dizziness (n = 3/43), nausea (n = 3/43), headache (n = 3/43), dyspepsia (n = 3/43), somnolence (n = 0/43), asthenia (n = 1/43), coordination abnormalities (n = 3/43), vomiting (n = 4/43), rash (n = 1/43), tremor (n = 2/43) **Comparator** Titration period Patients with ≥ 1 AE (n = 63/80); dizziness (n = 18/80), nausea (n = 15/80), headache (n = 10/80), dyspepsia (n = 11/80), somnolence (n = 11/80), asthenia (n = 10/80), coordination abnormalities (n = 0/80), vomiting (n = 7/80), rash (n = 6/80), tremor (n = 8/80), sudden unexplained death in epilepsy (n = 1/80) Monotherapy period Patients with ≥ 1 AE (n = 19/44); nausea (n = 1/44), headache (n = 6/44), dyspepsia (n = 1/44), somnolence (n = 1/44), rash (n = 1/44), tremor (n = 3/44)	discontinued owing to an inadequate response Data on plasma concentrations were also reported, but these have not been extracted. The authors report that mean plasma concentrations of LTG and VPA were similar in escapers and completers. Physical and neurological examinations and laboratory tests have not been extracted Efficacy analyses were adjusted by geographic region and centre (the study was carried out in 36 centres across the USA)

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
of time to escape. Efficacy analyses were adjusted by geographic region and centre. Analyses were performed on the per protocol population (n = 114), which was defined as all patients who correctly completed therapy (completers) or who met escape criteria (escapers) and the ITT population (n = 156), which was defined as all randomised patients. In the ITT population, patients were defined as treatment failures if they met escape criteria, had significant periods (≥ 1 week) of missing data, or were discontinued owing to an inadequate response The proportion of completers versus escapers was compared between treatment groups using the extended Cochran–Mantel–Haenzel test. The difference in time to escape was compared in the protocol-specified population using the log rank test and displayed using a Kaplan–Meier distribution curve The incidence of patients reporting AEs was tabulated for the ITT population along with the 95% CIs for the differences between treatment groups. All statistical tests were two-sided and p-values ≤ 0.05 were considered statistically significant **Length of trial/frequency of follow-up** 12 weeks; every 4 weeks	control seizures; psychoactive drugs including benzodiazapines; pregnancy, breastfeeding or inadequate contraception			

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Proportion of patients completing the study; patients who completed the monotherapy phase. The number of patients who were withdrawn from the study is also reported **Intervention 1** Completed monotherapy phase Per protocol analysis: 56% (28/50) ($p \leq 0.005$) ITT: 37% (28/76) ($p \leq 0.005$) Withdrawn: Per protocol analysis: not applicable ITT: 21% (16/76) **Comparator** Completed monotherapy phase: Per protocol analysis: 20% (13/64) ITT: 16% (13/80) Withdrawn: Per protocol analysis: not applicable ITT: 15% (12/80)	**Outcome** Time to exit/withdrawal; median time to exit in the per protocol population for the following reasons: doubling of average monthly seizure rate; doubling of the highest consecutive 2-day seizure rate; emergence of a new, more severe seizure type; or, clinically significant prolongation of GTC seizures compared with baseline **Intervention 1** Median = 168 days ($p \leq 0.001$) **Comparator** Median = 57 days	**Outcome** Exit/withdrawal rate; the number of patients who left (escaped) the study before completion. The number of patients who were withdrawn from the study is also reported **Intervention 1** Per protocol analysis: 44% (22/51) ITT: 42% (32/76) **Comparator** Per protocol analysis: 80% (51/64) ITT: 69% (55/80)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
GlaxoSmithKline, 2000[118] **Related publications** NRR entry,[358] NRR entry[359] **Country** UK **Source** Industry submission **Aim** To compare the efficacy and tolerability of LTG with physician's choice of either VPA or CBZ in a multicentre, open-label, parallel group study of patients aged ≥ 12 years with newly diagnosed epilepsy **Type of publication** Industry trial report **Funding** GlaxoSmithKline **Trial ID** 105-405R **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after enrolment	**Number of participants** 713 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 712): 35.6 years (SD 16.8); LTG (n = 355): 34.7 years (SD 17.2); physician's choice overall [VPA/CBZ (n = 357)]: 36.4 years (SD 16.3); VPA (n = 155): 33.6 years (SD 16.5); CBZ (n = 202): 38.6 years (SD 15.8); total (n = 712): 12–82 years; LTG (n = 355): 12–82 years; physician's choice overall [VPA/CBZ (n = 357)]: 13–82 years; VPA (n = 155): 13–82 years; CBZ (n = 202): 13–79 years **Gender** Total (n = 712): men = 371 (52%), women = 341 (48%); LTG (n = 355): men = 186 (52%), women = 169 (48%); physician's choice overall [VPA/CBZ (n = 357)]: men = 185 (52%), women = 172 (48%); VPA (n = 155): men = 85 (55%), women = 70 (45%); CBZ (n = 202): men = 100 (50%), women = 102 (50%) **Age at onset of seizures** Not stated **Pretrial medication** None stated	**Intervention 1** LTG; 200 mg/day; 20 weeks No. randomised: 355 No. completed: 224 **Comparator** Conventional treatment (CBZ or VPA); according to manufacturers' recommendations; 20 weeks No. randomised: 357 No. completed: 249	**Withdrawals prerandomisation** Total: did not return to clinic (n = 1) **Withdrawals postrandomisation** Total (n = 712): inadequate response (n = 15, 2%), consent withdrawn (n = 10, 1%), did not return to clinic (n = 81, 11%), protocol violation (n = 52, 7%), adverse experience (n = 81, 11%); LTG (n = 355): inadequate response (n = 10, 3%), consent withdrawn (n = 8, 2%), did not return to clinic (n = 42, 12%), protocol violation (n = 31, 9%), adverse experience (n = 40, 11%); physician's choice overall [VPA/CBZ (n = 357)]: inadequate response (n = 5, 1%), consent withdrawn (n = 2, 1%), did not return to clinic (n = 39, 11%), protocol violation (n = 21, 6%), adverse experience (n = 41, 11%); VPA (n = 155): inadequate response (n = 1, 1%), consent withdrawn (n = 1, 1%), did not return to clinic (n = 18, 12%), protocol violation (n = 11, 7%), adverse experience (n = 9, 6%); CBZ (n = 202): inadequate response (n = 4, 2%), consent withdrawn (n = 1, 0%), did not return to clinic (n = 21, 10%), protocol violation (n = 10, 5%), adverse experience (n = 32, 16%) **Adverse events** **Intervention 1** AEs experienced by at least 5% of patients in either treatment group	**Authors' conclusions** This study showed that LTG monotherapy was not significantly different in time to all causal withdrawal compared with physician's choice and that the proportion of 'successfully treated patients' was similar in both groups. In addition, significantly fewer patients on LTG monotherapy experienced AEs compared with those patients on physician's choice of either VPA or CBZ **Comments** The authors' power calculations suggest that an evaluable population of 1000 participants is required; however, fewer than half of this number of participants were finally included in the trial. Therefore, the trial is underpowered and the results should be treated with caution Of the 357 patients randomised to physician's choice, 155 received VPA and 202 received CBZ. In addition, some patients received concomitant medications, which may have affected the results of the study The following information was only available from the

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period After randomisation there was a 4-week dose escalation phase to either LTG or the physician's choice (VPA or CBZ). This was followed by a 16-week maintenance phase, during which the AED dose could be increased if the patient continued to have seizures, or decreased if the patient experienced unacceptable AEs Patients randomised to LTG were dosed once daily throughout the study. During weeks 1 and 2 of the dose escalation phase they received 25 mg/day LTG, and during weeks 3 and 4 of the dose escalation phase they received 50 mg/day LTG. Following the dose escalation phase, patients received maintenance within the dosage range of 100–500 mg/day LTG. The aim was to achieve seizure control by treating patients with 200 mg/day LTG. If not already instituted, therefore, the maintenance dose for all patients, in the absence of AEs, was adjusted to 200 mg/day by the end of week 6. If the patients were not seizure free during the maintenance phase, they could return to the clinic in addition to the protocol visits and have their LTG dose increased to a maximum of 500 mg/day. Similarly, if side-effects occurred, the dose could be reduced to a minimum of 100 mg/day. Patients were withdrawn from the trial either if a decrease in LTG dosage was required during the dose escalation phase or if the dose was reduced to below 100 mg during the maintenance phase. Patients randomised to VPA or CBZ were dosed according to the data sheet	**Ongoing concurrent medication** LTG (n = 355): amitriptyline (n = 1), betamethasone (n = 2), CBZ (n = 2), dexamethasone (n = 3), DZP (n = 6), haloperidol (n = 1), LTG (n = 1), proxetine (n = 4), PHT (n = 2), prednisolone (n = 5), prochlorperazine (n = 3), sertraline (n = 1), theophylline (n = 2), thiopental (n = 1), thioridazine (n = 1), trifluoperazine (n = 1), trimipramine (n = 1) Patients taking concomitant medications: n = 186 (52%) Patients taking selected concomitant medications (medications which may have had an effect on epilepsy): n = 27 (8%) One patient randomised to LTG took LTG as a concomitant medication Two patients randomised to LTG took CBZ as a concomitant medication Physician's choice overall [VPA/CBZ (n = 357)]: amitriptyline (n = 4), baclofen (n = 1), betamethasone (n = 1), CBZ (n = 1), clomethiazole (n = 1), clomipramine (n = 1), dexamethasone (n = 4), DZP (n = 6), fluozetine (n = 2), flupentixol (n = 1), imipramine (n = 1), methylprednisolone (n = 1), proxetine (n = 1), PHT (n = 1), prednisolone (n = 4), prochlorperazine (n = 7), risperidone (n = 1), sertraline (n = 1), theophylline (n = 3), thiopental (n = 2), thioridazine (n = 5), thipental (n = 1), trifluoperazine (n = 1), trimipramine (n = 2), VPA (n = 3)		LTG: somnolence (n = 52, 15%), headache (n = 64, 18%), dizziness (n = 24, 7%), nausea (n = 27, 8%), rash (n = 20, 6%), diarrhoea (n = 11, 3%), weight increase (n = 1, <1%), fatigue (n = 10, 3%) Total number of AEs in LTG: n = 503 Patients with at least 1 AE during the study in LTG: n = 218 (61%), $p < 0.0001$ Expected AEs (defined prestudy as being 'expected' as a result of treatment with AEDs) experienced by at least 5% of patients in either treatment group (LTG or physician's choice overall). LTG: somnolence (n = 52, 15%), headache (n = 66, 19%), vertigo (including dizziness) (n = 24, 7%), skin disorders (including acne, rash, rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact and allergic reaction with intense itch) (n = 24, 7%), weight gain (including weight increase and appetite increase) (n = 5, 1%), tiredness (including fatigue and apathy) (n = 11, 3%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) (n = 16, 5%) Total number of 'expected' AEs (LTG vs physician's choice) $p < 0.001$ Patients reporting no 'expected' AEs in LTG: n = 186 (52%)	protocol section of the trial report: The time/frequency of follow-up assessment of safety and efficacy The first paragraph under 'sample size calculations' The dose escalation and maintenance dosages The method of data collection The follow-up period of 20 weeks included a 4-week dose escalation period. Therefore, participants were not receiving the target dose for the whole follow-up period. In addition, although the target dose was 200 mg, depending on circumstances (already stated), patients were allowed to be maintained on a dose anywhere between 100 and 500 mg. This is particularly problematic, as the authors do not state anywhere how many patients achieved the target dose or mean/median maintenance dose achieved by patients. This may affect the results of the study. In addition, information on the dosages of VPA and CBZ is lacking – all that is stated is that dosages of VPA and CBZ were according to the data sheet recommendations

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
recommendations and could not exceed the maximum stated dose. For VPA, patients who were not in line with the data sheet requirements did not start dosing at an initial daily dose of 600 mg, and a maximum daily dose of 2500 mg was expected for maintenance. For CBZ, patients who were not in line with the data sheet requirements did not start dosing at an initial daily dose of 100–200 mg. The best response was expected at 800–1200 mg, although it was expected that 1600 or even 2000 mg/day may have been necessary. Doses could be altered during the maintenance phase depending on the occurrence of side-effects and/or seizures. Patients were withdrawn from the trial if either a decrease in dosage was required during the dose escalation phase or the dose was reduced below the recommended maintenance dose as stated in the data sheet **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The sample size calculation for LTG vs physician's choice (overall) was based on the primary end-point of 'time to causal withdrawal'. In estimating the sample size to detect a clinically significant treatment difference, proportional hazards were assumed. It was expected that there would be a withdrawal rate of 30% after 6 months. A sample size of 1000 evaluable patients provides power in excess of 80% to detect a 15% difference in the 'all causal withdrawal'	Patients taking concomitant medications: n = 208 (58%) Patients taking selected concomitant medications (medications which may have had an effect on epilepsy): n = 41 (11%) VPA (n = 155): baclofen (n = 1), CBZ (n = 1), clomethiazole (n = 4), clomipramine (n = 1), dexamethasone (n = 4), DZP (n = 1), imipramine (n = 1), methylprednisolone (n = 1), PHT (n = 1), prednisolone (n = 1), prochlorperazine (n = 2), risperidone (n = 1), sertraline (n = 1), theophylline (n = 3), thioridazine (n = 4), thipental (n = 1), trifluoperazine (n = 1), trimipramine (n = 2) Patients taking concomitant medications: n = 90 (58%) Patients taking selected concomitant medications (medications which may have had an effect on epilepsy): n = 19 (12%) 1 patient randomised to VPA took CBZ as a concomitant medication CBZ (n = 202): amitriptyline (n = 4), betamethasone (n = 1), clomethiazole (n = 1), DZP (n = 5), fluozetine (n = 2), flupentixol (n = 1), proxetine (n = 1), prednisolone (n = 3), prochlorperazine (n = 5), thiopental (n = 2), thioridazine (n = 1), VPA (n = 3) Patients taking concomitant medications: n = 118 (58%)		AEs assessed by the investigator as being related to study drug: LTG: <1% 13 LTG patients reported 16 serious AEs; 2 of these patients experienced fatal AEs **Comparator** AEs experienced by at least 5% of patients in either treatment group Physician's choice (VPA/CBZ) overall: somnolence (n = 116, 32%), headache (n = 46, 13%), dizziness (n = 39, 11%), nausea (n = 37, 10%), rash (n = 18, 5%), diarrhoea (n = 21, 6%), weight increase (n = 21, 6%), fatigue (n = 19, 5%), vertigo (including dizziness) (n = 40, 11%), skin disorders (including acne, rash, rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact and allergic reaction with intense itch) (n = 23, 6%), weight gain (including weight increase and appetite increase) (n = 26, 7%), tiredness (including fatigue and apathy) (n = 22, 6%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) (n = 12, 3%) VPA: somnolence (n = 37, 24%), headache (n = 14, 9%), dizziness (n = 14, 9%), nausea (n = 19, 12%), rash (n = 4, 3%), diarrhoea (n = 9, 6%), weight increase (n = 15, 10%), fatigue (n = 5, 3%), vertigo (including dizziness) (n = 14, 9%), skin disorders (including acne, rash,	Regarding serious AEs, the authors state that serious AEs are followed up in more detail and the complete data are held separately on a safety database, and that the information presented in the report is in narrative summary format. It is therefore possible that there are further data relating to serious AEs. Patience compliance: LTG: 15 (4%) patients did not follow the requirements for dose escalation (53 VPA, 32 CBZ). Of these, 4 withdrew owing to protocol violations. 256 (89%), 204 (87%) and 266 (80%) patients had excellent compliance at weeks 4, 12 and 20 respectively Physicians' choice: 85 (24%) patients did not follow the requirements for dose escalation. Of these, 10 withdrew owing to protocol violations (9 VPA, 1 CBZ). 262 (88%), 255 (88%) and 266 (79%) patients had excellent compliance at weeks 4, 12 and 20 respectively Further data and analyses are provided in the trial report and appendices, including time to all causal withdrawal for the subgroups of male and female, and for patients who withdrew

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
rate, using a 2-tail test at the 5% significance level The sample size was reviewed while the study was ongoing and recalculated as 712 patients in total. This was based on 80% power to detect a difference in time to all causal withdrawal between withdrawal rates of 30 and 40% in the two randomised groups, at a 5% significance level **Analysis methods** The analysis was performed on all final study data. As patients were randomised to LTG or physician's choice and not directly to VPA or CBZ, formal statistical methods were not valid to compare directly LTG with VPA or CBZ separately The primary outcome measure 'time to all causal withdrawal' was analysed using the Proportional Hazards Regression Model. The HR with 95% CI was calculated. The model included the effect of treatment; however, it was not possible to include the effect of centre or to investigate any potential treatment × centre interactions. Statistical analyses carried out on the 'number of patients withdrawing from the study' and 'patient success' used 95% CIs, and χ^2 tests were used to determine if differences between groups were statistically significant. A Cochran–Mantel–Haenszel test was used to assess patient acceptability All statistical hypothesis tests were performed at the 2-sided 5% significance level. No adjustments for	Patients taking selected concomitant medications (medications which may have had an effect on epilepsy): $n = 22$ (11%) 3 patients randomised to CBZ took VPA as a concomitant medication **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Number of patients experiencing seizures of type: total ($n = 712$): SPSs = 130 (18%), CPSs = 256 (36%), partial seizures evolving to SGTC, clonic or tonic seizures = 179 (25%), GTC seizures = 356 (50%); LTG: ($n = 355$): SPSs = 58 (16%), CPSs = 123 (35%), partial seizures evolving to SGTC, clonic or tonic seizures = 93 (26%), GTC seizures = 180 (51%); physician's choice overall [VPA and CBZ ($n = 357$)]: SPSs = 72 (20%), CPSs = 133 (37%), partial seizures evolving to SGTC, clonic or tonic seizures = 86 (24%), GTC seizures = 176 (49%); VPA ($n = 155$): SPSs = 19 (12%), CPSs = 38 (25%), partial seizures evolving to SGTC, clonic or tonic seizures = 26 (17%), GTC seizures = 102 (66%); CBZ ($n = 202$): SPSs = 53 (26%), CPSs = 95 (47%), partial seizures evolving to SGTC, clonic or tonic seizures = 60 (30%), GTC = 74 (37%)		rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact and allergic reaction with intense itch) ($n = 6$, 4%), weight gain (including weight increase and appetite increase) ($n = 17$, 11%), tiredness (including fatigue and apathy) ($n = 8$, 5%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) ($n = 5$, 3%) CBZ: somnolence ($n = 79$, 39%), headache ($n = 32$, 16%), dizziness ($n = 25$, 12%), nausea ($n = 18$, 9%), rash ($n = 14$, 7%), diarrhoea ($n = 12$, 6%), weight increase ($n = 6$, 3%), fatigue ($n = 14$, 7%), vertigo (including dizziness) ($n = 26$, 13%), skin disorders (including acne, rash, rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact and allergic reaction with intense itch) ($n = 17$, 8%), weight gain (including weight increase and appetite increase) ($n = 9$, 4%), tiredness (including fatigue and apathy) ($n = 14$, 7%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) ($n = 7$, 3%) Total number of AEs in physician's choice overall: $n = 640$ Patients with at least 1 AE during the study in physician's choice overall: $n = 271$ (76%) Expected AEs (defined prestudy as being 'expected' as a result of	owing to protocol violations as censored observations (also subdivided by male and female) Further analyses of number of causal withdrawals, handling patients who withdrew owing to protocol violations as withdrawals (all participants) and categorising patients who withdrew owing to protocol violations separately are provided in the trial report (also subdivided by male and female) Further analyses of patient acceptability and relating to AEs are available in the trial report

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
multiple testing were performed. Two analysis populations were used. The primary population for all analyses of efficacy and safety data was the ITT population. This population contains all patients who were randomised and who received at least one dose of the active treatment during the study. The other analysis population was all patients screened. This population contains all patients who had any data recorded during the screening phase of the study **Length of trial/frequency of follow-up** 20 weeks; weeks 4, 12, and 20	**Inclusion/exclusion criteria** Inclusion: aged ≥ 12 years; confident diagnosis of epilepsy uncomplicated by suspected pseudoseizures; seizures had to be easily recognisable by the patient or their carer, and had to be classified by the ICS; experienced at least two documented seizures prior to entry; written informed consent; willing and able to comply with study medication dosing and attend scheduled study assessments Exclusion: pregnant or at risk of pregnancy; lactating women; clinically significant impairment of hepatic or renal function; use of any other investigative (unlicensed) drug within the last 3 months; current or previous treatment with AEDs; patients who had experienced status epilepticus; elderly patients		treatment with AEDs) experienced by at least 5% of patients in either treatment group. Physician's choice overall: somnolence (n = 116, 32%); headache (n = 47, 13%), vertigo (including dizziness) (n = 40, 11%), skin disorders (including acne, rash, rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact and allergic reaction with intense itch) (n = 23, 6%), weight gain (including weight increase and appetite increase) (n = 26, 7%), tiredness (including fatigue and apathy) (n = 22, 6%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) (n = 12, 3%) VPA: somnolence (n = 37, 24%), headache (n = 14, 9%), vertigo (including dizziness) (n = 14, 9%), skin disorders (including acne, rash, rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact and allergic reaction with intense itch) (n = 6, 4%), weight gain (including weight increase and appetite increase) (n = 17, 11%), tiredness (including fatigue and apathy) (n = 8, 5%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) (n = 5, 3%) CBZ: somnolence (n = 79, 39%), headache (n = 33, 16%), vertigo (including dizziness) (n = 26, 13%), skin disorders (including acne, rash, rash erythematus, skin disorder, skin dry, dermatitis, dermatitis contact	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
			and allergic reaction with intense itch) (n = 17, 8%), weight gain (including weight increase and appetite increase) (n = 9, 4%), tiredness (including fatigue and apathy) (n = 14, 7%), disturbed sleep (including dreaming abnormal, insomnia and sleep disorder) (n = 7, 3%) Patients reporting no 'expected' AEs in physician's choice overall: n = 132 (37%) AEs assessed by the investigator as being related to study drug in physician's choice overall: <1% 5 VPA patients reported 5 serious AEs; none of these patients experienced fatal AEs 8 CBZ patients reported 13 serious adverse events; 1 of these patients experienced a fatal AE	

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Time to exit/withdrawal; time elapsing from entry to the last dose of study medication being taken **Intervention 1** LTG (n = 355): Patients with events (event = the patient withdrawing and not remaining on the study drug): 97 (27%) 85th percentile for all causal withdrawal: 28 days	**Outcome** Proportion of seizure-free patients Definition A: patients who completed the study and were seizure free in the last 8 weeks; Definition B: patients who completed the study, were seizure free in the last 8 weeks and did not experience any serious and severe AEs during the study for which the relationship to study medication was assessed as a reasonable possibility	**Outcome** Proportion of participants remaining on study drug; the number of patients remaining on study drug following involvement in the study **Intervention 1** LTG (n = 355): No. remaining on study drug following involvement in the study: 248 (70%) No. completing study and remaining on study drug: 214 (60%)	**Outcome** Patient preference; how acceptable the participants find the treatment in terms of how much they think the drug has helped control their epilepsy. The numbers of patients reporting the treatment as not at all helpful, not very much help, a little bit of help, very much helped, extremely good, not known were reported **Intervention 1** LTG (n = 355): not at all helpful = 29

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
HR = 1.12, (95% CI: 0.84 to 1.49), p = 0.430 **Comparator** Physician's choice overall (VPA/CBZ, n = 357): Patients with events: 91 (25%) 85th percentile for all causal withdrawal: 56 days VPA (n = 155): Patients with events: 31 (20%) 85th percentile for all causal withdrawal: 84 days CBZ (n = 202): Patients with events: 60 (30%) 85th percentile for all causal withdrawal: 34 days	**Intervention 1** LTG (n = 355): Definition A = 164 (46%), p = 0.826; Definition B = 160 (45%), p = 0.603 **Comparator** Physician's choice (VPA or CBZ, n = 357): Definition A = 162 (45%); Definition B = 154 (43%) VPA (n = 155): Definition A = 78 (50%); Definition B = 75 (48%) CBZ (n = 202): Definition A = 84 (42%); Definition B = 79 (39%)	No. withdrawing from study but remaining on study drug: 34 (10%) **Comparator** Physician's choice overall (VPA/CBZ, n = 357): No. remaining on study drug following involvement in the study: 245 (69%) No. completing study and remaining on study drug: 228 (64%) No. withdrawing from study but remaining on study drug: 17 (5%) VPA (n = 155): No. remaining on study drug following involvement in the study: 113 (73%) No. completing study and remaining on study drug: 104 (67%) No. withdrawing from study but remaining on study drug: 9 (6%) CBZ (n = 202): No. remaining on study drug following involvement in the study: 132 (65%) No. completing study and remaining on study drug: 124 (61%) No. withdrawing from study but remaining on study drug: 8 (4%)	(10%), not very much help = 29 (10%), a little bit of help = 60 (21%), very much helped = 58 (21%), extremely good = 106 (38%), not known = 73; (LTG vs physician's choice) p = 0.785 **Comparator** Physician's choice overall (VPA/CBZ, n = 357): not at all helpful = 15 (5%), not very much help = 33 (12%), a little bit of help = 62 (22%), very much helped = 77 (27%), extremely good = 96 (34%), not known = 74 VPA (n = 155): not at all helpful = 5 (4%), not very much help = 18 (14%), a little bit of help = 36 (28%), very much helped = 29 (23%), extremely good = 39 (31%), not known = 28 CBZ (n = 202): not at all helpful = 10 (6%), not very much help = 15 (10%), a little bit of help = 26 (17%), very much helped = 48 (31%), extremely good = 57 (37%), not known = 46 **Note** During the course of the study, feedback from investigators indicated that poor form design was leading to inaccurate reporting of all three questions in the patient acceptability section. The authors state that for this reason, these results are not reported any further

Outcome 5	
Outcome Weight gain **Intervention 1** Mean weight of patients at screening: LTG: 71.1 kg (SD 14.90); Mean changes in weight per 28 days: LTG: 0.01 kg (SD 0.71); 95% of patients who reported weight increase as an AE during the study were in the physician's choice group	**Comparator** Mean weight of patients at screening: Physician's choice overall (VPA/CBZ): 72.7 kg (SD 16.17) Mean changes in weight per 28 days: Physician's choice overall (VPA/CBZ): 0.33 kg (SD 0.83); VPA: 0.45 kg (SD 0.68); CBZ: 0.22 kg (SD 0.93)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
GlaxoSmithKline, 2001[62] **Related publications** NRR entry.[357] **Country** South Africa and Singapore **Source** Industry submission **Aim** To compare the efficacy and safety profile of LTG with VPA as monotherapy in idiopathic generalised epilepsy **Type of publication** Full paper (industry trial report) **Funding** GlaxoSmithKline **Trial ID** 105-126 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** Following screening, patients were randomised to LTG or VPA	**Number of participants** 211 **Type of epilepsy** Newly diagnosed **Type of seizures** Generalised onset **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged at least 2 years (although this was amended during the study to recruit only patients who were at least 13 years old); confident diagnosis	**Intervention 1** LTG; 100–500 mg/day (age >12 years), 2–10 mg/kg/day (paediatrics); 24 weeks No. randomised: 211 No. completed: 162 **Comparator** VPA; not stated; 24 weeks No. randomised: 102 No. completed: 81	**Withdrawals prerandomisation** NA **Withdrawals postrandomisation** Adult population LTG (n = 211): AEs (n = 16), death (n = 0), inadequate response to study drug (n = 3), withdrew consent (n = 6), lost to follow-up (n = 12), protocol violations (n = 11), other reasons (n = 1) VPA (n = 102): AEs (n = 6), death (n = 0), inadequate response to study drug (n = 3), withdrew consent (n = 4), lost to follow-up (n = 5), protocol violations (n = 3), other reasons (n = 0) **Adverse events** **Intervention 1** Adult population: 106/211 (50%) patients experienced AEs 67/211 (32%) patients had AEs considered to be drug-related 18/211 (9%) patients withdrew from the study owing to an AE 10/211 (5%) patients reported a serious AE Summary of drug-related AEs. % experiencing any AE related to: Body as a whole 26/211 (12%) Cardiovascular system 1/211 (<1%) Digestive system 10/211(5%) Haemic and lymphatic system 1/211 (<1%) Metabolic and nutritional disorder 4/211 (2%) Musculoskeletal system 1/211(<1%) Nervous system 26/211(12%) Skin and appendages 17/211 (8%) Special senses 1/211 (<1%) Urogenital system 0/211 (0%)	**Authors' conclusions** Adult patients: the data from this study demonstrate that LTG was efficacious (seizure occurrence) as monotherapy in newly diagnosed adult epilepsy patients with primary generalised seizures and that this efficacy was similar to that of VPA LTG was better tolerated than VPA. Although similar numbers of patients in both treatment groups reported AEs and similar numbers withdrew owing to adverse events, more patients on VPA reported drug-related AEs than did those on LTG. In addition, LTG was not associated with the weight gain seen with VPA **Comments** All data are extracted from a trial report that is marked confidential. Total no. randomised: 458 No. randomised to LTG: 310 (211 adult, 99 paediatric) No. randomised to VPA: 148 (102 adult, 46 paediatric) No. randomised to LTG who completed the trial: 235 (162 adults, 73 paediatric) No. randomised to VPA who completed the trial: 119 (81 adults, 38 paediatric) Only data relating to the adult population is presented in this table

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
in a ratio of 2:1. There was a 4-week dose escalation phase, followed by a 20-week dose maintenance phase. LTG (5, 25, 100, 200 mg) tablets were taken orally once daily (unless clinically indicated that daily doses should be divided). Recommended daily LTG dosing regimens were as follows: for patients aged 2–12 years: weeks 1–2, 0.5 mg/kg; weeks 3–4, 1 mg/kg; weeks 5–24, 2–10 mg/kg (maximum 500 mg); For patients aged >12 years: weeks 1–2, 25 mg; weeks 3–4, 50 mg; weeks 5–24: 100–500 mg. During the maintenance phase, patients could have their LTG dose increased if they were not seizure free and there had been no clinically significant AEs. Patients who discontinued LTG had their dose tapered by 50% decrements over 2 weeks for maintenance doses of up to 200 mg or 4 weeks for maintenance doses of >200 mg. VPA was taken orally and dosed in accordance with the data sheet recommendations **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated	of epilepsy; suffering from primary GTC seizures (other primary generalised seizures could also be present); experienced at least 2 tonic–clonic seizures in the previous 6 months and at least 1 in the past 3 months, or 1 tonic–clonic seizure in the past 3 months and other evidence of idiopathic generalised epilepsy such as family history, generalised epileptiform activity on EEG without focal features, photosensitivity or history of early morning myoclonic jerks Exclusion: use of LTG or VPA within the past 3 months; current treatment with AEDs or treatment with other medication that would contraindicate treatment with LTG or VPA; pregnancy, breast feeding or not using adequate contraception		Specific drug-related AEs reported by at least 5% of participants for either study group: Nausea 6/211 (3%) Weight increase 2/211 (<1%) Somnolence 9/211 (4%) Tremor 3/211 (1%) Summary of serious AEs. % experiencing any AE related to: Body as a whole 2/211 (<1%) Cardiovascular system 0/211 (0%) Digestive system 2/211 (<1%) Haemic and lymphatic system 1/211 (<1%) Metabolic and nutritional disorder 1/211 (<1%) Nervous system 4/211 (2%) Respiratory system 1/211 (<1%) **Comparator** Adult population: 58/102 (57%) of patients experienced AEs 49/102 (48%) patients had AEs considered to be drug-related 7/102 (7%) patients withdrew from the study owing to an AE 3/102 (3%) patients reported a serious AE Summary of drug-related AEs. % experiencing any AE related to: Body as a whole 14/102 (14%) Cardiovascular system 0/102 (0%) Digestive system 13/102 (13%) Haemic and lymphatic system 0/102 (0%) Metabolic and nutritional disorder 14/102 (14%) Musculoskeletal system 0/102 (0%) Nervous system 24/102 (24%) Skin and appendages 9/102 (9%) Special senses 0/102 (0%) Urogenital system 2/102 (2%)	No data relating to participant baseline characteristics are provided. All that is stated is that 'in general, groups (adult and paediatric) were balanced for demographic characteristics such as age, weight, baseline seizure rates'; the exception was that in the paediatric group, more males were randomised to VPA (59%) compared to LTG (51%) The follow-up period of 24 weeks included a 4-week dose escalation phase. Therefore, patients were not receiving the recommended target dose of LTG for the full 24 weeks The dose of LTG given above is the recommended daily dose. The dose of VPA is not specifically stated, all that is stated is that VPA was dosed in accordance with data sheet recommendations Median daily dose during weeks 4–24: LTG, adult patients: 100 mg; LTG, paediatric patients: 2.2 mg/kg; VPA, adult patients: 1000 mg; VPA, paediatric patients: 23.1 mg/kg According to licensed use of VPA as adjunctive therapy to LTG in adults, usual maintenance dose is 100–200 mg daily. However, the mean daily VPA maintenance dose for adults in this study was 1000 mg

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods All analyses were carried out on the ITT, adult and paediatric populations. Only data from the adult populations will be reported in this table **Length of trial/frequency of follow-up** 24 weeks; not stated			Specific drug-related AEs reported by at least 5% of participants for either study group: Nausea 6/102 (6%) Weight increase 13/102 (13%) Somnolence 11/102 (11%) Tremor 8/102 (8%) Summary of serious AEs. % experiencing any adverse event related to: Body as a whole 0/102 (0%) Cardiovascular system 1/102 (<1%) Digestive system 0/102 (0%) Haemic and lymphatic system 1/102 (0%) Metabolic and nutritional disorder 0/102 (0%) Nervous system 2/102 (2%) Respiratory system 0/102 (0%)	The trial report contains further data relating to seizure freedom, weight changes and adverse events, not reported in this table An ITT analysis was only performed for the population as a whole. Data presented separately for adult and paediatric groups are per protocol
Results				
Outcome 1				
Outcome Proportion of seizure-free patients; the percentage of patients who were seizure free for the last 12 weeks of the study, including/excluding patients who withdrew before 18 weeks **Intervention 1** Adult population (per protocol analysis) including patients who withdrew before week 18 Follow-up data LTG: 131/211 (62%), (95% CI: –17 to 5.6), $p = 0.330$ Adult population (per protocol analysis) excluding patients who withdrew before week 18 Follow-up data LTG: 131/167 (78%), (95% CI: –17 to 3), $p = 0.184$ **Comparator** Adult population (per protocol analysis) including patients who withdrew before week 18 Follow-up data VPA: 69/102 (68%) Adult population (per protocol analysis) excluding patients who withdrew before week 18 Follow-up data VPA: 69/81 (85%)				

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Kerr, 2001[122] **Related publications** Abstract,[362] abstract,[353] abstract,[363] unpublished QoL data[113] **Country** Multinational **Source** Literature search **Aim** To compare the safety and efficacy of add-on LTG versus CBZ and add-on LTG versus VPA, withdrawing to LTG or CBZ/VPA monotherapy, in patients with treatment resistant epilepsy **Type of publication** Industry trial report **Funding** GlaxoSmithKline **Trial ID** SCAB3001 **Study design** Monotherapy after add-on titration; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 877 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** LTG vs CBZ: at baseline the majority of patients (includes adults and children) were on VPA or PHT (numbers not stated) LTG vs VPA: at baseline the majority of patients (includes adults and children) were on CBZ, PHT or OXC (numbers not stated) **Ongoing concurrent medication** See pretrial medication **Co-morbidities** Not stated **Baseline seizure frequency** Number of seizure types in last 8 weeks prior to screening visit LTG vs CBZ Partial: total 40 (n = 304); LTG 26 (n = 181); CBZ 14 (n = 123)	**Intervention 1** LTG; 200–500 mg/day; 28 weeks No. randomised: 181 No. completed: 96 **Intervention 2** CBZ; not stated; 28 weeks No. randomised: 123 No. completed: 65 **Intervention 3** LTG; 200–500 mg/day; 28 weeks No. randomised: 316 No. completed: 125 **Comparator** VPA; not stated; 28 weeks No. randomised: 257 No. completed: 77	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG: total n = 34/225; death n = 2, withdrew consent n = 14, lost to follow-up n = 8, protocol violation n = 6, discontinuation of study by sponsor n = 2, no reason stated n = 2 CBZ: total n = 23/154; death n = 1, withdrew consent n = 11, lost to follow-up n = 6, protocol violation n = 4, discontinuation of study by sponsor n = 0, no reason stated n = 1 LTG: total n = 60/368; death n = 2, withdrew consent n = 30, lost to follow-up n = 18, protocol violation n = 8, discontinuation of study by sponsor n = 2 VPA: total n = 41/295, death n = 0, withdrew consent n = 15, lost to follow-up n = 14, protocol violation n = 8, discontinuation of study by sponsor n = 6 **Adverse events** **Intervention 1** LTG (vs CBZ) All AEs, any event: 174/225 Drug-related AEs, any event: 115/225; adult patients 55% Most common (≥ 10%) drug-related AEs were somnolence 9%, dizziness 10%, asthenia 6%, and headache 6%	**Authors' conclusions** LTG is an effective treatment for adjunctive therapy and switch to monotherapy. Efficacy is similar to CBZ and VPA. Treatment effect was consistent between adults with primary generalised epilepsy and all adult patients included in the trials. QoL was significantly improved with LTG compared with VPA; no difference was shown between LTG and CBZ. LTG was better tolerated than CBZ or VPA with fewer patients withdrawing owing to AEs or experiencing drug-related AEs **Comments** Two separate trials are reported; these are abstracted as follows: LTG (intervention 1) vs CBZ (intervention 2); LTG (intervention 3) vs VPA (intervention 4). Both trials included paediatric patients (<13 years) and adults (75 in the LTG vs CBZ trial and 90 in the LTG vs VPA trial). This abstract represents the adults only (except AEs, see outcome data) The LTG vs CBZ trial was terminated early owing to difficulty in recruiting patients, reflecting the change in clinical practice over the study period VPA and CBZ were used at doses thought most appropriate by the

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Participants were screened during a pretrial period (duration not stated) and eligible patients were enrolled to LTG vs CBZ or LTG vs VPA, according to physician choice, then randomised (open label). Treatment was for 28 weeks: a 4-week dose-escalation phase in which LTG or CBZ/VPA was added to existing AED therapy; 8-week add-on phase in which patients were stabilised on their existing AED and study treatment; 8-week withdrawal phase (optional). Patients who achieved monotherapy continued with this treatment to week 28 **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** LTG vs CBZ was analysed as a separate study from LTG vs VPA. The van Elteren extension of the Wilcoxon rank sum test, stratified for cluster of centres, was used to compare seizure reduction rates from baseline at week 4, 12, 20 and 28. Analysis was performed for the total duration that patients were in the study, and for patients up to the point where they were withdrawn (ITT–during treatment population). Stratified Mantel–Haenszel chi-squared tests were used to compare proportion of patients seizure free at week 4, 12, 20 and 28, and the proportion that achieved at least 7 weeks monotherapy. Kaplan–Meier survival curves were used to summarise time to treatment failure and time to first seizure. Log rank test was used	Partial + generalised: total 5 (n = 304); LTG 2 (n = 181); CBZ 3 (n = 123) Generalised: total 62 (n = 304); LTG 36 (n = 181); CBZ 26 (n = 123) LTG vs VPA Partial: total 59 (n = 573); LTG 36 (n = 316); VPA 23 (n = 257) Partial + generalised: total 9 (n = 573); LTG 3 (n = 316); VPA 6 (n = 257) Generalised: total 63 (n = 573); LTG 36 (n = 316); VPA 27 (n = 257) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: at least 2 years old; with treatment-resistant epilepsy; on stable treatment with a single AED; and at least two seizures during the 8-week screening period Exclusion: pregnancy, breastfeeding, not taking adequate contraception; clinically significant hepatic or renal impairment; PB or PRM treatment that could not be withdrawn over 8 weeks; and other contraindicated medication (not specified)		Serious AEs: 12%; serious rash n = 2 (including Stevens–Johnson syndrome n = 1) **Intervention 2** CBZ All AEs, any event: 116/154 Drug-related AEs, any event: 90/154; adult patients 63% Most common (≥ 10%) drug-related AEs were somnolence 17%, dizziness 12%, asthenia 11% and headache 11% Serious AEs: 7%; serious rash n = 1 **Intervention 3** LTG (vs VPA) All AEs, any event: 259/368 Drug-related AEs: 48%; adult patients 51% Most common (≥ 10%) drug-related AEs were somnolence 7%, dizziness 11%, tremor 3%, asthenia 4% and nausea 5% Serious AEs: 8%; serious rash n = 0 **Comparator** VPA All AEs, any event: 228/295 Drug-related AEs: 60%; adult patients 63% Most common (≥ 10%) drug-related AEs were somnolence	investigator and in accordance with the drug data sheets CBZ/VPA were given as considered appropriate by the investigators and in accordance with data sheet recommendations. It is not possible to tell whether the dose given was within licensed recommendations The number of seizure types in the last 8 weeks prior to screening visit are also reported for simple, complex and combinations of these with partial and generalised seizures ITT was defined as all randomised patients who received at least one dose of study medication. The number who completed the trial corresponds to participants who completed to week 28 on monotherapy % change in seizure rate at week 4, 12 and 20 is also reported. All efficacy results are also reported for the subgroup of patients who had only primary generalised seizures in the 8 weeks prior to study entry. The denominator for number of patients withdrawn postrandomisation and AEs results represents all patients (adults and children) as adult data were not shown separately

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
to compare overall time to treatment failure and time to first seizure. ANCOVA used to compare mean scores on SEALS and QOLIE-31, adjusted for the effects of QoL state at baseline **Length of trial/frequency of follow-up** 28 weeks; 4, 12, 20 and 28 weeks			12%, dizziness 7%, tremor 11%, asthenia 12% and nausea 13% Serious AEs: VPA 9%; serious rash $n = 0$	Specific AEs (overall and drug-related) are reported, categorised by body system (but the drug-related results table for LTG vs VPA is missing from the report); again data are not reported separately for adults and children No statistically significant difference between LTG and CBZ was shown by the SEALS and QOLIE-31 instruments. The overall scores from SEALS ($p \leq 0.001$) and QOLIE-31 ($p = 0.004$) showed a statistically significantly better QoL with LTG versus VPA

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of seizure-free patients; over the period of 1 month between the scheduled visits at 20 and 28 weeks (end of study) **Intervention 1** LTG: $n = 58/179$ **Intervention 2** CBZ: $n = 36/122$ **Intervention 3** LTG: $n = 68/315$ **Comparator** VPA: $n = 40/253$	**Outcome** Exit/withdrawal rate; time to treatment failure. Reported as the estimated cumulative overall failure rate at end of study **Intervention 1** LTG 26% LTG vs CBZ $\chi^2 = 0.761$, $p = 0.383$ (log rank test) **Intervention 2** CBZ 29% **Intervention 3** LTG 26% LTG vs VPA $\chi^2 = 1.785$, $p = 0.181$ (log rank test)	**Outcome** Exit/withdrawal rate; the estimated cumulative overall failure rate at end of study **Intervention 1** LTG 86% LTG vs CBZ $\chi^2 = 3.475$, $p = 0.062$ (log rank test) **Intervention 2** CBZ 86% **Intervention 3** LTG 96% LTG vs VPA $\chi^2 = 0.472$, $p = 0.492$ (log rank test)	**Outcome** Proportion of responders; responders were defined as achieving at least a 50% reduction in seizure frequency between scheduled visits at weeks 20 and 28) at week 28 visit (end of study) **Intervention 1** LTG (vs CBZ) $n = 93/179$ **Intervention 2** CBZ $n = 67/122$ **Intervention 3** LTG (vs VPA) $n = 114/315$ **Comparator** VPA $n = 94/253$

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Comparator VPA 28%	**Comparator** VPA 97%	
Outcome 5			
Outcome Proportion of participants remaining on treatment; the number of patients who reached 28 weeks on monotherapy and achieved at least 7 weeks of monotherapy **Intervention 1** LTG $n = 96/181$, LTG vs CBZ $p = 0.972$ **Intervention 2** CBZ $n = 65/123$ **Intervention 3** LTG $n = 125/316$, LTG vs VPA $p = 0.022$ **Comparator** VPA $n = 77/257$			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Martinez, 2002[114] **Related publications** Abstract of QoL data[364] **Country** USA **Source** Industry submission **Aim** To evaluate the efficacy and tolerability of LTG monotherapy with older AEDs in patients converting from previous monotherapy because of inadequate seizure control or unacceptable side-effects **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** SCAA4005 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The study consisted of a 2-week screening phase, after which patients were	**Number of participants** 122 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 115): not stated; LTG (*n* = 57): 40.8 years (SD 13.5); conventional therapy (PHT, VPA or CBZ) (*n* = 58): 38.8 years (SD 14.5); not stated **Gender** Total (*n* = 115): men = 47, women = 68; LTG (*n* = 57): men = 25, women = 32; conventional therapy (PHT, VPA or CBZ) (*n* = 58): men = 22, women = 36 **Age at onset of seizures** Not stated **Pretrial medication** LTG (*n* = 57): CBZ *n* = 21, VPA *n* = 15, PHT *n* = 21; conventional therapy (PHT, VPA or CBZ) (*n* = 58): CBZ *n* = 19, VPA *n* = 15, PHT *n* = 24 Number of AEDs: total (*n* = 68): 1 AED (*n* = 5); 2 AEDs (*n* = 20); 3 AEDs (*n* = 36); 4 AEDs (*n* = 7) Median number of concurrent AEDs: 3 Mean number of concurrent AEDs: 2.7	**Intervention 1** LTG; 100–500 mg/day; 32 weeks No. randomised: 57 No. completed: 37 **Comparator** Conventional therapy (CBZ, PHT or VPA); not stated; 32 weeks No. randomised: 58 No. completed: 33	**Withdrawals prerandomisation** Total: consent withdrawn (*n* = 3/122), protocol violations (*n* = 3/122), other (*n* = 1/122) **Withdrawals postrandomisation** LTG Withdrawals prior to receiving treatment: AEs (*n* = 7/57), consent withdrawn (*n* = 2/57), protocol violations (*n* = 1/57), other (*n* = 2/57) Withdrawals after receiving treatment: AEs (*n* = 2/57), consent withdrawn (*n* = 2/57), protocol violations (*n* = 2/57), loss to follow-up (*n* = 1/57), other (*n* = 1/57) Conventional therapy (PHT, VPA or CBZ) Withdrawals prior to receiving treatment: AEs (*n* = 9/58), consent withdrawn (*n* = 1/58), protocol violations (*n* = 2/58) Withdrawals after receiving treatment: AEs (*n* = 6/58), consent withdrawn (*n* = 2/58), protocol violations (*n* = 4/58), other (*n* = 1/58) **Adverse events** **Intervention 1** Reported in >10% of patients in either treatment group: any drug-related AE (*n* = 28/58); tremor (*n* = 4/58), dizziness (*n* = 5/58),	**Authors' conclusions** Converting from monotherapy with a less effective or poorly tolerated older AED to monotherapy with LTG is associated with better clinical and humanistic outcomes than converting to an alternative conventional AED **Comments** Details about the process of randomisation are missing from the report. Randomisation was stratified according to reason for conversion from current monotherapy (i.e. lack of efficacy or poor tolerability) The study was not adequately powered to detect statistical differences between the two drugs The proportion of patients requiring as-needed AEDs in addition to the study drugs was 10% in the LTG group and 7% in the conventional therapy group

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
randomised to treatment groups. There was an 8-week titration phase, followed by a 24-week treatment phase. During titration, patients randomised to LTG monotherapy had LTG added while the current AED was removed; patients randomised to conventional monotherapy (with CBZ, PHT or VPA) had one of those 3 AEDs added while their current AED was withdrawn In converting from VPA monotherapy to LTG monotherapy LTG doses were increased by 25–50 mg/day every 1–2 weeks during the escalation phase. During the treatment phase LTG doses could be increased by 50–100 mg/day to a maximum of 500 mg/day as needed to control seizures In converting from CBZ or PHT monotherapy to LTG monotherapy, LTG doses were increased by 50–100 mg/day every 1–2 weeks during the escalation phase. During the treatment phase, LTG doses could be increased by 50–100 mg/day to a maximum of 500 mg/day as needed to control seizures Patients could discontinue at any time at the investigator's or their discretion. The comparator AED could not be the same AED as that taken by the patient at entry to screening **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The study was not powered to detect statistical differences in efficacy between	**Ongoing concurrent medication** Patients were allowed acute use of AEDs in addition to study drug only if needed for medical management **Co-morbidities** Not stated **Baseline seizure frequency** Total (n = 115): not stated; LTG (n = 57): Mean = 4.5 (SD 6.9); conventional therapy (PHT, VPA or CBZ) (n = 58): Mean = 3.8 (SD 8.7) **Other characteristics** Presenting seizure type (a patient could present with more than one seizure type): total (n = 115): not stated; LTG (n = 57): simple partial n = 11, complex partial n = 42, secondarily generalised n = 35, generalised n = 15; conventional therapy (PHT, VPA or CBZ) (n = 58): simple partial n = 13, complex partial n = 40, secondarily generalised n = 25, generalised n = 21 Lack of seizure control was the primary reason for converting from prestudy AED in 54% of the patients randomised to LTG (n = 57) and 59% of patients randomised to conventional therapy (n = 58) for the maintenance phase. The remainder of patients in each randomised group converted because of unacceptable side-effects		somnolence (n = 2/58), asthenia (n = 4/58), headache (n = 4/58), nausea (n = 10/58), rash (n = 7/58) **Comparator** Any drug-related AE (n = 43/58); tremor (n = 11/58), dizziness (n = 10/58), somnolence (n = 10/58), asthenia (n = 9/58), headache (n = 8/58), nausea (n = 10/58), rash (n = 1/58)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
LTG and the older AEDs, but to provide a descriptive assessment **Analysis methods** QOLIE-31 scores were transformed to scores falling in the range of 0 (worst) to 100 (best). The scale score for each domain was determined by summing and then dividing them by the number of items in a domain. The QOLIE-31 overall score was obtained by weighting and summing the product of scale scores and their weight and then summing over all domains. QOLIE-31 scores were tested for between-group differences using ANCOVA **Length of trial/frequency of follow-up** 32 weeks; baseline and follow-up at weeks 1, 12 and 24	The AED used in the conventional group in the maintenance phase was VPA (n = 30) 52%, CBZ (n = 24) 41% and PHT (n = 4) 7% The average maintenance doses (SD) were LTG 356.9 mg/day (SD 148.9), CBZ 781.3 mg/day (SD 287.3), VPA 1691.8 mg/day (SD 564.2) and PHT 423.2 mg/day (SD 54.7) **Inclusion/exclusion criteria** Inclusion: age ≥ 16 years; diagnosed with epilepsy; experiencing any seizure type classifiable by the ILAE; females were eligible only if they had a negative urine or serum pregnancy test at screening and agreed to use acceptable contraceptive methods during the study or were not able to have children; patients needing a change of CBZ, PHT or VPA monotherapy due to inadequate seizure control or unacceptable side-effects were included Exclusion: patients with previous experience with LTG or felbamate; treatment with more that 1 AED; use of any investigational drug within 4 weeks prior to the beginning of the study; use of the ketogenic diet; planned vagal stimulation or surgery during the study period to control seizures			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of responders; responders were defined as patients with a ≥ 50% reduction in seizure frequency **Intervention 1** *n* = 14/37 (38%) **Comparator** *n* = 12/33 (37%)	**Outcome** Proportion of seizure-free patients; percentage of patients seizure free at end of 24-week maintenance phase **Intervention 1** *n* = 9/37 (23%) Seizure free in last 8 weeks of maintenance phase: 32% **Comparator** *n* = 7/33 (22%) Seizure free in last 8 weeks of maintenance phase: 24%	**Outcome** Physician global evaluation of improvement/efficacy/ tolerability; investigators' assessment of patient's clinical status at week 22 based on 7 clinical factors (seizure frequency, duration and intensity; AEs, social, intellectual, motor functioning and the overall status assessment at week 22). Reported as % patients assessed as experiencing mild, moderate or marked improvement **Intervention 1** % patients assessed as experiencing mild, moderate or marked improvement (*n* = 57): seizure frequency (37%); seizure duration (35%); seizure intensity (37%); AEs (33%); social functioning (24%); intellectual functioning (29%); motor functioning (18%); overall status at week 22 (31%) **Comparator** % patients assessed as experiencing mild, moderate or marked improvement (*n* = 58): seizure frequency (20%); seizure duration (19%); seizure intensity (19%); AEs (15%); social functioning (13%); intellectual functioning (9%); motor functioning (7%); overall status at week 22 (13%)	**Outcome** Patient global evaluation of improvement/efficacy/ tolerability; patients' self-assessment at week 24 according to 5 categories (much worse, somewhat worse, same, somewhat better, and much better). Reported as % participants in each category **Intervention 1** (*n* = 37): much worse 4%, somewhat worse 4%, same 18%, somewhat better 24%, much better 49% **Comparator** (*n* = 33): much worse 15%, somewhat worse 15%, same 12%, somewhat better 29%, much better 29%
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome Change in seizure frequency; mean change in seizure frequency from baseline to week 24 **Intervention 1** LTG (*n* = 37): mean % reduction in seizure rate over maintenance phase: 53% (SD 55.1)	**Outcome** Proportion of treatment success/number of completers; number of patients completing the 24-week maintenance phase with premature discontinuation of the study because of inadequate seizure control or unacceptable side-effects	**Outcome** Time to exit/withdrawal; reported as mean time (in days) **Intervention 1** LTG (n = 57): 175 days (SD 83.1) **Comparator** Conventional therapy (PHT, VPA or CBZ) (*n* = 58): 156 days (SD 80.7)	**Outcome** Change in patient-related QoL; measured using the QOLIE-31 questionnaire for seizure worry, overall QoL, emotional well-being, energy/fatigue, cognitive functioning, medication effects and social functioning. A higher score indicates a better QoL (extracted from Ref. 364) **Intervention 1** Mean change-from-baseline QOLIE-31 scores reflected statistically significant improvement ($p < 0.01$) in HRQoL for LTG compared with conventional therapy for both the

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Outcome 5	Outcome 6	Outcome 7	Outcome 8
Comparator Conventional therapy (n = 33): mean % reduction in seizure rate over maintenance phase: 52% (SD 149.9)	**Intervention 1** LTG (n = 57): 65% **Comparator** Conventional therapy (PHT, VPA or CBZ) (n = 58): 57%		overall score (9.6 LTG versus 3.1 conventional therapy, p = 0.01) and the domains ($p \leq 0.02$): Overall QoL: 6.2 Patient's health perception: 6.7 Energy/fatigue: 8.6 Cognitive functioning: 12.4 Medication effects: 19.0 **Comparator** Overall QoL: –1.3 Patient's health perception: 0.2 Energy/fatigue: –0.4 Cognitive functioning: 4.3 Medication effects: 4.2

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Matsuo, 1993[142] **Related publications** Industry trial report[365] **Country** USA **Source** Literature search **Aim** To evaluate the efficacy and safety of LTG (300 and 500 mg/day) as add-on therapy in a multicentre, randomised, double-blind, parallel-group, placebo-controlled study of 216 patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** US-05 (P42-05)/ GSK16 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 216 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 216): 33 years; LTG (500 mg) (n = 72): 32 years; LTG (300 mg) (n = 71): 33 years; placebo (n = 73): 34 years (SD not reported); total (n = 216): 18–63 years; LTG (500 mg) (n = 72): 18–59 years; LTG (300 mg) (n = 71): 20–57 years; placebo (n = 73): 18–63 years **Gender** Total (n = 216): men = 67, women = 149; LTG (500 mg) (n = 72): men = 15, women = 57; LTG (300 mg) (n = 71): men = 30, women = 41; placebo (n = 73): men = 22, women = 51 **Age at onset of seizures** Mean duration of epilepsy: total (n = 216): 21.9 years; LTG (500 mg) (n = 72): 21.8 years; LTG (300 mg) (n = 71): 22.4 years; placebo (n = 73): 21.5 years Mean age at onset: total (n = 216): 11.0 years; LTG (500 mg) (n = 72): 10.3 years; LTG (300 mg) (n = 71): 10.4 years; placebo (n = 73): 12.3 years **Pretrial medication** Up to 3 currently marketed AEDs	**Intervention 1** LTG; 500 mg/day; 24 weeks No. randomised: 72 No. completed: 59 **Intervention 2** LTG; 300 mg/day; 24 weeks No. randomised: 71 No. completed: 65 **Comparator** Placebo; 24 weeks No. randomised: 73 No. completed: 67	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: AEs (n = 14/216), a variety of reasons including loss of seizure control, intercurrent illness, non-compliance or other protocol violations (n = 13/216) (only AEs specified by treatment group) **Adverse events** **Intervention 1** Includes only those AEs that occurred in ≥ 10% of patients, that demonstrated statistically significant differences between placebo and LTG groups or that were reported as a reason for premature withdrawal from the study Dizziness n = 39/72 (54%), diplopia n = 35/72 (49%), headache n = 23/72 (32%), ataxia n = 20/72 (28%), blurred vision n = 18/72 (25%), nausea n = 18/72 (25%), somnolence n = 7/72 (10%), vomiting n = 13/72 (10%), rash n = 7/72 (10%), pain n = 5/72 (7%) Incidence significantly different from placebo ($p \leq 0.05$): dizziness, diplopia, ataxia, blurred vision, nausea, vomiting	**Authors' conclusions** LTG was safe, effective and well tolerated as an add-on therapy for refractory partial seizures **Comments** The authors included the titration phase as part of the follow-up period. Therefore, for ~1–5 weeks of the 24-week follow-up period some participants were not on their maximum target dose The authors report the investigator's global evaluation in graph format, therefore it is not possible to extract accurate data. However, they report that a significantly greater number of patients in the LTG (500 mg) group showed marked or moderate improvement after 12 and 24 weeks of treatment compared with the placebo group The authors report the results for seizure reduction for weeks 13–24. However, it is not clear whether there was a significant difference for the other time periods The authors do not report the results of the ITT analysis; however, they report that when all patients who were randomised to double-blind treatment were evaluated (regardless of the

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 12-week baseline period during which vital signs, ECG data, physical, neurological and ophthalmological examinations and clinical laboratory test results were monitored. This was followed by a dose titration and maintenance treatment period of 24 weeks. LTG was initiated at 50 mg/day and increased by 100 mg/day increments at weekly intervals until the appropriate target dose of 300 or 500 mg/day was achieved. The target dose could be reduced by 100 mg if the patient did not tolerate the full dose. Patient's maximum tolerated dose was continued for the remainder of the 24-week treatment period. This was followed by an LTG taper/follow-up period of 3 weeks **ITT analysis performed/method** Authors state yes; average counts were used as substitute values **Sample size calculation** A sample size calculation estimated that 165 patients (55 per group) were needed to complete the study and detect a 50% difference in seizure frequency between the two treatment groups with a power of 80%. A completed patient was defined as having completed a minimum of 12 weeks of treatment **Analysis methods** The ITT analysis included all patients who were randomised to double-	**Ongoing concurrent medication** CBZ (alone or in combination with other AEDs): total (n = 216) 73%; LTG (500 mg) (n = 72) 77%; LTG (300 mg) (n = 71) 70%; placebo (n = 73) 83% PHT (alone or in combination with other AEDs): total (n = 216) 35%; LTG (500 mg) (n = 72) 34%; LTG (300 mg) (n = 71) 45%; placebo (n = 73) 29% One concurrent AED: total (n = 216) 40%; LTG (500 mg) (n = 72) 40%; LTG (300 mg) (n = 71) 30%; placebo (n = 73) 49% Two concurrent AEDs: total (n = 216) 53%; LTG (500 mg) (n = 72) 50%; LTG (300 mg) (n = 71) 63%; placebo (n = 73) 45% Three concurrent AEDs: total (n = 216) 7%; LTG (500 mg) (n = 72) 10%; LTG (300 mg) (n = 71) 7%; placebo (n = 73) 5% VPA was not allowed during the period of the trial **Co-morbidities** Not stated **Baseline seizure frequency** Median seizure frequency (per month) Simple or complex partial or secondarily generalised seizures (n = 216): total 12.2%; LTG (500 mg) 12.7%; LTG (300 mg) 12.0%; placebo 12.7% Simple or complex partial seizures (n = 207): total 12.0%; LTG (500 mg) 11.5%; LTG (300 mg) 12.0%; placebo 12.3% Secondarily generalised seizures (n = 69): total 2.0%; LTG (500 mg) 4.7%; LTG (300 mg) 1.7%; placebo 0.7%		**Intervention 2** Dizziness n = 22/71 (31%), diplopia n = 17/71 (24%), headache n = 23/71 (32%), ataxia n = 7/71 (10%), blurred vision n = 8/71 (11%), nausea n = 13/71 (18%), somnolence n = 15/71 (21%), vomiting n = 8/71 (11%), rash n = 12/71 (17%), pain n = 9/71 (13%) Incidence significantly different from placebo ($p \leq 0.05$): diplopia, somnolence, pain **Comparator** Dizziness n = 20/73 (27%), diplopia n = 6/73 (8%), headache n = 19/73 (26%), ataxia n = 7/73 (10%), blurred vision n = 7/73 (10%), nausea n = 8/73 (11%), somnolence n = 5/73 (7%), vomiting n = 3/73 (4%), rash n = 7/73 (10%), pain n = 2/73 (3%)	extent of actual drug exposure), the results for all measurements were qualitatively similar to those extracted above The authors do not specify what type of statistical tests they used to establish where the significant effects occurred in the ANOVA The authors also report data on plasma AED concentrations, which have not been extracted Since the effects of the three treatments did not vary significantly among the 15 clinical centres, data from all centres were pooled for subsequent analysis

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
blind treatment regardless of the extent of actual drug exposure. For seizure frequency the treatment phase was divided into two 12-week periods and the difference between the log total seizure counts compared with baseline was calculated. Similar log comparisons were made for the total number of seizure days. Data from the investigators' global evaluation were collected at the end of each 12-week treatment period comparing the participants' condition with baseline. Comparisons were made across treatment groups using the Cochran–Mantel–Haenszel statistic. All tests were two-sided and statistically significant results were defined as those for which $p \leq 0.05$. The statistical significance of the difference between treatment groups in the proportion of patients with treatment-emergent adverse experiences was based on confidence interval estimation **Length of trial/frequency of follow-up** 24 weeks; at 12 and 24 weeks	**Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: age 18–65 years; simple or complex partial seizures (with or without secondary generalisation) that were refractory to treatment with up to 3 currently marketed AEDs (seizures were classified according to the ICs); refractory was defined as at least 4 partial seizures in a 4-week period despite treatment with therapeutic levels of 1–3 currently marketed AEDs; no changes in concurrent AEDs including dose adjustments within 2 weeks of study entry (4 weeks in the case of PB). Exclusion: newly diagnosed epilepsy (<32 weeks); pseudoseizures or primary generalised seizures; seizures secondary to drugs, alcohol, infection, neoplasia, demyelination, metabolic illness or progressive degenerative disease; experienced status epilepticus within 24 weeks of baseline; progressive neurological disorder that was not stable for at least 24 weeks prior to baseline; use of any investigational drug within 24 weeks of baseline; VPA within 4 weeks of study entry or use of VPA as concomitant AED; abuse of any prescription or non-prescription drug including alcohol; current consumption of any psychoactive drug; a severe psychiatric condition requiring hospitalisation; an IQ <50; any medical condition that would interfere with the absorption, distribution, metabolism or excretion of drugs; a history of non-compliance; a clinically significant chronic medical disorder involving the renal,			

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
	hepatic, cardiac, vascular, haematopoietic, reticuloendothelial, endocrine, pulmonary, gastrointestinal, genitourinary or ophthalmological systems; for women of childbearing age a negative pregnancy test, use of an approved contraceptive method and a signed 'intent to avoid pregnancy' waiver			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; overall (24 weeks) median % reduction in seizure frequency **Intervention 1** LTG (500 mg) (n = 59): 36% reduction (LTG 500 mg vs placebo p = 0.007) **Intervention 2** LTG (300 mg) (n = 65): 20% reduction (LTG 300 mg vs placebo p = non-significant but positive trend in favour of 300 mg LTG) **Comparator** Placebo (n = 67): 8%	**Outcome** Proportion of responders; percentage of patients in each category of response (reduction/increase in seizure frequency) from baseline for weeks 1–12 and weeks 13–24 **Intervention 1** Weeks 1–12: ≥ 50% decrease: n = 21/63 (33%) 26–49% decrease: n = 18/63 (29%) ±25% (no change): n = 17/63 (27%) 26–49% increase: n = 3/63 (5%) ≥ 50% increase: n = 4/63 (6%) Weeks 13–24: ≥ 50% decrease: n = 20/59 (34%) 26–49% decrease: n = 14/59 (22%) ±25% (no change): n = 19/59 (32%) 26–49% increase: n = 2/59 (3%) ≥ 50% increase: n = 4/59 (7%) The proportion of patients experiencing ≥ 26% reduction in seizure frequency was significantly greater (p < 0.05) in the LTG (500 mg) group than the placebo group	**Outcome** Proportion of responders; percentage of patients in each category of change in the number of seizure days from baseline for weeks 1–12 and weeks 13–24 **Intervention 1** Weeks 1–12: ≥ 50% decrease: n = 12/63 (19%) 26–49% decrease: n = 20/63 (32%) ±25% (no change): n = 26/63 (41%) 26–49% increase: n = 2/63 (3%) ≥ 50% increase: n = 3/63 (5%) Weeks 13–24: ≥ 50% decrease: n = 16/59 (27%) 26–49% decrease: n = 14/59 (24%) ±25% (no change): n = 27/59 (42%) 26–49% increase: n = 1/59 (2%) ≥ 50% increase: n = 3/59 (5%) The proportion of patients experiencing ≥ 26% reduction in seizure days was significantly greater (p < 0.05) in the LTG (500 mg) group than the placebo group (this was taken from a table in the paper; however, in the text the authors refer to	**Outcome** Seizure days; median % reduction from baseline to the last 12 weeks of the trial in terms of seizure days **Intervention 1** 26.3% reduction, p = significant in favour of 500 mg LTG vs placebo **Intervention 2** 20.7% reduction, p = non-significant compared with placebo **Comparator** 15.4% reduction

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Intervention 2 Weeks 1–12: ≥ % decrease: *n* = 12/67 (18%) 26–49% decrease: *n* = 18/67 (27%) ±25% (no change): *n* = 19/67 (28%) 26–49% increase: *n* = 6/67 (9%) ≥ 50% increase: *n* = 12/67 (18%) Weeks 13–24: ≥ 50% decrease: *n* = 13/65 (20%) 26–49% decrease: *n* = 17/65 (26%) ≥ 25% (no change): *n* = 20/65 (31%) 26–49% increase: *n* = 5/65 (8%) ≥ 50% increase: *n* = 10/65 (15%) **Comparator** Weeks 1–12: ≥ 50% decrease: *n* = 10/70 (14%) 26–49% decrease: *n* = 11/70 (16%) ±25% (no change): *n* = 36/70 (51%) 26–49% increase: *n* = 4/70 (6%) ≥ 50% increase: *n* = 9/70 (13%) Weeks 13–24: ≥ 50% decrease: *n* = 12/67 (18%) 26–49% decrease: *n* = 18/67 (19%) ±25% (no change): *n* = 19/67 (45%) 26–49% increase: *n* = 6/67 (12%) ≥ 50% increase: *n* = 12/67 (6%)	the effect being on at least a 50% reduction in seizure days) **Intervention 2** Weeks 1–12: ≥ 50% decrease: *n* = 11/67 (16%) 26–49% decrease: *n* = 9/67 (13%) ±25% (no change): *n* = 38/67 (57%) 26–49% increase: *n* = 6/67 (9%) ≥ 50% increase: *n* = 3/67 (5%) Weeks 13–24: ≥ 50% decrease: *n* = 15/65 (23%) 26–49% decrease: *n* = 15/65 (23%) ±25% (no change): *n* = 27/65 (42%) 26–49% increase: *n* = 4/65 (6%) ≥ 50% increase: *n* = 4/65 (6%) **Comparator** Weeks 1–12: ≥ 50% decrease: *n* = 4/70 (6%) 26–49% decrease: *n* = 10/70 (14%) ±25% (no change): *n* = 46/70 (66%) 26–49% increase: *n* = 8/70 (11%) ≥ 50% increase: *n* = 2/70 (3%) Weeks 13–24: ≥ 50% decrease: *n* = 8/67 (12%) 26–49% decrease: *n* = 17/67 (25%) ±25% (no change): *n* = 35/67 (52%) 26–49% increase: *n* = 2/67 (3%) ≥ 50% increase: *n* = 5/67 (8%)	
Outcome 5			
Outcome Proportion of seizure-free participants Defined as seizure free during the whole 24-week double-blind treatment period **Intervention 1** LTG (500 mg): *n* = 5/59	**Intervention 2** LTG (300 mg): *n* = 7/65 **Comparator** Placebo: *n* = 1/67		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Matsuo, 1996[328] **Related publications** Industry submission[366] **Country** USA **Source** Literature search **Aim** To evaluate the dose tolerability and safety of a chronic ascending twice-daily (b.d.) dosage regimen of 700 mg/day or less LTG and to include determination of the LTG pharmacokinetic profile at doses of ≥ 500 mg/day in patients receiving concomitant enzyme-producing AEDs **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** US14 (P42-14) **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Combination in- and outpatient **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 12 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 31.6 years (SD 7.6 years); LTG (n = 8): 30.3 years (SD 5.1 years); placebo (n = 4): 34.3 years (SD 12.1 years); total (n = 12): 24–51 years; LTG (n = 8): 25–40 years; placebo (n = 4): 24–51 years **Gender** Total (n = 12): men = 12, women = 0; LTG (n = 8): men = 8, women = 0; placebo (n = 4): men = 4, women = 0 **Age at onset of seizures** Years of seizure history: total (n = 12): mean = 17.6 years (SD 9.7 years); LTG (n = 8): mean = 22.3 years (SD 7.7 years); placebo (n = 4): mean = 8.3 years (SD 5.7 years) **Pretrial medication** Not stated **Ongoing concurrent medication** CBZ (n = 9); PHT (n = 8); PB (n = 4); PRM (n = 2); chloazepate (n = 1); CZP (n = 1) **Co-morbidities** Not stated	**Intervention 1** LTG; max. 700 mg/day; 63 days No. randomised: 8 No. completed: 7 **Comparator** Placebo; 63 days No. randomised: 4 No. completed: 3	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG (n = 8): diffuse papular skin rash (n = 1); placebo (n = 4): persistent behavioural problems (n = 1) **Adverse events** **Intervention 1** Most commonly reported treatment-emergent AE occurring in at least 50% of patients in either treatment group: headache (n = 5/8, 63%), drowsiness (n = 5/8, 63%), faintness (n = 4/8, 50%), diplopia (n = 4/8, 50%), dyspepsia (n = 1/8, 13%), nasal congestion (n = 1/8, 13%), fatigue (n = 0/8, 0%), flushing (n = 0/8, 0%) Serious AE: headache (n = 1) Treatment-emergent neurological abnormalities: balance (n = 2/8, 25%), coordination (n = 2/8, 25%), gait (n = 1/8, 13%), increased reflexes (n = 1/8, 13%), mental status (n = 1/8, 13%), nystagmus (n = 4/8, 50%), tone, increased (n = 0/8, 0%), tremor (n = 1/8, 13%)	**Authors' conclusions** LTG appears to be safe and well tolerated when administered chronically at doses up to 500 mg/day (b.d. regimen) for 42 days to epileptic patients maintained on concurrent AEDs. At doses >500 mg/day LTG still appears to be safe, but 2 of 8 patients experienced mild neurological side-effects that required dosage reductions. Chronic dosing of LTG does not appear to markedly affect plasma concentrations of concomitantly administered AEDs **Comments** Additional information taken from the industry submission trial report US14

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 2-week baseline/screening phase. Following successful screening, patients were randomised to two consecutive 3-week treatment phases (an outpatient phase followed by an inpatient phase), a 2-week dose-taper phase and a follow-up evaluation. During the 3-week outpatient phase, LTG or placebo was administered in doses of 100 mg/day for 3 days, followed by 200 mg/day for 4 days, 300 mg/day for 7 days and 400 mg/day for 7 days. Patients who tolerated 400 mg/day were admitted to hospital and the study drug was increased in 100-mg increments each week for 3 weeks, to a maximum of 700 mg/day. Patients remained as inpatients for the first week of the 2-week dose taper phase, during which time patients received 50% of their maximum tolerated dose. The study drug was then reduced to 25% of the maximum tolerated dose for the second week of taper and then discontinued **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 63 days; baseline, then weekly from day 21	**Baseline seizure frequency** Not stated **Other characteristics** Seizure type (partial controlled): total (n = 12): 2 (17%); LTG (n = 8): 1 (13%); placebo (n = 4): 1 (25%) Seizure type: (partial uncontrolled): total (n = 12): 10 (83%); LTG (n = 8): 7 (88%); placebo (n = 4): 3 (75%) **Inclusion/exclusion criteria** Inclusion: aged 18–65 years; otherwise in good general health with no major organ system dysfunction; female patients had to be postmenopausal or surgically sterilised; have had 40 or less seizures during the month before study entry and must not have experienced status epilepticus for the 6 months before receiving study drug; allowed as many as 3 currently marketed AEDs; stable (within 50%) therapeutic plasma AED concentrations, with no dosage or drug regimen changes within 2 weeks (4 weeks for barbiturates) before the baseline of the study Exclusion: history of hypersensitivity to drugs chemically related to LTG; VPA was not allowed for 8 weeks prior to the study, and 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		**Comparator** Most commonly reported treatment-emergent AE occurring in at least 50% of patients in either treatment group: headache (n = 3/4, 75%), drowsiness (n = 2/4, 50%), faintness (n = 2/4, 50%), diplopia (n = 0/4, 0%), dyspepsia (n = 2/4, 50%), nasal congestion (n = 2/4, 50%), fatigue (n = 2/4, 50%), flushing (n = 2/4, 50%) Serious AE: headache (n = 1/4) Treatment-emergent neurological abnormalities: balance (n = 0/4, 0%), coordination (n = 0/4, 0%), gait (n = 1/4, 25%), increased reflexes (n = 1/4, 25%), mental status (n = 0/4, 0%), nystagmus (n = 3/4, 75%), tone, increased (n = 1/4, 25%), tremor (n = 0/4, 0%)	

continued

Results
Outcome 1
Outcome Physician/patient global evaluation of improvement/efficacy/tolerability; the number of patients who tolerated the maximum dose of drug **Intervention 1** LTG (n = 8): 5 patients tolerated the maximum dose for 1 week. One patient was reduced to 600 mg/day owing to mild diplopia; and one patient was reduced to 500 mg/day owing to mild oscillopsia and diplopia. One patient was withdrawn from the study while receiving 300 mg/day LTG because of a diffuse papular skin rash of moderate intensity that was attributed to LTG **Comparator** Placebo (n = 4): 2 patients completed dose ascension as scheduled. Study drug was reduced for 1 patient during the third week of the outpatient phase owing to persistent behavioural problems. One patient was withdrawn from the study during the second week of the the outpatient phase because of an intercurrent illness

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Nieto Barrera, 2001[119] **Related publications** None **Country** European **Source** Literature search **Aim** To evaluate monotherapy with LTG or CBZ in a multicentre open trial of patients aged ≥ 2 years with newly diagnosed epilepsy **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** 105-136 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** Participants were randomised to receive LTG or CBZ in a 2:1 ratio with stratification by age (2–12, 13–64 or ≥ 65 years) and country. There was a 6-week titration phase	**Number of participants** 618 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** LTG (n = 417): median = 19 years; CBZ (n = 201): median = 20 years; LTG (n = 417): 2–83 years; CBZ (n = 201): 2–77 years **Gender** LTG (n = 417): men = 53%, women = 47%; CBZ (n = 201): men = 53%, women = 47% **Age at onset of seizures** Not stated **Pretrial medication** Not stated (no previous AEDs permitted) **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** LTG (n = 417): mean (seizures/month) = 10.07, median = 0.67, range = 0.2–1500.0; CBZ (n = 201): mean (seizures/month) = 6.84, median = 0.50, range = 0.2–600.0	**Intervention 1** LTG; median 200 mg/day; 18 weeks No. randomised: 259 No. completed: 201 **Comparator** CBZ; median 600 mg/day; 18 weeks No. randomised: 126 No. completed: 91	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** ≥ 13 years old LTG: AEs (n = 30), withdrawals due to all causes (n = 58); CBZ: AEs (n = 22), withdrawals due to all causes (n = 35) **Adverse events** **Intervention 1** AEs reported by >6% of patients ≥ 13 years old (n = 259) No. of AEs reported (n = 318) No. of patients experiencing any AE (n = 138) No. of serious AEs (n = 14) No. of drug-related AEs (n = 97) Headache (n = 30), asthenia (n = 19), somnolence (n = 10), rash (n = 23), dizziness (n = 23) **Comparator** ≥ 13 years old (n = 126) No. of AEs reported (n = 165) No. of patients experiencing any AE (n = 73) No. of serious AEs (n = 8) No. of drug-related AEs (n = 53) Headache (n = 13), asthenia (n = 14), somnolence (n = 14), rash (n = 12), dizziness (n = 6)	**Authors' conclusions** Monotherapy with LTG is as effective as CBZ in patients with newly diagnosed partial epilepsy. Patients were able to tolerate LTG better than CBZ, so more patients receiving LTG were able to remain in therapy **Comments** Although this study includes participants from 2 to 83 years old, only the data for ≥ 13-years-old have been extracted. The demographic data for age, gender and baseline seizures extracted above refer to all the participants (2–83 years old) as this was the only format in which the data were available The number of participants randomised to each treatment group and the number completing the trial for each group is for the ≥ 13 years age group only. The total number of participants randomised to LTG (n = 417); the number completing the trial in this group (n = 338). The total number of participants randomised to CBZ (n = 201); the number completing the trial in this group (n = 155) The 18-week follow-up period does not include the titration phase

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
followed by an 18-week maintenance phase. The 13–64-year-old group and the ≥ 65-year-old group received 25 mg/day in weeks 1–2, 50 mg/day in weeks 3–4, 100 mg/day in week 5 and in week 6 the 13–64-year-old group received 150 mg/day and the ≥ 65 year-old group 100 or 150 mg/day. During the maintenance phase the ≥ 13 years old age group could have the dose increased by a maximum of 50–100 mg every 1–2 weeks until an optimal response was achieved with a target range of 200–700 mg/day. The dose could also be decreased in the maintenance phase if required in the opinion of the investigator. Participants were withdrawn if a dose reduction was required during titration or when on the lowest maintenance dose. Participants ≥ 13 years old randomised to CBZ received 100–1500 mg/day with a slow increase in dosage until the best response was obtained **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Efficacy was assessed by calculating the difference between treatments in the proportion of patients seizure free during the last 16 weeks of treatment. A 95% CI calculated using the normal approximation to the binomial distribution and associated significance test are also presented. Discontinuation due to AEs was compared using the two-sided Fisher's exact test. The	Simple partial seizures LTG (n = 88); CBZ (n = 32) Complex partial seizures LTG (n = 185); CBZ (n = 78) Partial evolving to secondarily generalised LTG (n = 228); CBZ (n = 126) Generalised LTG (n = 6); CBZ (n = 1) **Other characteristics** The trial is an open-label study **Inclusion/exclusion criteria** Inclusion: newly diagnosed or with currently untreated partial epilepsy; seizures easily recognised by the patient or carer and able to be classified by the ICs; at least two partial seizures in the 6 months preceding the study; at least one partial seizure or secondarily generalised seizure in the preceding 3 months; evidence of focal radiological or EEG abnormalities			The minimum dose received for both CBZ and LTG was below the lower limit of the usual dose used; however, the mean and median doses fell within the usual recommended dose Adjustment of the drug treatment dose was allowed during the maintenance phase The exclusion criteria were not as extensive as some other studies Dose of intervention: median 200 mg/day (50–500 mg/day) Dose of comparator: median 600 mg/day (100–1500 mg/day) There was no significant difference in efficacy between the two groups as assessed by freedom from seizures and efficacy success. The time course for seizure occurrence was also similar between the two study groups A significantly higher proportion of patients receiving CBZ discontinued treatment owing to AEs compared with the LTG group (21 vs 12%, p = 0.032) (Note: the withdrawals due to adverse events in Figure 1 of the paper do not seem to tally with the number of withdrawals due to AEs in Table 6 on global effectiveness)

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
distribution of time to withdrawal from the study was estimated using Kaplan–Meier plots. All tests were conducted at the two-sided level of significance **Length of trial/frequency of follow-up** 18 weeks; weeks 4, 12 and 24 (or on withdrawal)				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**		
Outcome Proportion of seizure-free patients; patients free of seizures during the last 16 weeks of treatment in patients who had at least 18 weeks of data after the clinic visit made at week 4 **Intervention 1** Patients ≥ 13 years old: n = 126/195 (65%) (95% CI: –19 to 5) **Comparator** Patients ≥ 13 years old: n = 63/88 (72%)	**Outcome** Proportion of seizure-free patients; the 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 **Intervention 1** Patients ≥ 13 years old: n = 126/259 (49%) (95% CI: –12 to 9) **Comparator** Patients ≥ 13 years old: n = 63/126 (50%)	**Outcome** Number of completers; the number of patients completing the study (≥ 13 years old) **Intervention 1** n = 201/259 **Comparator** n = 91/126		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Reunanen, 1996[120] **Related publications** Abstract,[368] interim abstract,[369] final paper Italian centre,[370] preliminary paper, Italian centre,[371] abstract[372] **Country** European **Source** Literature search **Aim** The efficacy and safety of LTG and CBZ as monotherapy in patients with untreated, newly diagnosed or recurrent partial and/or GTC seizures were compared in a randomised, open, multicentre study **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30025 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after enrolment	**Number of participants** 343 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** LTG 100 mg: 33 years; LTG 200 mg: 30 years; CBZ: 32 years (SD not stated); LTG 100 mg: 13–72 years; LTG 200 mg: 12–66 years; CBZ: 13–71 years **Gender** LTG 100 mg (n = 115): men = 54%, women = 46%; LTG 200 mg (n = 111): men = 58%, women = 42%; CBZ (n = 117): men = 50%, women = 50% **Age at onset of seizures** Age at onset LTG 100 mg (n = 115): mean = 29 years (range 0–71 years); LTG 200 mg (n = 111): mean = 26 years (range 1–61 years); CBZ (n = 117): mean = 28 years (1–70 years) **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated	**Intervention 1** LTG; 100 mg/day; 26 weeks No. randomised: 115 No. completed: 71 **Intervention 2** LTG; 200 mg/day; 26 weeks No. randomised: 111 No. completed: 76 **Comparator** CBZ; 600 mg/day; 26 weeks No. randomised: 117 No. completed: 76	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG 100 mg (n = 115): deaths (n = 1), intercurrent illness (n = 2), personal event (n = 2), protocol deviation (n = 11), inadequate response (n = 1), withdrew consent (n = 1), AE (n = 5), other (n = 1); LTG 200 mg (n = 111): deaths (n = 1), protocol deviation (n = 4), withdrew consent (n = 1), AE (n = 5); CBZ (n = 117): intercurrent illness (n = 1), personal event (n = 1), protocol deviation (n = 10), withdrew consent (n = 5), adverse event (n = 12) **Adverse events** **Intervention 1** Treatment-emergent AEs with incidence of at least 5% in any treatment group LTG 100 mg: asthenia (12.0%), dizziness (6.1%), headache (18.0%), insomnia (4.3%), nausea (6.1%), rash (5.2%), somnolence (6.1%) One death due to a myocardial infarction in a patient with long-standing severe cardiovascular disease	**Authors' conclusions** Overall, LTG appeared equally effective but better tolerated compared with CBZ **Comments** The baseline seizure data were gathered retrospectively, which may provide an unreliable measure The length of treatment and follow-up does not include the titration period The dose of CBZ is below the usual minimum suggested dose of 800 mg None of the efficacy analyses showed a significant difference between the treatment groups The authors report that pairwise comparison of those AEs occurring in at least 10 patients showed that headache occurred significantly more frequently on LTG 200 mg than CBZ. Somnolence was significantly more common in the CBZ group than both LTG groups Laboratory data and plasma drug concentrations are also reported, but these have not been extracted

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Patients were randomised into three treatment groups: LTG 100 mg/day, LTG 200 mg/day and CBZ 600 mg/day. There was a 4-week titration phase followed by 26 weeks at maintenance dose. Both LTG groups received 25 mg/day during weeks 1–2, 50 mg/day during weeks 3–4. From week 5 the 100-mg group received the full dose of 100 mg and the 200-mg group the full dose of 200 mg. The CBZ group commenced on a dose of 200 mg in weeks 1–2, 400 mg in weeks 3–6 and 600 mg from week 5. In the instance of a patient experiencing any clinically significant adverse experience considered attributable to the study drug, the total daily dose could be reduced to 50% of the maintenance dose. Patients requiring a dose reduction to less than this were discontinued from the trial. Other criteria for withdrawal were withdrawal of consent, development of other severe illness, exposure to risk of pregnancy or serious non-compliance. Patients experiencing a seizure after the first 6 weeks recorded seizure type and date and terminated then or at the next clinic visit **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Efficacy was assessed by pairwise comparison of: proportion completing the trial seizure free after the first 6 weeks of treatment using ORs with 95% CI; time to first seizure; and time to withdrawal. The last two measures were analysed using Kaplan–Meier plots with the	**Co-morbidities** Not stated **Baseline seizure frequency** Seizures in 6 months prior to study LTG 100 mg (n = 115): mean = 9.3, median = 3.0; LTG 200 mg (n = 111): mean = 11.9, median = 3.0; CBZ (n = 117): mean = 14.5, median = 3.0 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: >12 years old; a confident diagnosis of newly diagnosed or recurrent epilepsy with partial and/or GTC seizures classifiable by the ICS; patients with current epilepsy were defined as those who had previous chronic treatment for epilepsy but no more than 2 doses of AED in the 6 months before inclusion; at least 2 seizures in the previous 6 months with at least one in the previous 3 months but no more than 30 in any one of the preceding 6 months Exclusion criteria: a history of status epilepticus; antiepileptic medication in the previous 6 months other than one or two doses of acute treatment; presence of other significant organic or psychiatric disease;		**Intervention 2** LTG 200 mg: asthenia (13.0%), dizziness (4.5%), headache (18.0%), insomnia (9.9%), nausea (6.3%), rash (8.1%), somnolence (6.3%) One death due to suicide **Comparator** CBZ: asthenia (20.0%), dizziness (10.0%), headache (9.4%), insomnia (1.7%), nausea (7.7%), rash (8.5%), somnolence (17.0%)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
proportional hazards model to calculate hazard ratios and 95% CI. For time to first seizure, patients withdrawing before day 42 were not included. For time to withdrawal, all randomised patients were included in the analysis Some patients did not attend clinics at the scheduled visit week (nominal week). In this case, data were assigned to a nominal week number using appropriate time windows **Length of trial/frequency of follow-up** 26 weeks; weeks 2, 6, 12 and 30 commencing from titration	abnormal laboratory values; use or abuse of any medication or substances which might have interfered with the study objectives; pregnancy, lactation or exposure of risk to pregnancy			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of seizure-free patients; proportion of patients completing the trial seizure free after the first 6 weeks of treatment **Intervention 1** LTG 100 mg (*n* = 115): 51.3% OR LTG 100 mg vs LTG 200 mg: 0.7 (95% CI: 0.4 to 1.2) OR LTG 100 mg vs CBZ: 0.9 (95% CI: 0.5 to 1.5) **Intervention 2** LTG 200 mg (*n* = 111): 60.4% OR LTG 200 mg vs CBZ: 1.3 (95% CI: 0.8 to 2.1) **Comparator** CBZ (*n* = 117): 54.7%	**Outcome** Time to first seizure **Intervention 1** LTG 100 mg vs LTG 200 mg: HR = 0.9 (95% CI: 0.5 to 1.5) LTG 100 mg vs CBZ: HR = 0.8 (95% CI: 0.5 to 1.4) **Intervention 2** LTG 200 mg vs CBZ: HR = 0.9 (95% CI: 0.5 to 1.6) **Comparator** See above	**Outcome** Exit/withdrawal rate; defined as proportion of patients remaining in study at the end of 1, 3 and 6 months **Intervention 1** End of month 1: 90.4% End of month 3: 70.4% End of month 6: 61.7% **Intervention 2** End of month 1: 96.4% End of month 3: 81.1% End of month 6: 68.5% **Comparator** End of month 1: 85.3% End of month 3: 73.3% End of month 6: 64.7%	**Outcome** Time to exit/withdrawal **Intervention 1** LTG 100 mg vs LTG 200 mg: HR = 0.7 (95% CI: 0.5 to 1.03) LTG 100 mg vs CBZ: HR = 0.9 (95% CI: 0.6 to 1.3) **Intervention 2** LTG 200 mg vs CBZ: HR = 1.3 (95% CI: 0.8 to 1.9) **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sackellares, 2000[126] **Related publications** Abstract,[116] industry trial report[345] **Country** USA **Source** Industry submission **Aim** To compare LTG monotherapy with VPA monotherapy on HRQoL in a randomised, double-blind trial designed to evaluate treatment-emergent weight changes in patients with epilepsy **Type of publication** Full paper (final analysis) unpublished **Funding** GlaxoSmithKline **Trial ID** SCAA4001 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** There was a 2-week screening phase followed by an 8-week dose-escalation period and	**Number of participants** 141 **Type of epilepsy** Combination of newly diagnosed/refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** LTG: 39 years (SD 13.8); VPA (n = 68): 33.8 years (SD 12.4); LTG: 12–68 years; VPA (n = 68): 12–76 years **Gender** LTG: men = 42%, women = 58%; VPA (n = 68): men = 45%, women = 55% **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Average monthly seizure frequency: LTG (n = 65): 2.3 (SD 4.5); VPA (n = 68): 1.5 (SD 5.6)	**Intervention 1** LTG; 200 mg/day; 32 weeks No. randomised: 65 No. completed: 46 **Comparator** VPA; 20 mg/kg/day; 32 weeks No. randomised: 68 No. completed: 38	**Withdrawals prerandomisation** Lost prior to randomisation (reason not stated): n = 8 **Withdrawals postrandomisation** LTG: AEs (n = 6), withdrew consent (n = 7), protocol violations (n = 2), lost to follow-up (n = 2), other (n = 2); VPA: AEs (n = 9), withdrew consent (n = 7), protocol violations (n = 2), lost to follow-up (n = 7), other (n = 5) **Adverse events** **Intervention 1** Stated under linked study #4780 **Comparator** Stated under linked study #4780	**Authors' conclusions** These data show that LTG monotherapy provides benefits over VPA monotherapy in improving several aspects of HRQoL in patients with epilepsy. The observation that QoL improvements during LTG monotherapy occurred concurrently with improvements in mood suggest that the QoL and mood changes may be causally related. Although LTG was weight neutral and was associated with greater improvements in HRQoL and lower discontinuation rates than VPA, it conferred a comparable degree of seizure control. This observation highlights the importance of including QoL measures in clinical trials in order to gain a holistic assessment of the impact of disease and pharmacotherapy on the patient. Furthermore, the data suggest that seizure frequency alone is an inadequate gauge of treatment effect **Comments** Some data extracted from industry submission (GSK, SCAA4001, and Biton, 2001). Further efficacy outcomes for this trial are reported in Ref. 116 The mean doses of LTG and VPA during the maintenance phase were 251.3 mg/day (SD 64) and

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
24-week maintenance period. LTG was started at a dosage of 25 mg/day with a target dose of 200 mg/day. Investigators were then permitted to alter dosage based on clinical efficacy within 100–500 mg/day. VPA was started at 10–15 mg/kg/day with a target dose of 20 mg/kg/day. Adjustments were then permitted within the range 10–60 mg/kg/day. Double dummy dosing was used **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The sample size was calculated to detect differences in weight change but not efficacy. Based on an SD for weight gain of 8.8 lb, Type 1 error set at 0.05 and Type 2 at 0.8, 50 participants were considered sufficient to detect a mean difference of 4.4–6.6 lb **Analysis methods** Data were analysed for 53 LTG-treated patients and 55 VPA-treated patients QOLIE-89 scores at screening and at the end of the 8-month treatment period were computed for each subscale according to the developers' instructions. For each of the 17 QoL subscales, the proportions of patients with QoL improvements were summarised by treatment group and compared using the Cochran–Mantel–Haenszel test. The probability of experiencing improvement was compared between the LTG and VPA groups using stepwise logistic regression controlling for age, gender and seizure frequency. Last-observation-carried-forward scores from screening were used to provide a conservative estimate for the logistic regression analysis.	**Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: age ≥ 12 years; with any epilepsy seizure type. Female patients had to have a negative urine or serum pregnancy test at screening and agree to use acceptable contraceptive methods during the study or be incapable of bearing children Exclusion: previous use for more than 90 days of LTG, divalproex sodium, valproic acid or GBP; current use of an AED unless the drug could be withdrawn safely prior to randomisation; use of any investigational drug within the previous 12 weeks; chronic use of any medication that could influence seizure control; any acute or progressive neurological or severe psychiatric disease; any medical condition associated with significant changes in body weight; adherence to the ketogenic diet; participation in a weight-change programme; or current or planned use of vagal stimulation to control seizures			1912 mg/day (SD 669.6), respectively The authors state that since this study was designed to assess weight changes in patients receiving LTG and VPA monotherapy for the treatment of epilepsy, the small number of participants in this study did not provide sufficient power to detect statistically significant changes in QoL

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Differences between groups were tested with the Wald χ^2 test. To test the robustness of results, sensitivity analysis was performed by repeating the analysis to compare the proportions of patients who experienced a ≥ 10% improvement of QOLIE-89 scores from baseline between treatment groups. Spearman correlation coefficients between the change-from-screening at week 32 in QOLIE-89 scores and for the following variables were calculated in a *post hoc* analysis: body weight; seizure frequency; and psychological status (measured with the POMS, the BDI, and the CDRS) **Length of trial/frequency of follow-up** 32 weeks; during screening phase, at week 10 and at the end of the maintenance phase (week 32)				

Results

Outcome 1	Outcome 2
Outcome Change in patient-related QoL; Measured using the QOLIE-89 scale **Intervention 1** LTG ($n = 53$) At the end of 32 weeks of treatment, significantly more patients using LTG monotherapy compared with VPA monotherapy experienced QoL improvements on the Health Perceptions, Energy/Fatigue, and Social Isolation subscales ($p < 0.05$). Logistic regression analysis confirmed that LTG was significantly associated with the QoL improvements in the Health Perceptions ($p = 0.004$), Energy/Fatigue ($p = 0.040$), and the Social Isolation ($p = 0.036$) subscales. Compared with VPA-treated patients, LTG-treated patients were 4 times more likely to experience improvement in Health Perceptions, 2.3 times more likely to experience improvement in Energy/Fatigue and 2.8 times more likely to experience improvement in Social Isolation ($p < 0.05$). LTG-treated patients compared with VPA-treated patients were 2.3 times more likely to experience improvement in	**Outcome** QoL correlations; relationships among QOLIE-89 scores and clinical and mood variables, measured using the POMS, the BDI and the CDRS **Intervention 1** At week 32, mean change-from-screening scores on the Health Perceptions, Energy/Fatigue and Social Isolation subscales of the QOLIE-89 were significantly negatively correlated with mean change-from-screening mood scores. In contrast, mean change-from-screening QOLIE-89 scores and changes in seizure frequency or body weight were not statistically significantly correlated Health Perceptions: seizure frequency 0.065; body weight –0.178; BDI: –0.437 ($p < 0.001$); POMS: –0.508 ($p < 0.001$); CDRS: –0.292 ($p < 0.05$) Energy/Fatigue: seizure frequency 0.097; body weight –0.218; BDI: –0.606 ($p < 0.001$); POMS: –0.578 ($p < 0.001$); CDRS: –0.547 ($p < 0.001$).

continued

Outcome 1	Outcome 2
Medication Effects and 2.1 times more likely to experience improvement in Attention/Concentration, but these results were not statistically significant. The proportion of patients experiencing improvement and the likelihood of improvement were similar between the LTG group and the VPA group for the other 12 subscales of the QOLIE-89 QOLIE-89 subscale scores: Health Perceptions: baseline = 63.1 (SD 18.4), week 32 = 63.9 (SD 20.8); mean change 0.4 (SD 15.9); % participants with an improved score = 42%; mean change (improved subjects) 12.5 (SD 8.6) Energy/Fatigue: baseline = 46.6 (SD 22.4), week 32 = 51.9 (SD 24.1); mean change 4.7 (SD 21.2); % participants with an improved score = 47%; mean change (improved subjects) 21.1 (SD 14.4) Social Isolation: baseline = 72.9 (SD 28.2), week 32 = 78.4 (SD 23.4); mean change 4.4 (SD 23.0); % participants with an improved score = 35%; mean change (improved subjects) 25.9 (SD 21.5) Medication Effects: baseline = 53.3 (SD 22.9), week 32 = 63.7 (SD 22.5); mean change 7.0 (SD 19.4); % participants with an improved score = 42%; mean change (improved subjects) 20.2 (SD 16.4) Attention/Concentration: baseline = 67.5 (SD 23.6), week 32 = 71.0 (SD 22.7); mean change 2.4 (SD 13.8); % participants with an improved score = 47%; mean change (improved subjects) 11.0 (SD 11.6) **Comparator** VPA (n = 55) QOLIE-89 subscale scores: Health perception: baseline = 65.4 (SD 18.2), week 32 = 63.1 (SD 19.2); mean change –3.5 (SD 11.0); % participants with an improved score = 15%; mean change (improved subjects) 12.0 (SD 7.9). Energy/Fatigue: baseline = 51.9 (SD 24.6), week 32 = 52.5 (SD 25.2); mean change –0.8 (SD 13.2); % participants with an improved score = 28%; mean change (improved subjects) 12.3 (SD 10.0) Social Isolation: baseline = 74.6 (SD 26.4), week 32 = 75.8 (SD 25.8); mean change 0.0 (SD 17.6); % participants with an improved score = 16%; mean change (improved subjects) 30.0 (SD 10.7) Medication Effects: baseline = 66.7 (SD 23.9), week 32 = 64.3 (SD 24.6); mean change –3.2 (SD 20.6); % participants with an improved score = 24%; mean change (improved subjects) 24.0 (SD 14.6) Attention/Concentration: baseline = 68.0 (SD 25.2), week 32 = 71.3 (SD 24.4); mean change 0.3 (SD 11.0); % participants with an improved score = 30%; mean change (improved subjects) 10.9 (SD 10.5)	Social Isolation: seizure frequency –0.083; body weight –0.009; BDI: –0.553 ($p < 0.001$); POMS: –0.597 ($p < 0.001$); CDRS: –0.483 ($p < 0.001$) **Comparator** Not reported

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Schachter, 1995[251] **Related publications** Industry trial report[374] **Country** USA **Source** Literature search **Aim** To compare the safety profile of add-on LTG with that of add-on placebo during long-term treatment (6 months) in patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** P42-16 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Blocks of 4 within treatment centre; after pre-trial period **Details of pretrial period** A baseline period of ≤4 weeks was followed by a double-blind treatment	**Number of participants** 446 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** LTG (n = 334): 35 years (SD not stated); placebo (n = 112): 35 years (SD not stated).; LTG (n = 334): 18–64 years; placebo (n = 112): 18–64 years **Gender** LTG (n = 334): men = 173 (52%), women = 161 (48%); placebo (n = 112): men = 63 (56%), women = 49 (44%) **Age at onset of seizures** Age at onset of epilepsy: LTG (n = 334): 12.0 years; placebo (n = 112): 11.5 years Mean duration of epilepsy: LTG (n = 334): 21.0 years; placebo (n = 112): 21.0 years **Pretrial medication** CBZ (LTG = 75%, placebo = 71%), PHT (LTG = 38%, placebo = 45%), PRM (LTG = 16%, placebo = 13%), PB (LTG = 13%, placebo = 14%). VPA was excluded **Ongoing concurrent medication** CBZ, PHT, PRM, PB. VPA was excluded	**Intervention 1** LTG; max. 500 mg/day; 28 weeks No. randomised: 334 No. completed: 281 **Comparator** Placebo; 28 weeks No. randomised: 112 No. completed: 93	**Withdrawals prerandomisation** None **Withdrawals postrandomisation** LTG (n = 334): AEs (n = 28); protocol violations (n = 5); death (n = 0); other (n = 20) Placebo (n = 112): AEs (n = 9); protocol violations (n = 2); death (n = 1); other (n = 7) **Adverse events** **Intervention 1** AEs with at least a 5% difference between LTG and placebo: LTG: dizziness (n = 167/334, $p < 0.05$), diplopia (n = 110/334, $p < 0.05$), ataxia (n = 80/334, $p < 0.05$), blurred vision (n = 77/334, $p < 0.05$), nausea (n = 73/334), somnolence (n = 47/334, $p < 0.05$), coordination abnormality (n = 40/334), rash (n = 33/334), dyspepsia (n = 33/334), respiratory disorder (n = 23/334), vaginitis (n = 20/334, $p < 0.05$). One participant developed a rash leading to a diagnosis of Stevens–Johnson syndrome requiring hospitalisation. (All AEs showing a significant difference between treatment groups had a higher incidence in LTG than placebo)	**Authors' conclusions** Significantly more patients treated with LTG than with placebo improved as measured by the Investigators' Global Evaluations. The measures used in this study and the data acquired indicate that LTG doses of ≤500 mg/day are well tolerated when administered as add-on therapy for a 6-month treatment period in outpatients with refractory partial seizures **Comments** Sample size calculations were not reported, and the referenced prior study does not contain these details either, so it was not possible to determine whether an adequate number of participants were enrolled in this study The mean dosage of LTG during the monotherapy phase is within the highest doses allowed, but more than the usual 100–200 mg/day stated by the manufacturers

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
period of 27 weeks (dose titration and maintenance of 24 weeks, followed by a 3-week taper/follow-up period). After completion of the study, all patients were given the option to enrol in an open-label treatment protocol. Patients randomised to LTG treatment began dose titration at 100 mg/day for 7 days, followed by 200 mg/day for the next 7 days, and continuing with increases to 300, 400 and 500 mg/day at weekly intervals, if tolerated. An analogous dosing scheme was used for the placebo patients. If AEs occurred, the dose of study medication could be adjusted downwards by decrements of 100 mg/day. Patients who could tolerate the lower dose were to be rechallenged by adjusting the dose upward by 100 mg/day increments to the target dose (500 mg/day). At the conclusion of the 24-week treatment period, study medication was tapered gradually in a blinded fashion in a 2-week period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Descriptive statistics for vital signs, clinical laboratory test and ECG results were generated and comparisons were made between treatment groups. The frequency of treatment-emergent neurological abnormalities were	**Co-morbidities** Not stated **Baseline seizure frequency** Not assessed **Other characteristics** At each study visit, vital signs and weight were obtained, and each patient was asked to describe any AEs. A comprehensive neurological examination and ECG and physical examination were conducted at baseline and at the end of maintenance treatment (week 24). An abbreviated neurological examination was made at weeks 8 and 16. Haematology, blood chemistry and urinalysis tests were made at baseline and at weeks 8 and 24. Any tests could be repeated at week 27 if indicated When each AE was reported, the investigator assessed its intensity (mild, moderate or severe), seriousness and possible cause **Inclusion/exclusion criteria** Inclusion: age 18–65 years; history of SPSs or CPSs (with or without becoming secondarily generalised) that were refractory to treatment with a stable regimen of 1–3 marketed AEDs (excluding VPA); at least one seizure in the 12 weeks preceding randomisation Exclusion: patients with newly diagnosed epilepsy (<32 weeks) if they had a diagnosis of primary generalised seizures (including absence seizures) or psychogenic seizures; progressive neurological disorder that was not stable		**Comparator** Placebo: dizziness (n = 20/112), diplopia (n = 12/112), ataxia (n = 6/112), blurred vision (n = 10/112), nausea (n = 17/112), somnolence (n = 8/112), coordination abnormality (n = 7/112), rash (n = 6/112), dyspepsia (n = 6/112), respiratory disorder (n = 15/112), vaginitis (0%); death (n = 1, 1%)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
determined. The results of the Investigators' Global Evaluations were summarised for each treatment and compared using the Cochran–Mantel–Haenszel statistic. Because baseline seizure frequency was not evaluated under controlled conditions, no inferential analysis of these seizure frequency data before and during treatment was made. All CIs were 95%, and all were two-sided **Length of trial/frequency of follow-up** 28 weeks; baseline and treatment weeks 4, 8, 16, 24 and 27	for at least 24 weeks before baseline; seizures were caused by other disease or drugs or alcohol; received any investigational drug within 12 weeks of baseline; concomitant AED dose adjustments within 2 weeks of baseline (4 weeks for PB); VPA within 4 weeks of baseline; history of non-compliance, or other chronic medical conditions; women of childbearing potential were required to have a negative pregnancy test result and had to be using a contraceptive method judged acceptable by the investigator			

Results

Outcome 1	Outcome 2	Outcome 3
Outcome Physician global evaluation of improvement/efficacy/tolerability; improvement in patient's condition as measured using the Investigators' Global Evaluation Scale ranging from 1 (marked deterioration) to 7 (marked improvement). The % participants deemed to have improved/moderately or markedly improved was recorded **Intervention 1** LTG (n = 334): improved: 65%; moderately or markedly improved: 38%. The difference between the LTG group and the placebo group for improvement was statistically significant **Comparator** Placebo (n = 112): improved: 35%; moderately or markedly improved: 12%	**Outcome** Proportion of seizure-free patients; the proportion of participants deemed free from seizures during the study **Intervention 1** LTG: n = 4/334 **Comparator** Placebo: n = 2/112	**Outcome** Seizure frequency; mean and median weekly seizure frequencies at week 26 of follow-up. Baseline seizure frequency was not recorded **Intervention 1** Baseline: not recorded Follow-up (26 weeks): SPSs/CPSs (n = 259) mean = 6.2, median = 1.0 (SD 29.7); secondarily generalised (n = 102) mean = 1.4, median = 0 (SD4.0) **Comparator** Baseline: not recorded Follow-up (26 weeks): SPSs/CPSs (n = 80) mean = 5.0, median = 1.0 (SD 12.1); secondarily generalised (n = 46) mean = 4.1, median = 0 (SD 14.8)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Steiner, 1999[75] **Related publications** Abstracts,[379,380] industry trial report[381] **Country** UK **Source** Literature search **Aim** To compare the efficacy and tolerability of LTG with PHT monotherapy in previously untreated patients with newly diagnosed epilepsy **Type of publication** Full paper (final analysis) **Funding** GlaxoSmithKline **Trial ID** LAM30026 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** 6-month qualifying period before entry to establish seizure rates. The first 6 weeks of the 48-week treatment period are referred to as a dose titration period; for the first 2 weeks the	**Number of participants** 181 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 181): median = 28 years; LTG (n = 86): median = 27 years; PHT (n = 95): median = 27 years; total (n = 181): 13–74 years; LTG (n = 86): 13–70 years; PHT (n = 95): 13–74 years **Gender** Total (n = 181): men = 101, women = 80; LTG (n = 86): men = 47, women = 39; PHT (n = 95): men = 54, women = 41 **Age at onset of seizures** Median (range) age at first seizure: total (n = 181): 25 years (1–71 years); LTG (n = 86): 25 years (2–70 years); PHT (n = 95): 25 years (1–71 years) **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated	**Intervention 1** LTG; max. 400 mg/day; 48 weeks No. randomised: 86 No. completed: 41 **Comparator** PHT; max. 600 mg/day; 48 weeks No. randomised: 95 No. completed: 45	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG (n = 86): AE (n = 13), inadequate response (n = 1), protocol deviation (n = 12), withdrawn consent (n = 10), other illness (n = 1), other reasons (n = 8). Total withdrawals = 45/85 PHT (n = 95): AE (n = 18), inadequate response (n = 2), protocol deviation (n = 9), withdrawn consent (n = 5), death (n = 2), other reasons (n = 17). Total withdrawals = 50/95 **Adverse events** **Intervention 1** 50/86 (58%) patients reported AEs, 4 were serious; drug-related events attributed to LTG in 36/86 (42%) patients. 13 patients discontinued because of 1 or more AEs: rash (n = 10), chest pain (n = 2), pruritus (n = 1), other (n = 3) AEs reported by at least 5% of participants (n = 86): asthenia (n = 14/86), rash (n = 12), headache (n = 9), dizziness (n = 8), nausea (n = 7); somnolence (n = 6); insomnia (n = 5); tremor (n = 2); lung disorder (n = 1); amnesia (n = 1)	**Authors' conclusions** LTG and PHT monotherapy were similarly effective. LTG was better tolerated, more frequently causing rash but with a lower incidence of CNS AEs. **Comments** Maximum dose of PHT (600 mg/day) exceeds BNF usual dose (200–500 mg/day); BNF says that higher doses may be used exceptionally. Mean plasma concentration at week 48 was LTG 3.4 mg/l, PHT 13.4 mg/l. However, in the trial report the authors state that PHT was used according to manufacturer's data sheet Compliance was assessed by count of returned capsules; consumption of <75% of prescribed medication was allowed on no more than one occasion between 2 visits, otherwise the patient was withdrawn Seven protocol violators are reported to be excluded from the efficacy analysis (6 failed to return after first study visit, 1 had taken VPA and did not take study medication) More than 50% of patients were discontinued from both treatment groups by the end of the study and analyses were not ITT.

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
dose was LTG 100 mg/day and PHT 200 mg/day, increased to 150 and 300 mg/day, respectively, for the second 2 weeks. From then on the dose could be increased by one capsule if seizure control was inadequate and if no significant AEs occurred. The last 24 weeks is referred to as after stabilisation of medication. Blindness was maintained throughout the treatment period **ITT analysis performed/method** Authors state no; not stated **Sample size calculation** Assuming that 80% of patients would remain seizure free on PHT, the study was designed with 90% power to show a difference between PHT and LTG if LTG was inferior by 20% as measured by the percentage of patients who remained seizure free ($\alpha = 0.05$). 89 patients were required in each treatment group **Analysis methods** 95% CI: for the difference between treatments calculated for percentage of patients remaining on treatment and seizure free, numbers of seizures during the last 24 and 40 weeks of the study and numbers of AEs. Percentage change in seizure rates from baseline with 95% CI for the differences were calculated. HR (95% CI) estimated by Kaplan–Meier plots and Cox's proportional hazards model used to test significance of differences in time to first seizure after the first 6 weeks of treatment, and time to discontinuation. Means of total SEALS scores including all patients with post-treatment values were subjected to repeated measures analysis using the pretreatment score and visit week as covariates. Pretreatment SEALS scores were used as a covariate in a proportional hazards analysis of	**Co-morbidities** Not stated **Baseline seizure frequency** Median (range) seizures in the last 6 months: total ($n = 181$): 4 (1–600); LTG ($n = 86$): 3 (2–600); PHT ($n = 95$): 4 (1–200) **Other characteristics** Seizure type at baseline Partial seizures only: total 50/181; LTG 24/86; PHT 26/95 Partial with secondary generalisation: total 40/181; LTG 20/86; PHT 20/95 Primary GTC: total 91/181; LTG 42/86; PHT 49/95 **Inclusion/exclusion criteria** Inclusion: aged 14–75 years; 2 or more seizures in the previous 6 months and at least 1 in the previous 3 months Exclusion: patients with absence seizures; previous treatment for epilepsy with any AED; abnormal laboratory values; other chronic disorders; severe mental subnormality; alcohol and other substance abuse; pregnancy or risk of becoming pregnant		**Comparator** 70/95 (74%) patients reported AEs, 10 were serious; drug-related events attributed to PHT in 59 (62%) patients. 18 patients discontinued because of 1 or more AEs: rash ($n = 5$), somnolence ($n = 4$), asthenia ($n = 3$), headache (n = 2), ataxia ($n = 2$), pruritus ($n = 1$), other ($n = 8$) AEs reported by at least 5% of participants: asthenia ($n = 28/95$), rash ($n = 9$), headache ($n = 18$), dizziness ($n = 11$), nausea ($n = 4$); somnolence ($n = 27$); insomnia ($n = 3$); tremor ($n = 8$); lung disorder ($n = 6$); amnesia ($n = 5$); ataxia ($n = 11$); pain ($n = 5$); thinking abnormally ($n = 5$)	Denominator for LTG in analysis of patients remaining on treatment and seizure free stated in the text as 81 but in tables appears to be 79. Analysis of seizures by type includes all patients who reported at least one seizure of that type in the period before entry (some patients had more than one type) Protocol violators were excluded from Kaplan–Meier analyses. Numbers of patients at risk of first seizure at weeks 6, 24 and 40 were LTG 38, 31, 19 and PHT 46, 31, 23. Numbers of patients at risk of discontinuation at weeks 6, 24 and 36 were LTG 59, 45, 42 and PHT 77, 53, 47 Reported rates of asthenia, somnolence and ataxia were significantly higher with PHT. Additional non-serious AEs data and blood tests also reported Neuropsychological tests were carried out but only on a few patients (too few to make a meaningful comparison between treatment groups, therefore not reported in this table) and SEALS was performed on only 99 patients (44 LTG and 55 PHT)

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
time to discontinuation. Relationship between pretreatment SEALS scores and seizure rates examined using Spearman's correlation **Length of trial/frequency of follow-up** 48 weeks; at entry, after 2, 4, 6, 8, 12, 18, 24, 36 and 48 weeks				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Proportion of seizure-free patients; the number of patients remaining on treatment and seizure free during the last 24 and the last 40 weeks of treatment, according to the types of seizure experienced at baseline. Participants experiencing more than one type of seizure are reported in more than one category **Intervention 1** In last 24 weeks All seizure types: 34/79 (43%); (95% CI for difference vs PHT: –8 to 21%) Partial seizures: 13/32 (41%); (95% CI for difference vs PHT: –33 to 18%) Secondarily generalised: 6/12 (50%); (95% CI for difference vs PHT: –37 to 37%) Primary generalised: 19/43 (44%); (95% CI for difference vs PHT: –10 to 30%) In last 40 weeks All seizure types: 19/79 (24%); (95% CI for difference vs PHT: –13 to 12%) Partial seizures: 5/31 (16%); (95% CI for difference vs PHT: –27 to 14%) Secondarily generalised: 4/12 (33%); (95% CI for difference vs PHT: –33 to 37%)	**Outcome** Time to first seizure; after the first 6 weeks of treatment **Intervention 1** All seizure types: HR 1.4 (95% CI: 0.8 to 2.3) Partial seizures: HR 1.0 (95% CI: 0.5 to 2.2) Primary generalised seizures: HR 1.5 (95% CI: 0.7 to 3.2) Secondarily generalised seizures: none occurred in the LTG group so no HR could be calculated Difference between LTG and PHT was not significant **Comparator** See Intervention 1 data	**Outcome** Time to exit/withdrawal; this may be due to a number of reasons including withdrawal due to AEs, lack of effect or other reasons **Intervention 1** Difference between LTG and PHT was not significant Unadjusted HR = 0.885 (95% CI: 0.555 to 1.410) Adjusted (for baseline seizure counts) HR = 0.935 (95% CI: 0.583 to 1.499) **Comparator** See Intervention 1 data	**Outcome** Change in patient-related QoL; measured using SEALS. Reported as median scores. Higher scores indicate a higher level of satisfaction **Intervention 1** Estimated difference between treatments in overall change from baseline was 4.0 points in favour of LTG (95% CI: 0.7 to 7.3), $p = 0.02$, (n not stated) SEALS I: total score Week 4 ($n = 44$): median = –0.01 (95% CI: –0.06 to 0.19) Week 12 ($n = 37$): median = 0.05 (95% CI: 0.02 to 0.29) Week 24 ($n = 38$): median = 0.00 (95% CI: –0.07 to 0.23) SEALS II: total score Week 4 ($n = 44$): median = 0.03 (95% CI: –0.05 to 0.08) Week 12 ($n = 37$): median = 0.05 (95% CI: –0.04 to 0.12) Week 24 ($n = 38$): median = –0.01 (95% CI: –0.11 to 0.06) SEALS III: total score	

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Primary generalised: 13/43 (30%); (95% CI for difference vs PHT: –21 to 17%) **Comparator** In last 24 weeks All seizure types: 33/92 (36%) Partial seizures only: 13/27 (48%) Partial with secondary generalisation: 8/16 (50%) Primary GTC: 17/50 (34%) In last 40 weeks All seizure types: 22/92(24%) Partial seizures only: 6/27 (22%) Partial with secondary generalisation: 5/16 (31%) Primary GTC: 16/50 (32%)			Week 4 (n = 43): median = –0.02 (95% CI: –0.11 to 0.05) Week 12 (n = 36): median = 0.00 (95% CI: –0.08 to 0.06) Week 24 (n = 37): median = 0.00 (95% CI: –0.11 to 0.09) **Comparator** SEALS I: total score Week 4 (n = 55): median = –0.10 Week 12 (n = 49): median = –0.10 Week 24 (n = 34): median = –0.09 SEALS II: total score Week 4 (n = 54): median = 0.00 Week 12 (n = 48): median = 0.00 Week 24 (n = 35): median = 0.05 SEALS III: total score Week 4 (n = 53): median = 0.00 Week 12 (n = 48): median = 0.00 Week 24 (n = 35): median = 0.00

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Veendrick-Meekes, 2000[137] **Related publications** None **Country** The Netherlands **Source** Industry submission **Aim** To evaluate the efficacy, safety and behavioural effects of adjunctive Lamictal (LTG) therapy in patients with mental retardation **Type of publication** Poster **Funding** GlaxoSmithKline **Trial ID** LAM40004 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Inpatient **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** The study consisted of a 2-week screening phase, a 4-week (no treatment) baseline phase, a 6-week escalation (titration) phase,	**Number of participants** 68 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (n = 68): 39 years (SD not stated); total (n = 68): 16–67 years **Gender** Total (n = 68): men = 39, women = 29 **Age at onset of seizures** Not stated **Pretrial medication** CBZ (n = 51/68), VPA (n = 37/68), PHT (n = 23/68), CLB (n = 18/68), PB (n = 11/68) Number of AEDs: total (n = 68): 1 AED (n = 5); 2 AEDs (n = 20); 3 AEDs (n = 36); 4 AEDs (n = 7) Median number of concurrent AEDs: 3 Mean number of concurrent AEDs: 2.7 **Ongoing concurrent medication** During the whole study, the number and doses of concurrent AEDs were kept constant. Median no. of concurrent AEDs = 3, mean = 2.7	**Intervention 1** LTG; 100 mg/day for patients on valproate, and 200 mg/day for patients on enzyme inducers; 16 weeks No. randomised: 44 No. completed: 40 **Intervention 2** NA No. randomised: 0 No. completed: 0 **Intervention 3** NA No. randomised: 0 No. completed: 0 **Comparator** Placebo; NA; 16 weeks No. randomised: 24 No. completed: 21	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LTG (n = 44): AEs (n = 2), lack of efficacy (n = 1), lost to follow-up (n = 1) Placebo (n = 24): AEs (n = 2), lack of efficacy (n = 0), lost to follow-up (n = 1) **Adverse events** **Intervention 1** Ataxia (n = 10/44), dizziness (n = 7/44), stomach complaints (n = 6/44), sleepiness (n = 5/44), restlessness (n = 4/44), decreased appetite (n = 4/44) **Intervention 2** NA **Intervention 3** NA **Comparator** Ataxia (n = 1/24), dizziness (n = 0/24), stomach complaints (n = 0/24), sleepiness (n = 5/24), restlessness (n = 1/24), decreased appetite (n = 0/24)	**Authors' conclusions** The data suggest LTG adjunctive therapy is effective and well tolerated and can improve the overall clinical status (i.e. QoL) of mentally retarded patients. **Comments** Randomisation details are missing from the report, as are details on the sample size calculation and statistical methods The carers' assessment data noted that the carers did not complete questionnaires correctly for a few patients and those questionnaires were not included in the analysis. The authors note that the AEs ataxia and/or dizziness mostly disappeared in patients after reducing CBZ

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
a 6-week optimisation (dose adjustment) phase and a 4-week maintenance (constant dose) phase. In the escalation phase LTG or placebo was titrated up to a target dose of 100 mg/day for patients on VPA and 200 mg/day for patients on enzyme inducers **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** Seizure frequency outcomes were reported using an ITT analysis, but other outcomes were reported as per protocol analyses. Comparisons were made between baseline and week 22 data (this is time from entry into trial and includes the 2-week screening and 4-week baseline phases when the participants were not receiving treatment). No further details were reported **Length of trial/frequency of follow-up** 16 weeks; at baseline and at week 22	**Co-morbidities** All enrolled patients were diagnosed as mentally retarded as defined by DSM IV. Total (n = 68): mild 13%, moderate 24%, severe 24%, profound 39% LTG (n = 44): mild 14%, moderate 21%, severe 30%, profound 36% Placebo (n = 24): mild 13%, moderate 24%, severe 13%, profound 46% **Baseline seizure frequency** Total (n = 68): median not stated; LTG (n = 44): median = 12; placebo (n = 24): median = 16 **Other characteristics** Types of seizure at baseline: total (n = 68): partial 10%; generalised 58%; partial and generalised 30%, unclassified 2% Ethnic origin: total (n = 68): whites 94%, blacks 3%, Asian/Oriental 3% Aetiology of epilepsy: total (n = 68): idiopathic 12%, symptomatic 88% (38% prenatal, 30% perinatal, 32% postnatal) Seizure types: total (n = 68): partial (simple/complex/secondary) 10%, generalised 58%, partial and generalised 30%, unclassified 2% Most common epilepsy syndrome was symptomatic generalised epilepsy (65%) LTG doses of patients completing week 22: on concurrent VPA (n = 21), median dose 150 mg/day;			

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
	not on concurrent VPA (n = 19), median dose 400 mg/day **Inclusion/exclusion criteria** Inclusion: inpatients aged ≥ 12 years; weighing at least 25 kg; confident diagnosis of both epilepsy and mental retardation; must have had 2 or more seizures per month in the previous 2 months and during the 4-week baseline period; must be receiving stable doses of up to 4 concurrent AEDs; not being treated currently with LTG or been treated with LTG in the past Exclusion: not stated			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; responders were defined as having achieved at least a 50% reduction in seizure frequency between baseline and follow-up week 22 (16 weeks of treatment, 4 weeks on constant maintenance dose) **Intervention 1** LTG (n = 44): 17/44 (39%), p = 0.277 Subanalysis generalised seizures: 8/21 (38%), p = 0.704	**Outcome** Proportion of seizure-free patients; number of patients who were seizure free at follow-up week 22 (16 weeks of treatment, 4 weeks on constant maintenance dose) **Intervention 1** All seizures: n = 3/44 (7%) Generalised seizures only: n = 3/21 (14%) **Comparator** All seizures: n = 0/24 (0%) Generalised seizures only: n = 0/13 (0%)	**Outcome** Physician global evaluation of improvement/efficacy/tolerability; investigators' assessment of patient's clinical status at week 22 (16 weeks of treatment, 4 weeks on constant maintenance dose). Based on 7 clinical factors (seizure frequency, duration and intensity, AEs, social, intellectual, motor functioning and the overall status assessment at week 22) (% of patients) **Intervention 1** All seizures (n = 44): Seizure frequency (p = 0.007 in favour of LTG): mild, moderate or marked deterioration 10%; no change 30%; mild, moderate or marked improvement 60% Seizure duration (p = 0.003 in favour of LTG): mild, moderate or marked deterioration 5%; no change 55%; mild, moderate or marked improvement 40% Seizure intensity (p = 0.004 in favour of LTG): mild, moderate or marked deterioration 3%; no change 60%; mild, moderate or marked improvement 38%	**Outcome** Change in patient-related QoL; carers' assessment of the patient's QoL using validated questionnaires examining seizure severity, AEs, medical treatment effects on behaviour, psychological functions (i.e. mood, temperament) (no further details) **Intervention 1** Seizure severity scale (n = 33): Mean sum score 30.7–27.9, p = 0.054 No. (%) of patients (n = 18) 16%, p = 0.33 (not significant, positive trend)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Comparator Placebo (n = 24): 6/24 (25%) Subanalysis generalised seizures: 4/13 (31%)		AEs (p = 0.197): mild, moderate or marked deterioration 23%; no change 70%; mild, moderate or marked improvement 8% Social functioning (p = 0.017 in favour of LTG): mild, moderate or marked deterioration 5%; no change 58%; mild, moderate or marked improvement 38% Intellectual functioning (p = 0.225, non-significant): mild, moderate or marked deterioration 3%; no change 78%; mild, moderate or marked improvement 20% Motor functioning (p = 0.077): mild, moderate or marked deterioration 28%; no change 63%; mild, moderate or marked improvement 10% Overall status (p = 0.015 in favour of LTG): mild, moderate or marked deterioration 13%; no change 38%; mild, moderate or marked improvement 50% Subgroup analysis generalised seizures (n = 19): Seizure frequency (p = 0.02 in favour of LTG): mild, moderate or marked deterioration 10%; no change 11%; mild, moderate or marked improvement 79% Seizure duration (p = 0.152): mild, moderate or marked deterioration 11%; no change 47%; mild, moderate or marked improvement 42% Seizure intensity (p = 0.164): mild, moderate or marked deterioration 5%; no change 53%; mild, moderate or marked improvement 42% AEs (p = 0.435): mild, moderate or marked deterioration 15%; no change 79%; mild, moderate or marked improvement 5% Social functioning (p = 0.205): mild, moderate or marked deterioration 5%; no change 53%; mild, moderate or marked improvement 42% Intellectual functioning (p = 0.435): mild, moderate or marked deterioration 5%; no change 63%; mild, moderate or marked improvement 32% Motor functioning (p = 0.412): mild, moderate or marked deterioration 26%; no change 58%; mild, moderate or marked improvement 16% Overall status (p = 0.205): mild, moderate or marked deterioration 11%; no change 51%; mild, moderate or marked improvement 38% **Comparator** All seizures (n = 24): Seizure frequency: mild, moderate or marked deterioration 29%; no change 38%; mild, moderate or marked improvement 33% Seizure duration: mild, moderate or marked deterioration 5%; no change 95%; mild, moderate or marked improvement 0%	AEs severity scale (n = 33): Mean sum score all AEs 23.8–28.8, p = 0.052 Mean sum score physical AEs 15.5–18.9, p = 0.013 (significant for uncertainty when walking, double/blurred vision and hyperactivity) Mean sum score behaviour AEs 8.3–9.9, p = 0.409 No. of patients with deterioration 8 (24%), p = 0.052 Global behaviour assessment (n = 30): Mood: mild, moderate or marked deterioration (n = 9) 30%; no change (n = 10) 33% mild, moderate or marked improvement (n = 11) 37%, no significant differences Temperament data: not analysed for report **Comparator** Seizure severity scale (n = 21): Mean sum score 31.0–29.9 No. (%) of patients (n = 8) 38% AEs severity scale (n = 19): Mean sum score all AEs 24.9–24.5 Mean sum score physical AEs 16.6–16.0 Mean sum score behaviour AEs 8.1–8.5 No. of patients with deterioration 3 (16%)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
		Seizure intensity: mild, moderate or marked deterioration 10%; no change 86%; mild, moderate or marked improvement 5% AEs: mild, moderate or marked deterioration 5%; no change 91%; mild, moderate or marked improvement 5% Social functioning: mild, moderate or marked deterioration 5%; no change 91%; mild, moderate or marked improvement 5% Intellectual functioning: mild, moderate or marked deterioration 0%; no change 95%; mild, moderate or marked improvement 5% Motor functioning: mild, moderate or marked deterioration 0%; no change 95%; mild, moderate or marked improvement 5% Overall status: mild, moderate or marked deterioration 5%; no change 90%; mild, moderate or marked improvement 5% Subgroup analysis generalised seizures (n = 12): Seizure frequency: mild, moderate or marked deterioration 33%; no change 25%; mild, moderate or marked improvement 42% Seizure duration: mild, moderate or marked deterioration 0%; no change 100%; mild, moderate or marked improvement 0% Seizure intensity: mild, moderate or marked deterioration 0%; no change 92%; mild, moderate or marked improvement 8% AEs: mild, moderate or marked deterioration 0%; no change 92%; mild, moderate or marked improvement 8% Social functioning: mild, moderate or marked deterioration 0%; no change 92%; mild, moderate or marked improvement 8% Intellectual functioning: mild, moderate or marked deterioration 0%; no change 92%; mild, moderate or marked improvement 8% Motor functioning: mild, moderate or marked deterioration 0%; no change 92%; mild, moderate or marked improvement 8% Overall status: mild, moderate or marked deterioration 4%; no change 84%; mild, moderate or marked improvement 12%	Global behaviour assessment (n = 16): Mood: mild, moderate or marked deterioration (n = 1) 6%; no change (n = 10) 63%; mild, moderate or marked improvement (n = 5) 31% Temperament data: not analysed for report

Levetiracetam (licensed use)

Crossover studies (*n* = 1)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Boon, 2002[80] **Related publications** Data from first phase of crossover study;[145] abstract[385] **Country** European **Source** Literature search **Aim** To evaluate the efficacy, dose–response, tolerability and withdrawal effects of LEV as add-on therapy in adult patients with refractory partial epilepsy **Type of publication** Full paper (final analysis) **Funding** UCB Pharma **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient	**Number of participants** 324 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (*n* = 324): 37 years (SD 11); placebo crossover to LEV 1000 mg/day (*n* = 58): 37 years (SD 11); placebo crossover to LEV 2000 mg/day (*n* = 54): 37 years (SD 13); LEV 1000 mg/day crossover to placebo (*n* = 53: 37 years (SD 9); LEV 2000 mg/day crossover to placebo (*n* = 54): 37 years (SD 11); LEV 1000 mg/day crossover to LEV 2000 mg/day (*n* = 53): 36 years (SD 11); LEV 2000 mg/day crossover to LEV 1000 mg/day (*n* = 52): 37 years (SD 12); total (*n* = 324): 14–69 years; placebo crossover to LEV 1000 mg/day (*n* = 58): 18–64 years; placebo crossover to LEV 2000 mg/day (*n* = 54): 16–69 years; LEV 1000 mg/day crossover to placebo (*n* = 53): 17–68 years; LEV 2000 mg/day crossover to placebo (*n* = 54): 18–64 years; LEV 1000 mg/day crossover to LEV 2000 mg/day (*n* = 53): 16–56 years; LEV 2000 mg/day crossover to LEV 1000 mg/day (*n* = 52): 14–65 years **Gender** Total (*n* = 324): men = 157, women = 167; placebo crossover to LEV 1000 mg/day	**Intervention 1** LEV; 1000 mg/day; 16 weeks No. randomised: 106 No. completed: 81 **Intervention 2** LEV; 2000 mg/day; 16 weeks No. randomised: 106 No. completed: 72 **Comparator** Placebo; 16 weeks No. randomised: 112 No. completed: 79	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Withdrawal after randomisation to treatment period (A) LEV 1000 mg/day: AE (*n* = 8), withdrew consent (*n* = 2), other (includes ineligibility, protocol violation, lack of efficacy, decision of UCB) (*n* = 2) LEV 2000 mg/day: adverse event (*n* = 15), withdrew consent (*n* = 3), other (*n* = 1) Placebo: AE (*n* = 6), withdrew consent (*n* = 5), other (*n* = 4) Withdrawal-related AEs during cross-titration LEV crossover to placebo: convulsions 3.7% (4/107), partial status epilepticus 1.8% (2/107) Placebo crossover to LEV: convulsions 4.5% (5/112), confusion 0.9% (1/112) LEV 2000 mg/day crossover to LEV 1000 mg/day: convulsions 3.8% (2/52) Withdrawal after entry to treatment period (B) Placebo crossover to LEV 1000 mg/day: *n* = 5 Placebo crossover to LEV 2000 mg/day: *n* = 13	**Authors' conclusions** LEV was effective and well-tolerated and decreased seizure frequency in a dose-dependent manner, with no evidence of typical withdrawal-related AEs or rebound phenomena after withdrawal or down-titration **Comments** Safety was evaluated in the ITT population (all randomised patients who received at least one dose of study medication). Efficacy was evaluated in the inferential ITT population (all patients in the ITT population who had efficacy data available for at least one study visit of evaluation period A and one visit of evaluation period B) The number of concomitant AEDs taken during the study appears from the table to be reasonably evenly distributed among the treatment groups Results of compliance not reported. AEs reported less thoroughly than efficacy results

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Method/timing of randomisation Computerised; not stated **Details of pretrial period** 12- or 8-week (protocol amendment) baseline period. Treatment period A comprised a 4-week titration, during which LEV was titrated up (1000 mg/day at 2-week intervals) until patients were stabilised on their assigned dose, then a 12-week evaluation. This was followed by treatment period B (crossover), a 4-week titration (up or down at 1000 mg/day at 2-week intervals), and 12-week evaluation **ITT analysis performed/method** Authors state yes; not stated **Sample size calculations** Sample size of 234 evaluable patients was calculated to detect a reduction in seizure frequency of ≥ 24%, measured by a difference between the log transformed treatment means of 0.27 (two-tailed test, power 80%, $\alpha = 0.05$, SD 0.60) **Analysis methods** Primary outcome seizure frequency during parallel (A) and crossover (B) evaluation periods was calculated using least-squares means (LSMs) to determine percentage reduction over placebo. Two-tailed significance tests were used to assess the significance level adjusted for multiple comparisons. Continuous variables were analysed using ANOVA. Data	($n = 53$): men = 30, women = 28; placebo crossover to LEV 2000 mg/day ($n = 54$): men = 25, women = 29; LEV 1000 mg/day crossover to placebo ($n = 53$): men = 27, women = 26; LEV 2000 mg/day crossover to placebo ($n = 54$): men = 24, women = 30; LEV 1000 mg/day crossover to LEV 2000 mg/day ($n = 53$): men = 24, women = 29; LEV 2000 mg/day crossover to LEV 1000 mg/day ($n = 52$): men = 27, women = 25 **Age at onset of seizures** Onset of epilepsy: total ($n = 324$): 13.7 years (SD 11); placebo crossover to LEV 1000 mg/day ($n = 53$): 13.1 years (SD 10.5); placebo crossover to LEV 2000 mg/day ($n = 58$): 15.4 years (SD 11.2); LEV 1000 mg/day crossover to placebo ($n = 53$): 13.6 years (SD 11.7); LEV 2000 mg/day crossover to placebo ($n = 54$): 13.6 years (SD 10.7); LEV 1000 mg/day crossover to LEV 2000 mg/day ($n = 53$): 12.7 years (SD 11.4); LEV 2000 mg/day crossover to LEV 1000 mg/day ($n = 52$): 13.9 years (SD 11.2) **Pretrial medication** CBZ, PHT, VPA, VGB, LTG **Ongoing concurrent medication** All patients were taking between 1 and 3 or more AEDs during the study. See details of pretrial period **Co-morbidities** Not stated		LEV 1000 mg/day crossover to placebo: $n = 9$ LEV 2000 mg/day crossover to placebo: $n = 7$ LEV 1000 mg/day crossover to LEV 2000 mg/day: $n = 4$ LEV 2000 mg/day crossover to LEV 1000 mg/day: $n = 8$ Reasons given overall: protocol violation $n = 6$, AE $n = 27$, lack of efficacy $n = 6$, withdrew consent $n = 7$ **Adverse events** **Intervention 1** AEs led to 14 withdrawals ($n = 200$), reported causes were convulsions ($n = 4$), somnolence, headache and accidental injury. The incidence of serious AEs was 23/200 **Intervention 2** AEs led to 26 withdrawals ($n = 202$), reported causes were convulsions ($n = 9$), somnolence, headache, ataxia, asthenia and personality disorder. The incidence of serious AEs was 25/202 **Comparator** AEs led to 16 withdrawals ($n = 200$), reported causes were convulsions ($n = 10$), asthenia, confusion, somnolence and depression. The incidence of serious AEs was 23/200	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
were log transformed. Comparison between treatment means adjusted on means of the baseline covariable using Student's *t*-test and 98% CI. Back transformation of adjusted means (LSMs) differences with placebo were used to estimate % reduction over placebo **Length of trial/frequency of follow-up** 16 weeks; every 4 weeks during baseline, titration and evaluation in both treatment periods A and B	**Baseline seizure frequency** Total: median 2.62 per week; placebo crossover to LEV 1000 mg/day: median 2.01; placebo crossover to LEV 2000 mg/day: median 2.65; LEV 1000 mg/day crossover to placebo: median 3.03; LEV 2000 mg/day crossover to placebo: median 2.10; LEV 1000 mg/day crossover to LEV 2000 mg/day: median 2.55; LEV 2000 mg/day crossover to LEV 1000 mg/day: median 4.34 **Other characteristics** Results for compliance not reported **Inclusion/exclusion criteria** Inclusion: ILAE criteria for predominantly partial seizures, with or without secondary generalisation, for the past 2 years despite treatment with 1 or 2 AEDs; a stable dose regimen 4 weeks before enrolment and throughout the baseline period and at least 4 partial seizures during each 4-week period of baseline. Women of childbearing age had to have been surgically sterilised or using contraception Exclusion: renal insufficiency; progressive neurological or serious psychiatric disorders; significant laboratory abnormalities; current or recent substance abuse; questionable compliance; or concomitant disorders that could hinder evaluation of outcomes			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Seizure frequency; mean, LSMs and median reduction in weekly partial seizure frequency **Intervention 1** Inferential ITT population (n = 183): mean 2.46; LSM 2.41; median reduction from baseline 22.9%. Treatment effect, reduction over placebo 16.9% (98% CI: 9.6 to 23.6), $p < 0.001$ ITT population (n = 194): mean 2.52; LSM 2.50. Treatment effect, reduction over placebo 17.0% (98% CI: 9.7 to 23.6), $p < 0.001$ **Intervention 2** Inferential ITT population (n = 175): mean 2.39; LSM 2.34; median reduction from baseline 23.9%. Treatment effect, reduction over placebo 18.5% (98% CI: 11.2 to 25.2), $p < 0.001$ ITT population (n = 186): mean 2.44; LSM 2.43. Treatment effect, reduction over placebo 18.6% (98% CI: 11.4 to 25.4), $p < 0.001$ **Comparator** Inferential ITT population (n = 172): mean 2.93; LSM 3.10; median reduction from baseline 7.0% ITT population, n = 197: mean 2.73; LSM 3.22	**Outcome** Proportion of responders; the number of patients with specified reductions in seizure frequency **Intervention 1** ≥ 50% reduction: 48/183 (26.2%), $p = 0.004$ versus placebo ≥ 75% reduction: 25/183 (13.7%), $p = 0.043$ **Intervention 2** ≥ 50% reduction: 60/175 (34.3%), $p = 0.001$ versus placebo ≥ 75% reduction: 35/175 (20%), $p < 0.001$ **Comparator** ≥ 50% reduction: 21/172 (12.2%) ≥ 75% reduction:7/172 (4%)	**Outcome** Proportion of seizure-free patients; the number of seizure-free patients during the entire evaluation period, either period A or B **Intervention 1** n = 10/183 (5.5%) **Intervention 2** n = 10/175 (5.7%) **Comparator** n = 2/172 (1.2%)	**Outcome** Change in seizure frequency; the LSM reduction in weekly seizure frequency of the intervention group over placebo **Intervention 1** Inferential ITT population (n = 183) Simple partial: LSM 1.64. Treatment effect, reduction over placebo 18.5% (98% CI: 4.7 to 30.3), $p = 0.003$ Complex partial: LSM 1.69. Treatment effect, reduction over placebo 11.9% (98% CI: 2.9 to 20.0), $p = 0.002$ Secondarily generalised: LSM 0.42. Treatment effect, reduction over placebo 11.6% (98% CI: 0.1 to 21.7), $p = 0.019$ **Intervention 2** Inferential ITT population (n = 175) Simple partial: LSM 1.59. Treatment effect, reduction over placebo 19.8% (98% CI: 5.8 to 31.8), $p = 0.002$ Complex partial: LSM 1.57. Treatment effect, reduction over placebo 15.8% (98% CI: 7.2 to 23.7), $p < 0.001$ Secondarily generalised: LSM 0.45. Treatment effect, reduction over placebo 9.9% (98% CI: –2.6 to 20.9), $p = 0.060$ **Comparator** Inferential ITT population (n = 172) Simple partial: LSM 2.23 Complex partial: LSM 2.06 Secondarily generalised: LSM 0.61

Parallel studies (*n* = 4)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Ben-Menachem, 2000[144] (add-on phase only) **Related publications** Abstract,[382] abstract[383] **Country** European **Source** Literature search **Aim** To evaluate the efficacy and tolerability of LEV monotherapy in selected patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** UCB Pharma **Trial ID** Not stated **Study design** Monotherapy and adjunct; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 343 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (*n* = 286): 36 years (SD 12); LEV (*n* = 181): 37 years (SD 12); placebo (*n* = 105): 36 years (SD 12); not stated **Gender** Total (*n* = 286): men = 48%, women = 52%; LEV (*n* = 181): men = 48%, women = 52%; placebo (*n* = 105): men = 49%, women = 51% **Age at onset of seizures** Age at onset: total (*n* = 286): 18 years (SD 14); LEV (*n* = 181): 18 years (SD 14); placebo (*n* = 105): 18 years (SD 13) Mean duration of epilepsy: total (*n* = 286): 19 years (SD 11); LEV (*n* = 181): 19 years (SD 11); placebo (*n* = 105): 19 years (SD 12) **Pretrial medication** Mean number of previous AEDs: total (*n* = 286): 4.01 (SD 2.57); LEV (*n* = 181): 3.92 (SD 2.59); placebo (*n* = 105): 4.17 (SD 2.53)	**Intervention 1** LEV; 3000 mg/day; 12-week add-on follow-up and 12-week monotherapy follow-up No. randomised: 181 No. completed: 36 **Comparator** Placebo; 12-week add-on follow-up and 12-week monotherapy follow-up No. randomised: 105 No. completed: 10	**Withdrawals prerandomisation** Total (*n* = 343): ineligibility (*n* = 44), AE (*n* = 1), withdrawal of consent (*n* = 10), lost to follow-up (*n* = 1), other (*n* = 1) **Withdrawals postrandomisation** Add-on up-titration phase LEV (*n* = 181): AE (*n* = 9), withdrawal of consent (*n* = 1); placebo (*n* = 105): AE (*n* = 2), lost to follow-up (*n* = 1) Add-on maintenance phase LEV (*n* = 171): protocol violation (*n* = 6), AE (*n* = 8), lack or loss of efficacy (*n* = 3), withdrawal of consent (*n* = 5); placebo (*n* = 102): protocol violation (*n* = 3), AE (*n* = 7), lack or loss of efficacy (*n* = 1), withdrawal of consent (*n* = 1) Responder selection phase LEV (*n* = 149): did not meet responder criteria (*n* = 80); placebo (*n* = 90): did not meet responder criteria (*n* = 73) Monotherapy down-titration LEV (*n* = 69): AE (*n* = 1), lack or loss of efficacy (*n* = 5), withdrawal of consent (*n* = 1), escape criteria (*n* = 11), other (*n* = 2); placebo (*n* = 17): AE (*n* = 1), lack or loss of efficacy (*n* = 1), escape criteria (*n* = 2), other (*n* = 1)	**Authors' conclusions** Conversion to LEV monotherapy (1500 mg twice daily) is effective and well tolerated in patients with refractory partial seizures who responded to 3000 mg LEV as add-on therapy **Comments** The demographic data refer to the 286 participants who were randomised to placebo or LEV The monotherapy phase of the study included only responders in the add-on phase of the trial, which limits the applicability of the findings Of the 239 patients who completed the add-on phase, 86 were eligible to enter the monotherapy phase (placebo *n* = 17; LEV *n* = 69). For ethical reasons, 8 of the 17 patients taking placebo were switched to treatment with LEV but for analysis they remained in the placebo group. 25 patients (placebo *n* = 5; LEV *n* = 20) were withdrawn during the down-titration period, mostly because they met the escape criteria. 49 of the 69 patients receiving LEV were successfully down-titrated to LEV monotherapy and had at least one evaluation under monotherapy

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 12-week open baseline period during which patients were selected for entry according to the inclusion/exclusion criteria. Patients were then randomised to LEV or placebo in an 18-week double-blind add-on therapy phase that included 4 weeks up-titration of LEV or placebo. Medication was increased every 2 weeks from 500 mg twice daily to the target dose of 1500 mg twice daily. Patients were evaluated on the target dosage for a 12-week period. Patients were then assessed over a 2-week period for entry into the monotherapy phase of the trial. Criteria for entry to this phase were (relative to baseline) a 50% reduction in SPSs or CPSs or 35% reduction in SPSs provided that CPSs were reduced by 50% and secondarily generalised seizures were no higher than baseline; no doubling of CPSs or secondarily generalised seizures and no secondarily generalised seizures present during the add-on phase if they were not present during baseline. Patients who were not eligible for entry into the monotherapy phase were given the opportunity of entering an open-label study with LEV. The monotherapy phase included a maximum of 12 weeks of down-titration and 12 weeks of monotherapy. After entry into the monotherapy phase the standard AED was gradually withdrawn during a period of up to 12 weeks. Patients were withdrawn from the monotherapy phase if (relative to baseline) they doubled their monthly frequency of complex partial or secondarily generalised seizures; there was an occurrence of status epilepticus; secondarily generalised seizures occurred if none had	**Ongoing concurrent medication** Single AED at a stable dosage until initiation of monotherapy phase of trial: CBZ (74%); LTG (9%); VPA (8%); PHT (6%) **Co-morbidities** Not stated **Baseline seizure frequency** Median baseline partial seizure frequency (*n*/week): total ($n = 286$): median = 1.70; LEV ($n = 181$): median = 1.69; placebo ($n = 105$): median = 1.75 Seizure type: total ($n = 286$): simple partial seizures 23%; complex partial seizures 97%; secondarily generalised seizures 27% **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 16–70 years; clinically observed partial seizures for at least the year before study entry (seizures classified according to the ILAE's Commission on Classification and Terminology Criteria); at least 2 complex partial seizures per 4 weeks during baseline despite treatment with one AED; women of childbearing age surgically sterile or using a medically accepted form of contraception Exclusion: history of status epilepticus or a seizure pattern characterised by clusters during the previous 5 years		Monotherapy maintenance phase LEV ($n = 49$): protocol violation ($n = 1$), AE ($n = 1$), escape criteria ($n = 11$); placebo ($n = 12$): escape criteria ($n = 2$) **Adverse events** **Intervention 1** The incidence of AEs (with >5% incidence) compared with placebo was reported only for the add-on phase. Incidence of AEs ($n = 181$): 55% Asthenia (13.8%), infection (7.2%), somnolence (6.1%), headache (3.3%) ($p = 0.019$), accidental injury (2.2%) ($p = 0.009$) **Comparator** Incidence of AEs ($n = 105$): 53% Asthenia (6.7%), infection (3.8%), somnolence (3.8%), headache (10.5%), accidental injury (9.5%)	

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
occurred during baseline (escape criteria). The study was designed under the assumption that no more than 10% of patients taking placebo would fulfil the responder selection criteria (i.e. 9 out of 86 patients). When a total of 9 placebo responders was reached, for ethical reasons each subsequent placebo responder was switched to LEV for the monotherapy phase without breaking the blind. These patients were analysed as if they were still taking the placebo **ITT analysis performed/method** Authors state yes; not stated The sample size calculation was based on the assumption of a Type I error of 5% and a Type II error of 20%. With a LEV-to-placebo ratio a minimum of 258 evaluable patients were required to detect a 10% difference in the percentage of patients completing monotherapy. Assuming a drop-out rate of 30%, ~350 patients were required to enter the study **Analysis methods** Efficacy and safety analysis were conducted on the ITT population, which included all patients who were randomised and took at least one dose of study medication. The primary efficacy assessment (the percentage of patients who completed the monotherapy phase relative to the number of patients randomised to study medication) was analysed using Fisher's exact test. For the add-on phase, median percentage reduction was analysed using the Kruskal–Wallis test. Logistic regression was used to analyse the responder rate and	and the 12-week baseline period; history of progressive cerebral disease; cerebrovascular accident; severe cardiovascular disease; chronic treatment with digitalis, glucosides or coumarins; significant disturbance of haemostasis; insulin-dependent diabetes mellitus; unstable hyperthyroidism; impaired hepatic or renal function; poor compliance; drug or alcohol abuse within the previous 2 years; suicidal tendency or other psychiatric disorder; participation in any other clinical trial within the 4 weeks preceding study entry; participation in any previous LEV trial; use of barbiturates, benzodiazepines or other medications that influence the CNS; other compounds with intrinsic CNS activity were allowed only when administered at a constant dosage throughout the study			

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Fisher exact test for the number of seizure-free patients. The incidence of AEs during the add-on phase was analysed using logistic regression or the Cochran–Mantel–Haenszel test. Laboratory tests were compared using shift tables and mean changes from baseline and Kruskal–Wallis was used to conduct between-group comparisons. For the monotherapy phase, comparisons between the different phases of the study were performed in the LEV treatment group whenever appropriate **Length of trial/frequency of follow-up** 42 weeks; periodically and at 12 weeks				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Proportion of patients completing study; the percentage of patients who completed the monotherapy phase relative to the number randomised to study medication **Intervention 1** 19.9% (36/181) ($p = 0.029$) **Comparator** 9.5% (10/105)	**Outcome** Proportion of patients completing the add-on phase; the percentage of patients who completed the add-on phase relative to the number randomised to study medication **Intervention 1** 82% (149/181) **Comparator** 85% (90/105)	**Outcome** Change in seizure frequency; median percentage reduction in partial seizure frequency from baseline to add-on phase **Intervention 1** 39.9% ($p < 0.001$) Seizure frequency: 1.06 seizures/week **Comparator** 7.2% Seizure frequency: 1.75 seizures/week	**Outcome** Proportion of responders; defined as the proportion of patients with a reduction in partial seizure frequency of 50% in add-on phase compared with baseline **Intervention 1** 42.1% (72/181) ($p < 0.001$) **Comparator** 16.7% (17/105)	

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Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome Percentage of patients who remained seizure free during the add-on evaluation period **Intervention 1** LEV: 8.2% (14/181) ($p = 0.012$) **Comparator** Placebo: 1% (1/105)	**Outcome** The number of patients needed to treat to obtain one responder (in add-on phase) attributable to the LEV effect The number of patients needed to treat to obtain one seizure-free patient (in add-on phase) attributable to the LEV effect **Intervention 1** LEV: 3.9 (95% CI: 2.8 to 6.6) **Comparator** 13.9 (95% CI: 8.5 to 37.4)	**Outcome** Median absolute reduction in partial seizure frequency from baseline to the monotherapy evaluation period **Intervention 1** (In 49 of the 69 patients receiving monotherapy who were successfully down-titrated to LEV monotherapy): 0.61 ($p = 0.012$)	**Outcome** Median percentage reduction in partial seizure frequency from baseline to the monotherapy evaluation period **Intervention 1** (In 49 of the 69 patients receiving monotherapy who were successfully down-titrated to LEV monotherapy): 73.8% (0.027) Change in frequency of seizures during monotherapy evaluation period compared with add-on phase Median increase = 0.04 Percentage responders during monotherapy (the proportion of patients with a reduction in partial seizure frequency of 50% in monotherapy phase compared with baseline): 59.2% Proportion of patients who remained seizure free during the monotherapy evaluation period: LEV $n = 9/49$; placebo $n = 3/12$

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Betts, 2000[139] **Related publications** Abstract[384] **Country** European **Source** Literature search **Aim** To ascertain the tolerability and efficacy of LEV at doses of 2000 mg and 4000 mg daily as add-on therapy in patients with refractory epilepsy, administered without titration **Type of publication** Full paper (final analysis) **Funding UCB** Pharma **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after pretrial period Randomisation: done in blocks of three, defining the treatment numbers per investigator. In each block, a random computerised procedure performed the	**Number of participants** 136 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** LEV 2000 mg/day (n = 42): 39 years (SD 13); LEV 4000 mg/day (n = 38): 40 years (SD 12); placebo (n = 39): 35 years (SD 12); not stated **Gender** LEV 2000 mg/day (n = 42): men = 69%, women = 31%; LEV 4000 mg/day (n = 38): men = 53%, women = 47%; Placebo (n = 39): men = 62%, women = 38% **Age at onset of seizures** Mean age at epilepsy onset: LEV 2000 mg/day (n = 42): 18.3 years (SD 14.8); LEV 4000 mg/day (n = 38):15.4 years (SD 13.3); placebo (n = 39): 9.3 years (SD 9). **Pretrial medication** CBZ (n = 69), VPA (n = 38), PHT (n = 37), or PB (n = 25) **Ongoing concurrent medication** See above **Co-morbidities** Not stated	**Intervention 1** LEV; 2000 mg/day; 24 weeks No. randomised: 42 No. completed: 28 **Intervention 2** LEV; 4000 mg/day; 24 weeks No. randomised: 38 No. completed: 29 **Comparator** Placebo; 24 weeks No. randomised: 39 No. completed: 29	**Withdrawals prerandomisation** Total (n = 136): patients excluded (n = 17) **Withdrawals postrandomisation** LEV 2000 mg/day (n = 42): total withdrawals n = 14 (33.3%): AEs n = 11 (26.2%), withdrew consent n = 1 (2.4%), other n = 2 (4.8%). LEV 4000 mg/day (n = 38): total withdrawals n = 9 (23.7%): AEs n = 5 (13.2%), withdrew consent n = 2 (5.3%), other n = 2 (5.3%). Placebo (n = 39): total withdrawals n = 10 (25.6%): AEs n = 6 (15.4%), withdrew consent n = 2 (5.1%), other n = 2 (5.1%) **Adverse events** **Intervention 1** Most commonly reported AEs in the double-blind treatment period (incidence ≥10% in at least one of the levetiracetam treatment groups): LEV 2000 mg/day (n = 42): somnolence n = 11 (26.2%), asthenia n = 13 (31.0%), accidental injury n = 1 (2.4%), infection n = 1 (2.4%), dizziness n = 2 (4.8%) Serious AEs: n = 3 (7.1%) **Intervention 2** LEV 4000 mg/day (n = 38): somnolence 17 (44.7%), asthenia n = 5 (13.2%), accidental injury n = 5 (13.2%), infection n = 6	**Authors' conclusions** LEV initiated at doses of 2000 or 4000 mg daily without titration is well-tolerated and effective as add-on therapy in patients with partial and/or generalised seizures. The higher dose may be related to an increased incidence of somnolence and is not necessarily more effective than the lower dose **Comments** LEV was provided as white 500-mg tablets and placebo as matching tablets, equal in appearance and taste Intervention 2 used a dosage 1000 mg/day higher than the recommended dosage The authors also present outcome measurements for a responder rate at 4 weeks during the double-blind phase. These results can be obtained from the full paper. There were no significant changes in clinical laboratory parameters or in any physical or neurological examination among the 3 treatment groups throughout the study. No changes were observed in concomitant antiepileptic trough drug concentrations

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permutation of the three treatment numbers. Patients in each study centre were assigned treatment numbers according to the number of the country/principal investigator and the date order of their entry into the study **Details of pretrial period** The study had a 1–4-week baseline period during which participants were screened for inclusion. Included participants were randomised during baseline to one of the three treatment groups (LEV 2000 mg/day, LEV 4000 mg/day or placebo) for 24 weeks. There was no titration period. The assigned dose was initiated at the start of active treatment. The double-blind randomised phase of the study was 24 weeks in length. The study also included a further 24-week open-label treatment period and a 4-week run-out down-titration period **ITT analysis performed/method** Authors state yes; not stated **Sample size calculations** Not stated; however, the authors state that the study was not powered to detect a significant difference between the two LEV study arms **Analysis methods** The ITT population included all randomised patients who had received at least one dose of study medication. The inferential ITT population consisted of the set of patients from the ITT population who provided data for the relevant treatment period(s). All treatment comparisons were made using two-tailed tests at the 0.05 significance	**Baseline seizure frequency** Median seizure frequency: LEV 2000 mg/day ($n = 34$): 1.21; LEV 4000 mg/day ($n = 36$): 1.34; placebo ($n = 36$): 1.24. Number of patients seizure free: LEV 2000 mg/day: $n = 4$; LEV 4000 mg/day: $n = 6$; placebo: $n = 6$ **Other characteristics** Mean duration of epilepsy: LEV 2000 mg/day ($n = 34$): 21.1 years (SD 14.4 years); LEV 4000 mg/day ($n = 38$): 24.6 years (SD 15.6 years); placebo ($n = 39$): 26.0 years (SD 13.2 years) **Inclusion/exclusion criteria** Inclusion: aged 16–70 years; with well-characterised refractory epilepsy and any seizure type; maintained on a stable dosage regimen of up to three AEDs for at least 3 months prior to study entry; at least 4 seizures in the 24 weeks prior to study entry. Women of childbearing potential were eligible only if they were using a reliable method of contraception Exclusion: a history of allergy, alcohol or drug abuse; a serious medical condition that could interfere with the assessment of safety and efficacy; psychotic conditions, problems with absorption, metabolism, or elimination of drugs, including gastrointestinal dysfunction, or renal or hepatic insufficiency		(15.8%), nausea $n = 5$ (13.2%), dizziness $n = 4$ (10.5%), urinary tract infection $n = 4$ (10.5%) Serious AEs: $n = 4$ (10.5%) **Comparator** Placebo ($n = 39$): somnolence $n = 10$ (25.6%); asthenia $n = 6$ (15.4%), accidental injury $n = 6$ (15.4%), infection $n = 3$ (7.7%), nausea $n = 1$ (2.6%), urinary tract infection $n = 1$ (2.6%) Serious AEs: $n = 3$ (7.7%)	

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
level. The responder rate analyses were performed by means of logistic regression. ORs for obtaining a 50% seizure reduction and 95% CIs were calculated. Median percentage reduction of weekly seizure frequency per seizure type (I and II) were analysed using the Wilcoxon rank sum test. AEs were tabulated and compared using logistic regression. Baseline and study results of laboratory tests, vital signs and mean trough AED plasma levels were compared using the Kruskal–Wallis test on difference from baseline **Length of trial/frequency of follow-up** 24 weeks; visits were scheduled after 4, 12 and 24 weeks of treatment				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; the proportion of participants with ≥ 50% reduction in total seizure frequency after completing 24 weeks of double-blind treatment compared with baseline **Intervention 1** Inferential ITT population LEV 2000 mg/day (n = 27): 48.1% (13/27), p = 0.01 (LEV 2000 mg/day vs placebo) OR 4.9 (95% CI: 1.4 to 16.8) **Intervention 2** Inferential ITT population LEV 4000 mg/day (n = 28): 28.6% (8/28) OR 2.0 (95% CI: 0.6 to 7.2) **Comparator** Inferential ITT population Placebo (n = 31): 16.1% (5/31)	**Outcome** Seizure frequency; median number of seizures per week **Intervention 1** Inferential ITT population LEV 2000 mg/day (n = 27): 0.62 (1.21 at baseline) **Intervention 2** Inferential ITT population LEV 4000 mg/day (n = 28): 0.59 (1.34 at baseline) **Comparator** Inferential ITT population Placebo (n = 31): 1.40 (1.24 at baseline)	**Outcome** Proportion of seizure-free patients; number of participants seizure free **Intervention 1** Inferential ITT population LEV 2000 mg/day (n = 27): 4 **Intervention 2** Inferential ITT population LEV 4000 mg/day (n = 28): 2 **Comparator** Inferential ITT population Placebo (n = 31): 1	**Outcome** Change in seizure frequency; percentage change from baseline in weekly seizure frequencies by seizure type **Intervention 1** Inferential ITT population LEV 2000 mg/day: partial seizures (n = 17): 41.2%; generalised seizures (n = 15): 66.7% **Intervention 2** Inferential ITT population LEV 4000 mg/day: partial seizures (n = 17): 43.4%; generalised seizures (n = 17): 46.8% **Comparator** Inferential ITT population LEV 2000 mg/day: partial seizures (n = 19): 19.8%; generalised seizures (n = 15): 5.6%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Cereghino, 2000[143] **Related publications** Abstract,[386] abstract,[387] full study of QoL[166] **Country** USA **Source** Literature search **Aim** To evaluate the efficacy and safety of 500 and 1500 mg b.d. LEV as adjunctive therapy for refractory partial seizures in a double-blind, randomised, placebo-controlled, parallel-group, multi-centre trial **Type of publication** Full paper (final analysis) **Funding** UCB Pharma **Trial ID** N132 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** In blocks by study site; after pre-trial period **Details of pretrial period** There was a 12-week, single-blind, placebo baseline period during which patients were	**Number of participants** 385 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** LEV 1000 mg/day (n = 98): 38 years (SD 11 years); LEV 3000 mg/day (n = 101): 38 years (SD 11 years); placebo (n = 95): 38 years (SD 11 years); not stated **Gender** LEV 1000 mg/day (n = 98): men = 62, women = 36; LEV 3000 mg/day (n = 101): men = 66, women = 35; placebo (n = 95): men = 50, women = 45 **Age at onset of seizures** Not stated **Pretrial medication** See concurrent medications **Ongoing concurrent medication** CBZ (167/294), PHT (102/294), GBP (83/294), valproate (78/294), PB (26/294), PRM (20/294), LTG (12/294), CZP (6/294), other (20/294) (included methsuximide, AZM, lorazepam, TGB, clorazepate	**Intervention 1** LEV; 1000 mg/day; 38 weeks No. randomised: 98 No. completed: 86 **Intervention 2** LEV; 3000 mg/day; 38 weeks No. randomised: 101 No. completed: 93 **Comparator** Placebo; 38 weeks No. randomised: 95 No. completed: 89	**Withdrawals prerandomisation** Total (n = 91/385): failure to fulfil selection criteria (n = 33), withdrew consent (n = 19), AEs not related to study (n = 14), protocol violation (n = 12), other (n = 19) **Withdrawals postrandomisation** LEV 1000 mg/day (n = 98): withdrew consent (n = 2), AEs (n = 6), lost to follow-up (n = 3), other (n = 1); LEV 3000 mg/day (n = 101): withdrew consent (n = 1), AEs (n = 7); placebo (n = 95): withdrew consent (n = 1), adverse events (n = 5) **Adverse events** **Intervention 1** Treatment-emergent AEs occurring in ≥ 10% of patients in any treatment group: LEV 1000 mg/day (n = 98): abdominal pain (n = 5), accidental injury (n = 16), asthenia (n = 16), diarrhoea (n = 7), dizziness (n = 17), flu syndrome (n = 6), headache (n = 21), infection (n = 27), pain (n = 11), rhinitis (n = 13), somnolence (n = 20) Serious AEs (defined as any AE that was fatal, life-threatening or permanently or severely disabling or incapacitating; that resulted in prolonged hospitalisation; or that	**Authors' conclusions** Adjunctive therapy with LEV was effective and well tolerated in controlling partial seizures **Comments** No significant differences in demographics were noted between the 2 groups. Concomitant AEDs allowed included the newer AEDs GBP, LTG and TGB Further analyses and data relating to seizure subtypes are available in the paper

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evaluated to determine whether they met all the randomisation criteria. Participants had to have a minimum of 12 partial seizures within 12 weeks before study selection with a minimum of two partial seizures occurring per 4 weeks during the baseline period There was a 4-week double-blind drug titration period, followed by a 14-week double-blind treatment period, and an 8-week double-blind study medication withdrawal period During the 12-week placebo baseline period, eligible patients stabilised on one or two appropriate AEDs at the usual plasma concentrations. At the end, participants who met the entry criteria were randomised to placebo, LEV 1000 mg/day or LEV 3000 mg/day, given in two divided doses before meals LEV dosage was escalated at 2-week intervals during the 4-week, double blind, dose titration period to the dose assigned at randomisation. Dosages of LEV were 333 mg/day for 2 weeks, then 666 mg/day for 2 weeks and 1000 mg/day started on the first visit of the observation period, or 1000, 2000 then 3000 mg/day. The dose achieved at the final step of the titration period was maintained throughout the 14-week treatment period. If a clinical AE was considered associated with a rise in concomitant AED blood level, the investigator was permitted to modify that drug's dosage **ITT analysis performed/method** Authors state yes; not stated **Sample size calculations** Results from Phase II studies were evaluated and showed a minimum improvement in seizure reduction of 24% compared with baseline. This	dipotassium, DZP). Drugs affecting the CNS were to be avoided **Co-morbidities** Not stated **Baseline seizure frequency** Median weekly partial seizure frequency: LEV 1000 mg/day (n = 98): 2.53; LEV 3000 mg/day (n = 101): 2.08; placebo (n = 95): 1.77 **Other characteristics** Mean weight: LEV 1000 mg/day (n = 98): 79.4 kg (SD 19.1 kg); LEV 3000 mg/day (n = 101): 80.3 kg (SD 16.7 kg); placebo (n = 95): 77.3 kg (SD 17.9 kg) **Inclusion/exclusion criteria** Inclusion: aged 16–70 years with uncontrolled partial seizures with or without becoming secondarily generalised for at least 2 years; must have received at least 2 marketed AEDs, either simultaneously or consecutively. Women could not be of childbearing potential or had to be practising two simultaneous methods of birth control and have a negative serum pregnancy test Exclusion: patients with medical conditions other than epilepsy or with chronic progressive neurological disease;		was associated with congenital anomaly, cancer or overdose (either accidental or intentional) (n = 7) **Intervention 2** LEV 3000 mg/day (n = 101): abdominal pain (n = 3), accidental injury (n = 13), asthenia (n = 13), diarrhoea (n = 7), dizziness (n = 20), flu syndrome (n = 11), headache (n = 21), infection (n = 27), pain (n = 13), rhinitis (n = 7), somnolence (n = 19) Serious AEs (n = 2) **Comparator** Placebo (n = 95): abdominal pain (n = 10), accidental injury (n = 23), asthenia (n = 11), diarrhoea (n = 10), dizziness (n = 7), flu syndrome (n = 8), headache (n = 19), infection (n = 12), pain (n = 13), rhinitis (n = 8), somnolence (n = 13) Serious AEs (n = 10)	

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
study was designed to show a difference in log-transformed partial seizure frequency between treatment groups of at least 0.27 (equivalent to a 24% reduction in untransformed seizure frequency as compared with placebo). Projecting a drop-out rate of 20%, ~300 randomised patients were assumed to be required to achieve 240 fully evaluable patients (80 per treatment group) to be able to detect this difference with 80% power and a Type I error of 5% **Analysis methods** All analyses were based on patients who completed titration and entered the evaluation period. Analyses of the primary outcome parameter, median percentage reduction in seizure frequency, and the 50% responder rate were also performed on the total randomised population. The primary efficacy variable was analysed using ANCOVA with baseline seizure frequency as the covariate. Additionally, a repeated measures ANCOVA was applied using assessments from each visit during treatment period. For secondary efficacy variables based on reduction in seizure frequency during the treatment period compared with the baseline, the responder rate was analysed using a logistic regression model and the Cochran–Mantel–Haenszel test on the ranks. Two-tailed tests were performed with a significance level of 0.05. For all efficacy analyses, the Hochberg enhancement to the Bonferroni procedure was used to adjust for multiple comparisons **Length of trial/frequency of follow-up** 38 weeks; before each dose escalation, at 4-week intervals during the treatment period and at the final visit	participation in any other investigational drug trial within the 4 weeks preceding study entry; had a history of drug or alcohol abuse; or had impairments in renal or hepatic function			

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Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; median percentage reduction in seizure frequency versus baseline **Intervention 1** For the 14-week evaluation period: LEV 1000 mg/day ($n = 94$): 32.5%, $p < 0.001$ (LEV vs baseline) For the 18-week titration and evaluation period: LEV 1000 mg/day ($n = 98$): 36.9%, $p < 0.001$ (LEV vs baseline) **Intervention 2** For the 14-week evaluation period: LEV 3000 mg/day ($n = 98$): 37.1%, $p < 0.001$ (LEV vs baseline) For the 18-week titration and evaluation period: LEV 3000 mg/day ($n = 101$): 38.1%, $p < 0.001$ (LEV vs baseline) **Comparator** For the 14-week evaluation period: placebo ($n = 93$): 6.8% For the 18-week titration and evaluation period: placebo ($n = 95$): 6.9%	**Outcome** Proportion of responders; defined as having at least a 50% reduction from baseline in seizure frequency **Intervention 1** For the 14-week evaluation period: LEV 1000 mg/day ($n = 94$): 33.0%, $p < 0.001$ For the 18-week titration and evaluation period: LEV 1000 mg/day ($n = 98$): 37.1%, $p < 0.001$ Response rate of ≥75% For the 14-week evaluation period: LEV 1000 mg/day ($n = 94$): 12.8%, $p < 0.01$ **Intervention 2** For the 14-week evaluation period: LEV 3000 mg/day ($n = 98$): 39.8%, $p < 0.001$ For the 18-week titration and evaluation period: LEV 3000 mg/day ($n = 101$): 39.6%, $p < 0.001$ Response rate of ≥75% For the 14-week evaluation period: LEV 3000 mg/day ($n = 98$): 20.4%, $p < 0.001$ **Comparator** For the 14-week evaluation period: placebo ($n = 93$): 10.8% For the 18-week titration and evaluation period: placebo ($n = 95$): 7.4% Response rate of ≥75% For the 14-week evaluation period: placebo ($n = 93$): 1.1%	**Outcome** Change in seizure frequency; median % reduction in seizure frequency over placebo **Intervention 1** For the 14-week evaluation period: LEV 1000 mg/day ($n = 94$): 20.9%, $p < 0.001$ (LEV vs placebo) For the 18-week titration and evaluation period: LEV 1000 mg/day ($n = 98$): 26.1%, $p < 0.001$ (LEV vs placebo) Reduction in partial seizure frequency over placebo was higher for LEV at each evaluation visit ($p \leq 0.016$) **Intervention 2** For the 14-week evaluation period: LEV 3000 mg/day ($n = 98$): 27.7%, $p < 0.001$ (LEV vs placebo) For the 18-week titration and evaluation period: LEV 3000 mg/day ($n = 101$): 30.1%, $p < 0.001$ (LEV vs placebo) Reduction in partial seizure frequency over placebo was higher for LEV at each evaluation visit ($p \leq 0.016$) **Comparator** For the 14-week evaluation period: placebo ($n = 93$): NA For the 18-week titration and evaluation period: placebo ($n = 93$): NA	**Outcome** Proportion of seizure-free patients; 100% decrease from baseline in seizure frequency **Intervention 1** For the 14-week evaluation period: LEV 1000 mg/day ($n = 94$): 3.19%, NS **Intervention 2** For the 14-week evaluation period: LEV 3000 mg/day ($n = 98$): 8.16%, $p = 0.01$ **Comparator** For the 14-week evaluation period: placebo ($n = 93$): 0%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Cramer, 2000[166] **Related publications** Papers[143,386–388] **Country** USA **Source** Literature search **Aim** To evaluate the short-term effect of LEV as add-on therapy on HRQoL in the treatment of refractory POSs **Type of publication** Full paper (final analysis) **Funding** UCB Pharma **Trial ID** N132 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** In blocks by study site; after pretrial period **Details of pretrial period** There was a 12-week, single-blind, placebo baseline period during which patients were evaluated to determine whether they met all the randomisation criteria. Participants	**Number of participants** 385 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 246): 38.7 years (SD 10.9 years); LEV 1000 mg/day (n = 80): 39.1 years (SD 11.3 years); LEV 3000 mg/day (n = 85): 38.5 years (SD 10.2 years); placebo (n = 81): 38.5 years (SD 11.3 years); not stated **Gender** Total (n = 246): men = 60.2%, women = 39.8%; LEV 1000 mg/day (n = 80): men = 61.3%, women = 38.7%; LEV 3000 mg/day (n = 85): men = 64.7%, women = 35.3%; placebo (n = 81): men = 54.3%, women = 65.7% **Age at onset of seizures** Total (n = 246): 14.3 years (SD 11.8 years); LEV 1000 mg/day (n = 80): 15.3 years (SD 12.7 years); LEV 3000 mg/day (n = 85): 13.6 years (SD 10.8 years); placebo (n = 81): 13.9 years (SD 11.9 years) **Pretrial medication** Not stated for this subgroup of N132 Baseline number of AEDs: total (n = 246): one = 35%, two = 63%, three or more = 2%; LEV	**Intervention 1** LEV; 1000 mg/day; 38 weeks No. randomised: 98 No. completed: 80 **Intervention 2** LEV; 3000 mg/day; 38 weeks No. randomised: 101 No. completed: 85 **Comparator** Placebo; 38 weeks No. randomised: 95 No. completed: 81	**Withdrawals prerandomisation** Total from effectiveness data (n = 91/385): failure to fulfil selection criteria (n = 33), withdrew consent (n = 19), AEs not related to study (n = 14), protocol violation (n = 12) **Withdrawals postrandomisation** Total from QoL study (n = 48/294): questionnaires not administered at follow-up (n = 36), omitted one or more subscales at baseline or follow-up (n = 12) **Adverse events** **Intervention 1** Not stated **Intervention 2** Not stated **Comparator** Not stated	**Authors' conclusions** Addition of LEV to standard medication seems to have a positive impact on HRQoL, particularly among responders in this short-term study. These exploratory analyses require additional studies to evaluate long-term changes in a larger population **Comments** Additional data were taken from the effectiveness report[143] for participant characteristics, inclusion criteria and treatment descriptions and dosages. There are two missing patients (non-completers of the QOLIE-31) not accounted for in the study report None of the demographic or disease characteristics for the evaluable patients differed significantly among the three treatment groups The original clinical trial was not powered for the HRQoL analysis so these results should be viewed with caution

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
had to have a minimum of 12 partial seizures within 12 weeks before study selection with a minimum of two partial seizures occurring per 4 weeks during the baseline period There was a 4-week double-blind drug titration period, followed by a 14-week double-blind treatment period and an 8-week double-blind study medication withdrawal period During the 12-week placebo baseline period, eligible patients stabilised on one or two appropriate AEDs. At the end, participants who met the entry criteria were randomised to placebo, LEV 1000 mg/day or LEV 3000 mg/day, given in two divided doses before meals LEV dosage was escalated at 2-week intervals during the 4-week, double blind, dose titration period to the dose assigned at randomisation. Dosages of LEV were 333 mg/day for 2 weeks, then 666 mg/day for 2 weeks and 1000 mg/day started on the first visit of the observation period, or 1000, 2000, then 3000 mg/day. The dose achieved at the final step of the titration period was maintained throughout the 14-week treatment period. If a clinical AE was considered associated with a rise in concomitant AED blood level, the investigator was permitted to modify that drug's dosage **ITT analysis performed/method** Authors do not state yes or no; not stated	1000 mg/day (n = 80): one = 36.3%, two = 60%, three or more = 3.7%; LEV 3000 mg/day (n = 85): one = 38.8%, two = 60%, three or more = 1.2%; placebo (n = 81): one = 29.6%, two = 69.2%, three or more = 1.2% **Ongoing concurrent medication** Not stated for this subgroup of N132 **Co-morbidities** Not stated **Baseline seizure frequency** Mean weekly partial seizure frequency: total (n = 246): 6.10 (SD 16.20); LEV 1000 mg/day (n = 80): 7.55 (13.99); LEV 3000 mg/day (n = 85): 5.15 (SD15.58); placebo (n = 81): 5.66 (SD 18.79) **Other characteristics** Seizure type (%): total (n = 246): SPSs or CPSs = 66.3%, SPS or CPS + partial seizures secondarily generalised (PSSG) = 32.1%, PSSG = 1.6%; LEV 1000 mg/day (n = 80): SPS or CPS = 65%, SPS or CPS + PSSG = 31.3%, PSSG = 3.7%; LEV 3000 mg/day (n = 85): SPS or CPS = 69.4%, SPS or CPS + PSSG = 29.4%, PSSG = 1.2%; placebo (n = 81): SPS or CPS = 64.2%, SPS or CPS + PSSG = 35.8%, PSSG = 0%		

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sample size calculations The clinical trial (N132) was not powered for an HRQoL outcome **Analysis methods** Statistical analyses included Spearman correlation coefficients, paired *t*-tests, and ANOVA to differentiate among patients taking placebo, LEV 1000 mg/day or LEV 3000 mg/day **Length of trial/frequency of follow-up** 38 weeks; at end of baseline and at 18-week follow-up	**Inclusion/exclusion criteria** Inclusion: aged 16–70 years; with uncontrolled partial seizures with or without becoming secondarily generalised for at least 2 years; must have received at least 2 marketed AEDs, either simultaneously or consecutively. Women could not be of childbearing potential or had to be practising two simultaneous methods of birth control and have a negative serum pregnancy test Exclusion: patients with medical conditions other than epilepsy; or with chronic progressive neurological disease; had participated in any other investigational drug trial within the 4 weeks preceding study entry; had a history of drug or alcohol abuse; or had impairments in renal or hepatic function			
Results				
Outcome 1	**Outcome 2**			
Outcome Change in patient-related QoL; mean values of QOLIE-31 at follow-up assessment **Intervention 1** LEV 1000 mg/day ($n = 80$): seizure worry 65.8, overall QoL 67.3, emotional well-being 69.7, energy fatigue 54.4, cognitive functioning 64.6, medication effects 66.1, social function 58.6, health status 66.6, total score 63.4	**Outcome** Change in patient-related QoL; % change for responders and non-responders measured using the QOLIE-31 questionnaire (responders were defined as patients with a ≥50% reduction in seizure frequency from baseline to follow-up) **Intervention 1** LEV 1000 mg/day ($n = 79$): Responders ($n = 25$): seizure worry 16%, overall QoL 18%, emotional well-being 5%, energy fatigue 10%, cognitive functioning 9%, medication effects 3%, social function 9%, health status 17%, total score 10%			

continued

Outcome 1	Outcome 2
Intervention 2 LEV 3000 mg/day (n = 85): seizure worry 65.7 (p = 0.0003), overall QoL 67.6 (p = 0.04), emotional well-being 67.4 (p = 0.41), energy fatigue 55.2 (p = 0.62), cognitive functioning 66.6 (p = 0.01), medication effects 69.6 (p = 0.10), social function 59.9 (p = 0.36), health status 67.9 (p = 0.64), total score 64.1 (p = 0.009) The p-values indicate the difference between treatment groups on adjusted mean values at follow-up assessment (with baseline as covariate) **Comparator** Placebo (n = 81): seizure worry 55.9, overall QoL 62.7, emotional well-being 67.2, energy fatigue 52.7, cognitive functioning 60.0, medication effects 61.7, social function 55.6, health status 65.2, total score 59.4	Non-responders (n = 54): seizure worry 7%, overall QoL –1%, emotional well-being –1%, energy fatigue –6%, cognitive functioning –1%, medication effects 2%, social function –3%, health status –4%, total score –1% Statistically significant changes across treatment groups were seen in all subscales (all $p < 0.01$) except medication effects **Intervention 2** LEV 3000 mg/day (n = 85): Responders (n = 34): seizure worry 24%, overall QoL 15%, emotional well-being 4%, energy fatigue 10%, cognitive functioning 12%, medication effects 28%, social function 24%, health status 25%, total score 14% Non-responders (n = 51): seizure worry 7%, overall QoL 1%, emotional well-being –6%, energy fatigue –8%, cognitive functioning 0%, medication effects –2%, social function –4%, health status –3%, total score –2% Statistically significant changes across treatment groups were seen in all subscales (all $p < 0.01$) except medication effects **Comparator** Placebo (n = 80): Responders (n = 9): seizure worry –6%, overall QoL 7%, emotional well-being 9%, energy fatigue 10%, cognitive functioning –8%, medication effects –17%, social function 8%, health status 14%, total score 2% Non-responders (n = 71): seizure worry –2%, overall QoL –1%, emotional well-being –1%, energy fatigue –5%, cognitive functioning –7%, medication effects –4%, social function –2%, health status 0%, total score –4%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Shorvon, 2000[145] **Related publications** Paper[80] **Country** European **Source** Literature search **Aim** To evaluate the efficacy and tolerability of LEV as add-on therapy in patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** UCB Pharma **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; not stated **Details of pretrial period** 12- or 8-week baseline period followed by a 4-week titration period during which LEV was titrated upwards until patients were stabilised on their assigned dose	**Number of participants** 324 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 37 years (SD 11); LEV 1000 mg/day: 36 years (SD 10); LEV 2000 mg/day: 37 years (SD 12); placebo: 37 years (SD 12); total: 16–69 years; LEV 1000 mg/day: 16–68 years; LEV 2000 mg/day: 24–65 years; placebo 16–69 years **Gender** Total: men = 157, women = 167; LEV 1000 mg/day: men = 51, women = 55; LEV 2000 mg/day: men = 51, women = 55; placebo: men = 55, women = 57 **Age at onset of seizures** Total: 13.7 years (SD 11); LEV 1000 mg/day: 13.1 years (SD 11.5); LEV 2000 mg/day: 13.7 years (SD 10.9); placebo: 14.2 years (SD 10.9) **Pretrial medication** CBZ, PHT, VPA, VGB, LTG **Ongoing concurrent medication** All patients were taking between 1 and 3 or more AEDs during the study **Co-morbidities** Not stated	**Intervention 1** LEV; 1000 mg/day; 16 weeks No. randomised: 106 No. completed: 94 **Intervention 2** LEV; 2000 mg/day; 16 weeks No. randomised: 106 No. completed: 87 **Comparator** Placebo; 16 weeks No. randomised: 112 No. completed: 97	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** LEV 1000 mg/day: AE (n = 8), withdrew consent (n = 2), other (includes ineligibility, protocol violation, lack of efficacy, decision of UCB) (n = 2) LEV 2000 mg/day: AE (n = 15), withdrew consent (n = 3), other (n = 1) Placebo: AE (n = 6), withdrew consent (n = 5), other (n = 4) **Adverse events** **Intervention 1** LEV 1000 mg/day (n = 106): accidental injury (n = 13), headache (n = 14), asthenia (n = 8), convulsion (n = 9), somnolence (n = 10) **Intervention 2** LEV 2000 mg/day (n = 106): accidental injury (n = 14), headache (n = 17), asthenia (n = 14), convulsion (n = 9), somnolence (n = 12) **Comparator** Placebo (n = 112): accidental injury (n = 17), headache (n = 10), asthenia (n = 9), convulsion (n = 10), somnolence (n = 5)	**Authors' conclusions** Add-on treatment with LEV (1000 or 2000 mg/day) was superior to placebo in efficacy, without interactions with other AEDs, and had an AE profile comparable to placebo **Comments** Efficacy was evaluated in the inferential ITT population (all patients from the ITT population for whom efficacy data were obtained during the evaluation phase); safety was evaluated in the ITT population (all randomised patients who received at least one dose of study medication) Other reported adverse outcomes were infection, pharyngitis, dizziness, nausea, pain, abdominal pain, urinary tract infection, depression, back pain, flu syndrome

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
ITT analysis performed/method Authors state yes; not stated **Sample size calculations** Sample size of 234 evaluable patients was calculated to detect a reduction in seizure frequency of ≥24%, measured by the difference between the log-transformed treatment means of 0.27 (two-tailed test, power 80%, $\alpha = 0.05$, SD 0.60) **Analysis methods** Two-tailed significance tests were used. Significance levels were adjusted for multiple comparisons. Continuous variables analysed using ANOVA. Data were log transformed. Comparison between treatment means adjusted on means of the baseline covariable using Student's *t*-test and 98% CI. Back transformation of adjusted means (LSMs) differences with placebo used to estimate % reduction over placebo **Length of trial/frequency of follow-up** 16 weeks; every 4 weeks during baseline, titration and evaluation phases	**Baseline seizure frequency** Total: median = 2.62 per week; LEV 1000 mg/day: median = 2.82; LEV 2000 mg/day: median = 2.58; placebo median 2.50 **Other characteristics** Results for compliance not reported **Inclusion/exclusion criteria** Inclusion: ILAE criteria for predominantly partial seizures, with or without secondary generalisation, for the past 2 years despite treatment with 1 or 2 AEDs; patients had taken a stable dose regimen 4 weeks before enrolment and throughout the baseline period, and had to have at least 4 partial seizures during each 4-week period of baseline. Women of childbearing age had to have been surgically sterilised or using contraception Exclusion: renal insufficiency; progressive neurological or serious psychiatric disorders; significant laboratory abnormalities; current or recent substance abuse; questionable compliance; or concomitant disorders that could hinder evaluation of outcomes			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Seizure frequency; weekly partial seizure frequency **Intervention 1** Baseline: mean 3.44; median 2.82; $n = 106$ (interquartile range 1.75, 4.38) Evaluation period: mean 2.60; LSM 2.58; median 2.00 (interquartile range 1.21, 4.08); $n = 101$ Reduction over placebo: 16.4% (98% CI 2.7 to 28.1); $p = 0.006$ **Intervention 2** Baseline: mean 3.76; median 2.58; $n = 106$ (interquartile range 1.50, 6.25) Evaluation period: mean 2.71; LSM 2.52; median 1.85 (interquartile range 0.86, 5.60); $n = 95$ Reduction over placebo: 17.7% (98% CI 4.1 to 29.4); $p = 0.003$ **Comparator** Baseline: mean 3.22; median 2.50 (interquartile range 1.27, 4.94); $n = 112$ Evaluation period: mean 3.06; LSM 3.28; median 2.58 (interquartile range 1.25, 5.17); $n = 106$	**Outcome** Change in seizure frequency; defined as median percentage reduction in seizure frequency from baseline **Intervention 1** Median percentage reduction: all partial seizure types 17.7%, $n = 101$, $p < 0.001$ versus placebo; SPS 38.1%, $n = 31$, not significant; CPS 12.4%, $n = 79$, not significant; secondarily generalised 37.4%, $n = 28$ **Intervention 2** Median percentage reduction: all partial seizure types 26.5%, $n = 95$, $p < 0.001$ versus placebo; SPS 46.3%, $n = 27$, $0.07 < p < 0.02$ (trend); CPS 24.4%, $n = 83$; secondarily generalised 28.2%, $n = 21$, not significant **Comparator** Median percentage reduction: all partial seizure types 6.1%, $n = 106$; SPS 9.1%, $n = 39$; CPS 9.1%, $n = 89$; secondarily generalised –16.8%, $n = 24$	**Outcome** Proportion of responders; responders were defined as having at least a ≥ 50% reduction in seizure frequency (≥ 75% also reported) **Intervention 1** ≥ 50% reduction: 23/101 (22.8%); $p = 0.019$ versus placebo NNT to get a responder rate with ≥ 50% reduction = 6.9 (95% CI 4.3 to –17.9) ≥ 75% reduction: 11/101 (10.9%); $p < 0.02$ versus placebo **Intervention 2** ≥ 50% reduction: 30/95 (31.6%); $p < 0.001$ versus placebo NNT to get a responder rate with ≥ 50% reduction = 3.5 (95% CI 2.6 to –5.4) ≥ 75% reduction: 16/95 (16.8%); $p \leq 0.001$ versus placebo **Comparator** ≥ 50% reduction: 11/106 (10.4%) ≥ 75% reduction: 3/106 (2.8%)	**Outcome** Proportion of seizure-free patients **Intervention 1** 5/101 (5%) **Intervention 2** 2/95 (2%) **Comparator** 1/106 (0.9%)

Levetiracetam (unlicensed use)

Parallel studies (*n* = 1)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Ben-Menachem, 2000[144] **Related publications** Abstract,[382] abstract[383] **Country** European **Source** Literature search **Aim** To evaluate the efficacy and tolerability of LEV monotherapy in selected patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** UCB Pharma **Trial ID** Not stated **Study design** Monotherapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 343 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (*n* = 286): 36 years (SD 12); LEV (*n* = 181): 37 years (SD 12); placebo (*n* = 105): 36 years (SD 12); not stated **Gender** Total (*n* = 286): men = 48%, women = 52%; LEV (*n* = 181): men = 48%, women = 52%; placebo (*n* = 105): men = 49%, women = 51% **Age at onset of seizures** Age at onset: total (*n* = 286): 18 years (SD 14); LEV (*n* = 181): 18 years (SD 14); placebo (*n* = 105): 18 years (SD 13) Mean duration of epilepsy: total (*n* = 286): 19 years (SD 11); LEV (*n* = 181): 19 years (SD 11); placebo (*n* = 105): 19 years (SD 12) **Pretrial medication** Mean number of previous AEDs: total (*n* = 286): 4.01 (SD 2.57);	**Intervention 1** LEV; 3000 mg/day; 12-week add-on follow-up and 12-week monotherapy follow-up No. randomised: 181 No. completed: 36 **Comparator** Placebo; 12-week add-on follow-up and 12-week monotherapy follow-up No. randomised: 105 No. completed: 10	**Withdrawals prerandomisation** Total (*n* = 343): ineligibility (*n* = 44), AE (*n* = 1), withdrawal of consent (*n* = 10), lost to follow-up (*n* = 1), other (*n* = 1) **Withdrawals postrandomisation** Add-on up-titration phase LEV (*n* = 181): AE (*n* = 9), withdrawal of consent (*n* = 1); placebo (*n* = 105): AE (*n* = 2), lost to follow-up (*n* = 1) Add-on maintenance phase LEV (*n* = 171): protocol violation (*n* = 6), AE (*n* = 8), lack or loss of efficacy (*n* = 3), withdrawal of consent (*n* = 5); placebo (*n* = 102): protocol violation (*n* = 3), AE (*n* = 7), lack or loss of efficacy (*n* = 1), withdrawal of consent (*n* = 1) Responder selection phase LEV (*n* = 149): did not meet responder criteria (*n* = 80); placebo (*n* = 90): did not meet responder criteria (*n* = 73) Monotherapy down-titration LEV (*n* = 69): AE (*n* = 1), lack or loss of efficacy (*n* = 5), withdrawal of consent (*n* = 1), escape criteria (*n* = 11), other (*n* = 2); placebo (*n* = 17): AE (*n* = 1), lack or loss of efficacy	**Authors' conclusions** Conversion to LEV monotherapy (1500 mg twice daily) is effective and well tolerated in patients with refractory partial seizures who responded to 3000 mg LEV as add-on therapy **Comments** The demographic data refer to the 286 participants who were randomised to placebo or LEV The monotherapy phase of the study included only responders in the add-on phase of the trial which limits the applicability of the findings Of the 239 patients who completed the add-on phase, 86 were eligible to enter the monotherapy phase (placebo *n* = 17; LEV *n* = 69). For ethical reasons, 8 of the 17 patients taking placebo were switched to treatment with LEV but for analysis they remained in the placebo group. 25 patients (placebo *n* = 5; LEV *n* = 20) were withdrawn during the down-titration period, mostly because they met the escape criteria. 49 of the 69 patients receiving LEV were successfully down-titrated to LEV

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 12-week open baseline period during which patients were selected for entry according to the inclusion/exclusion criteria. Patients were then randomised to LEV or placebo in an 18-week double-blind add-on therapy phase that included 4 weeks up-titration of LEV or placebo. Medication was increased every 2 weeks from 500 mg twice daily to the target dose of 1500 mg twice daily. Patients were evaluated on the target dosage for a 12-week period. Patients were then assessed over a 2-week period for entry into the monotherapy phase of the trial. Criteria for entry to this phase were (relative to baseline) a 50% reduction in SPSs or CPSs or 35% reduction in SPSs provided that CPSs were reduced by 50% and secondarily generalised seizures were no higher than baseline; no doubling of CPSs or secondarily generalised seizures and no secondarily generalised seizures present during the add-on phase if they were not present during baseline. Patients who were not eligible for entry into the monotherapy phase were given the opportunity of entering an open-label study with LEV. The monotherapy phase included a maximum of 12 weeks of down-titration and 12 weeks of monotherapy. After entry into the monotherapy phase, the standard AED was gradually withdrawn during a period of up to 12 weeks. Patients were withdrawn from the monotherapy phase if (relative to baseline) they doubled their monthly frequency of CPSs or secondarily generalised seizures; there was an occurrence of status epilepticus; secondarily generalised seizures occurred if none had	LEV (n = 181): 3.92 (SD 2.59); placebo (n = 105): 4.17 (SD 2.53) **Ongoing concurrent medication** Single AED at a stable dosage until initiation of monotherapy phase of trial: CBZ (74%); LTG (9%); VPA (8%); PHT (6%) **Co-morbidities** Not stated **Baseline seizure frequency** Median baseline partial seizure frequency (n/week): total (n = 286): median = 1.70; LEV (n = 181): median = 1.69; placebo (n = 105): median = 1.75 Seizure type: total (n = 286): SPSs 23%; CPSs 97%; secondarily generalised seizures 27% **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 16–70 years; clinically observed partial seizures for at least the year before study entry (seizures classified according to the ILAE's Commission on Classification and Terminology Criteria); at least 2 CPSs per 4 weeks during baseline despite treatment with one AED; women of childbearing age surgically sterile or using a medically accepted form of contraception Exclusion: history of status epilepticus or a seizure pattern characterised by		(n = 1), escape criteria (n = 2), other (n = 1) Monotherapy maintenance phase LEV (n = 49): protocol violation (n = 1), AE (n = 1), escape criteria (n = 11); placebo (n = 12): Escape criteria (n = 2) **Adverse events** **Intervention 1** The incidence of AEs (with >5% incidence) compared with placebo was reported only for the add-on phase. Incidence of AEs (n = 181): 55% Asthenia (13.8%), infection (7.2%), somnolence (6.1%), headache (3.3%) (p = 0.019), accidental injury (2.2%) (p = 0.009) **Comparator** Incidence of AEs (n = 105): 53% Asthenia (6.7%), infection (3.8%), somnolence (3.8%), headache (10.5%), accidental injury (9.5%)	monotherapy and had at least one evaluation under monotherapy

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
occurred during baseline (escape criteria). The study was designed under the assumption that no more than 10% of patients taking placebo would fulfil the responder selection criteria (i.e. 9 out of 86 patients). When a total of 9 placebo responders was reached, for ethical reasons each subsequent placebo responder was switched to LEV for the monotherapy phase without breaking the blind. These patients were analysed as if they were still taking the placebo **ITT analysis performed/method** Authors state yes; not stated The sample size calculation was based on the assumption of a Type I error of 5% and a Type II error of 20%. With a LEV-to-placebo ratio a minimum of 258 evaluable patients were required to detect a 10% difference in the percentage of patients completing monotherapy. Assuming a drop-out rate of 30%, ~350 patients were required to enter the study **Analysis methods** Efficacy and safety analysis were conducted on the ITT population, which included all patients who were randomised and took at least one dose of study medication. The primary efficacy assessment (the percentage of patients who completed the monotherapy phase relative to the number of patients randomised to study medication) was analysed using Fisher's exact test. For the add-on phase, median percentage reduction was analysed using the Kruskal–Wallis test. Logistic regression was used to analyse the responder rate and	clusters during the previous 5 years and the 12-week baseline period; history of progressive cerebral disease; cerebrovascular accident; severe cardiovascular disease; chronic treatment with digitalis, glucosides or coumarins; significant disturbance of haemostasis; insulin-dependent diabetes mellitus; unstable hyperthyroidism; impaired hepatic or renal function; poor compliance; drug or alcohol abuse within the previous 2 years; suicidal tendency or other psychiatric disorder; participation in any other clinical trial within the 4 weeks preceding study entry; participation in any previous LEV trial; use of barbiturates, benzodiazepines or other medications that influence the CNS; other compounds with intrinsic CNS activity were allowed only when administered at a constant dosage throughout the study			

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Fisher's exact test for the number of seizure-free patients. The incidence of AEs during the add-on phase was analysed using logistic regression or the Cochran–Mantel–Haenszel test. Laboratory tests were compared using shift tables and mean changes from baseline and Kruskal–Wallis was used to conduct between-group comparisons. For the monotherapy phase, comparisons between the different phases of the study were performed in the LEV treatment group whenever appropriate **Length of trial/frequency of follow-up** 42 weeks; periodically and at 12 weeks				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Proportion of patients completing study; the percentage of patients who completed the monotherapy phase relative to the number randomised to study medication **Intervention 1** 19.9% (36/181) ($p = 0.029$) **Comparator** 9.5% (10/105)	**Outcome** Proportion of patients completing the add-on phase; the percentage of patients who completed the add-on phase relative to the number randomised to study medication **Intervention 1** 82% (149/181) **Comparator** 85% (90/105)	**Outcome** Change in seizure frequency; median percentage reduction in partial seizure frequency from baseline to add-on phase **Intervention 1** 39.9% ($p < 0.001$) Seizure frequency: 1.06 seizures/week **Comparator** 7.2% Seizure frequency: 1.75 seizures/week	**Outcome** Proportion of responders; defined as the proportion of patients with a reduction in partial seizure frequency of 50% in add-on phase compared with baseline **Intervention 1** 42.1% ($p < 0.001$) **Comparator** 16.7%	

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome Percentage of patients who remained seizure free during the add-on evaluation period **Intervention 1** LEV: 8.2% (14/181) (p = 0.012) **Comparator** Placebo: 1% (1/105)	**Outcome** The number of patients needed to treat to obtain one responder (in add-on phase) attributable to the LEV effect The number of patients needed to treat to obtain one seizure-free patient (in add-on phase) attributable to the LEV effect **Intervention 1** LEV: 3.9 (95% CI: 2.8 to 6.6) **Comparator** 13.9 (95% CI: 8.5 to 37.4)	**Outcome** Median absolute reduction in partial seizure frequency from baseline to the monotherapy evaluation period **Intervention 1** (In 49 of the 69 patients receiving monotherapy who were successfully down-titrated to LEV monotherapy): 0.61 (p = 0.012)	**Outcome** Median percentage reduction in partial seizure frequency from baseline to the monotherapy evaluation period **Intervention 1** (In 49 of the 69 patients receiving monotherapy who were successfully down-titrated to LEV monotherapy): 73.8% (0.027) Change in frequency of seizures during monotherapy evaluation period compared with add-on phase: median increase = 0.04 Percentage responders during monotherapy (the proportion of patients with a reduction in partial seizure frequency of 50% in monotherapy phase compared with baseline): 59.2% Proportion of patients who remained seizure free during the monotherapy evaluation period: LEV n = 9/49; placebo n = 3/12

Oxcarbazepine (licensed use)

Crossover studies (*n* = 1)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Houtkooper, 1987[84] **Related publications** Abstract[390] **Country** European **Source** Literature search **Aim** To assess OXC as a possible alternative to CBZ in patients with refractory epilepsy **Type of publication** Full paper (final analysis) **Funding** Ciba Geigy **Trial ID** Not stated **Study design** Add-on therapy; new vs old; crossover trial; superiority trial **Setting** Inpatient **Method/timing of randomisation** Not stated; after enrolment	**Number of participants** 48 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total (*n* = 48): median 29 years; range 15–50 years **Gender** Total (*n* = 48): men = 29, women = 19 **Age at onset of seizures** Not stated **Pretrial medication** CBZ (*n* = 48); VPA (*n* = 36); PHT (*n* = 27); PB (*n* = 7); ethosuximide (*n* = 4); benzodiazepines (*n* = 6) **Ongoing concurrent medication** See pretrial medications (note: CBZ was a study drug) **Co-morbidities** Mentally handicapped (*n* = 48?); polyneuropathy (*n* = 6); spastic hemiplegia (*n* = 5); nystagmus (*n* = 3)	**Intervention 1** OXC; 900–3600 mg/day; 20 weeks No. randomised: not stated No. completed: not stated **Comparator** CBZ; 500–2000 mg/day at steady state; 20 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Continued phase 1 treatment with OXC because of marked improvement (*n* = 2); premature change of study drug because of deterioration in period 1, from CBZ to OXC (*n* = 2), from OXC to CBZ (*n* = 1); return to phase 1 CBZ from phase 2 OXC because of deterioration (*n* = 1) **Adverse events** **Intervention 1** Not stated **Comparator** Eczema-like skin reaction (*n* = 2)	**Authors' conclusions** The high rate of preference for OXC in patients optimally treated with CBZ at the start of the study indicates that OXC can be of value for the type of patients enrolled in this study **Comments** Baseline characteristics not reported for the two randomised groups but for all patients together. It is not clear if randomisation was to treatment groups or if treatment was given to each patient individually in a random order Full paper does not say that patients were mentally handicapped, but the abstract report does Blood pressure, blood cell counts and serum levels of AEDs were measured at same time as seizure outcomes; EEG, ECG and other laboratory parameters were measured less frequently; preference was assessed at the end of the trial Statistical analysis of seizure frequency appears to be based on a one-sample test (Wilcoxon signed rank test) and a *p*-value for comparison of overall treatment means, and not a method for paired data. The numbers of seizures for the

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period All patients were stabilised on CBZ at the start of the trial. During the titration phase (maximum 8 weeks) CBZ was exchanged for OXC or CBZ again on a tablet-by-tablet basis over the first 1 or 2 weeks, the dose was gradually increased until symptoms of overdosage appeared and the dose was lowered to a level where the symptoms disappeared and was then kept constant. This was followed by a maintenance period of 12 weeks. The second treatment period followed the same procedure **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculations** Not stated **Analysis methods** Wilcoxon signed rank test (p 2-tailed 0.05) used to analyse seizure frequency. Change in serum levels of AEDs compared using Student's t-test for paired data **Length of trial/frequency of follow-up** 40 weeks; at onset, weekly during titration and weeks 2, 4, 8, 12 of steady-state period	**Baseline seizure frequency** Not stated; however, patients had to have a minimum of 2 seizures per month for study inclusion **Other characteristics** Partial seizures (n = 10), generalised seizures (n = 9), partial and generalised (n = 29) **Inclusion/exclusion criteria** Inclusion: hospitalised patients; aged 15–60 years; with partial, generalised or mixed types of seizures; receiving 2–4 AEDs with no change in AEDs in previous 2 months or in dose in previous month; minimal seizure frequency 2/mth; and for women, use of appropriate contraceptives Exclusion: cardiac disease; hepatic, renal, thyroid or resorption dysfunction; haematological abnormalities; progressive tumours; neurological/psychiatric diseases interfering with epilepsy; or pregnancy			groups having OXC followed by CBZ and vice versa are not reported Also reported are overall numbers of patients whose seizures (listed by type) increased, decreased or remained stable during steady state on OXC compared with CBZ. Tonic–clonic and tonic seizures tended to be reduced. Five patients showed increased alertness and concentration (as noticed by staff, parents, relatives) on OXC AEs: the 2 patients with eczema-like reactions to CBZ entered the trial with this condition, which showed complete remission on OXC treatment and recurred when switched to CBZ. Dizziness, drowsiness, nausea, headache, diplopia, ataxia were the same with both treatments (no data reported). No allergic reactions were reported No significant effects seen in EEG, ECG, blood pressure, haematology, blood chemistry (except lower serum sodium on OXC); mean serum VPA and PHT levels increased during OXC treatment At the end of the second steady-state phase, the investigator and nursing staff assessed their preference: 18 patients were kept on OXC, 13 on CBZ and 11 no preference

continued

Results
Outcome 1
Outcome Seizure frequency; mean number of seizures during maintenance period **Intervention 1** All seizures (n = 42): 60.3 Tonic–clonic 8.2; atonic 6.9; astatic 4.4; tonic 21.1; myoclonic 37.0; partial complex 12.4; simple partial 24.1; atypical absences 85.2 **Comparator** All seizures (n = 42): 66.0 Tonic–clonic 10.4; atonic 10.8; astatic 4.2; tonic 30.5; myoclonic 30.6; partial complex 13.0; simple partial 32.7; atypical absences 65.6

Parallel studies (*n* = 9)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Aikia, 1992[58] **Related publications** None **Country** Finland **Source** Literature search **Aim** To evaluate the effect of initial OXC monotherapy on memory, attention and simple psychomotor speed **Type of publication** Full paper (final analysis) **Funding** Ciba-Geigy **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** Following randomisation there was a 4–8-week titration period. The daily drug	**Number of participants** 37 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** OXC (*n* = 14): 33.6 years (SD 14.0); PHT (*n* = 15): 32.7 years (SD 12.5); not stated **Gender** OXC (*n* = 14): men = 5, women = 9; PHT (*n* = 15): men = 6, women = 9 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** IQ testing: OXC (*n* = 14): 98.4 (SD 12.3); PHT (*n* = 15): 100.3 (SD (13.9)	**Intervention 1** OXC; not stated; 12 months No. randomised: 19 No. completed: 14 **Comparator** CBZ; not stated; 12 months No. randomised: 18 No. completed: 15	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** OXC: inadequate seizure control (*n* = 1), non-compliance (*n* = 3), allergic skin reaction (*n* = 1); PHT: non-compliance (*n* = 1), allergic skin reaction (*n* = 1), hirsuitism (*n* = 1) **Adverse events** **Intervention 1** AEs are noted only where it led to study withdrawal. Allergic skin reaction (*n* = 1) **Comparator** Allergic skin reaction (*n* = 1); hirsuitism (*n* = 1)	**Authors' conclusions** The number of successfully treated patients was similar in both OXC and PHT groups. As far as cognitive side-effects are concerned, the results revealed no evidence favouring either AED over the other **Comments** Tests at baseline and at 12 months were the same, at 6 months parallel forms of the List Learning Test and the Trail Making Test were used The authors do not state how the data on seizure frequency were gathered. Baseline seizure data are not reported by the authors, therefore it is not possible to assess baseline differences between the two groups or change over time OXC: baseline data are reported only for the 29 participants who completed the entire 12-month follow-up PHT: the mean serum concentration was 57.1 μmol/l (SD 18.3) at 6 months and 61.3 μmol/l (SD 18.9) at 12 months The 12-month follow-up period does not include the titration phase

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
dose was individually increased until serum concentrations were 30–120 μmol/l for OXC and 40–80 μmol/l for PHT. This was followed by a 12-month maintenance period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculations** Not stated **Analysis methods** The differences between the pretreatment group means were analysed with Student's two-tailed *t*-test for independent samples. Fisher's exact test for independent samples was used for comparison of frequency differences. Neuropsychological follow-up data were analysed by repeated measures MANOVA with time as within subjects factor and drug as between subjects factor. Pearson's correlation test was used for comparison of correlations between neuropsychological test scores and the AED serum concentrations. A *p*-value of <0.01 was considered statistically significant **Length of trial/frequency of follow-up** 12 months; at 6 and 12 months	Seizure type: OXC ($n = 14$): complex partial ($n = 0$), complex partial with secondary generalisation ($n = 9$), primary generalised ($n = 2$), unclassified ($n = 3$); PHT ($n = 15$): complex partial ($n = 3$), complex partial with secondary generalisation ($n = 9$), primary generalised ($n = 2$), unclassified ($n = 1$) **Inclusion/exclusion criteria** Inclusion: newly diagnosed epilepsy; normal intellectual capacity; at least two epileptic seizures during the last 2 years or one seizure and epileptiform EEG Exclusion: progressive neurological disorders; severe cognitive defects; alcohol or drug abuse; severe psychiatric problems; other severe medical disorders			Mean serum concentration was 35.8 μmol/l (SD 10.2) at 6 months and 42.6 μmol/l (SD 12.2) at 12 months The authors report that baseline neuropsychological scores did not differ between the patient groups. There was no statistically significant interaction effect of group or time in any neuropsychological measure. The neuropsychological test scores did not correlate with AED serum concentrations The authors do not report whether the neuropsychological tests were administered in a standard sequence. They also do not appear to take into account the possible impact of mood on neuropsychological performance

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of seizure-free patients; the number of seizure-free patients during the 12-month maintenance period **Intervention 1** OXC: *n* = 9/14 **Comparator** CBZ: *n* = 11/15	**Outcome** Proportion of responders; proportion of patients seizure free or with adequate seizure control. Adequate was defined as 1–5 partial or generalised seizures during the 12-month maintenance phase **Intervention 1** OXC: *n* = 5/14 **Comparator** CBZ: *n* = 4/15	**Outcome** Stroop Test; this was used to measure sustained attention. There were two versions: Stroop I required naming the colour of dots as fast as possible and Stroop II required naming the colour of words printed in a colour other than that spelled by the letters **Intervention 1** Stroop I: baseline: mean = 31.4 (SD 7.1); 6-month follow-up: mean = 30.3 (SD 5.6); 12-month follow-up: mean = 28.7 (SD 4.1) Stroop II: baseline: mean = 63.6 (SD 25.0); 6-month follow-up: mean = 57.6 (SD 18.2); 12-month follow-up: mean = 51.4 (SD 15.9) **Comparator** Stroop I: baseline: mean = 32.3 (SD 8.8); 6-month follow-up: mean = 30.0 (SD 8.9); 12-month follow-up: mean = 30.7 (SD 10.1) Stroop II: baseline: mean = 54.3 (SD 15.6); 6-month follow-up: mean = 54.1 (SD 17.0); 12-month follow-up: mean = 50.6 (SD 14.8)	**Outcome** Trail Making Test; this was used as a measure of sustained attention. Part A required drawing a line connecting series of randomly arranged numbers in numerical sequence. Part B required drawing a line connecting numbers and letters in alternating sequence. Time to complete the test was recorded **Intervention 1** Trail Making A: baseline: mean = 41.0 (SD 12.7); 6-month follow-up: mean = 41.0 (SD 17.0); 12-month follow-up: mean = 39.4 (SD 20.0) Trail Making B: baseline: mean = 113.3 (SD 55.6); 6-month follow-up: mean = 135.4 (SD 94.8); 12-month follow-up: mean = 99.8 (SD 50.6) **Comparator** Trail Making A: baseline: mean = 43.5 (SD 10.6); 6-month follow-up: mean = 41.7 (SD 13.4); 12-month follow-up: mean = 44.1 (SD 20.4) Trail Making B: baseline: mean = 107.7 (SD 39.1); 6-month follow-up: mean = 117.7 (SD 50.8); 12-month follow-up: mean = 103.3 (SD 45.0)

continued

Outcome 5	Outcome 6
Outcome List Learning Test; a list of words was read 5 times and, after each presentation, an immediate free recall of words was asked. The score was the sum of the recalled words. The delayed recall was asked after a 1 hour delay filled with other tasks. The score was the number of words recalled after delay **Intervention 1** Immediate recall: baseline: mean = 39.4 (SD 5.7); 6-month follow-up: mean = 34.9 (SD 5.8); 12-month follow-up: mean = 39.2 (SD 4.0) Delayed recall: baseline: mean = 6.3 (SD 2.8); 6-month follow-up: mean = 4.2 (SD 3.8); 12-month follow-up: mean = 5.9 (SD 2.7) **Comparator** Immediate recall: baseline: mean = 35.7 (SD 6.0); 6-month follow-up: mean = 34.0 (SD 7.7); 12-month follow-up: mean = 37.5 (SD 5.0) Delayed recall: baseline: mean = 4.7 (SD 2.5); 6-month follow-up: mean = 4.5 (SD 2.5); 12-month follow-up: mean = 5.6 (SD 2.7)	**Outcome** Tapping; this assessed simple psychomotor speed. Tapping rate using the thumb was determined over 10 s in three trials for each hand. Total tapping score was summed from the average score in each hand **Intervention 1** Baseline: mean = 89.0 (SD 10.9); 6-month follow-up: mean = 87.2 (SD 14.1); 12-month follow-up: mean = 89.0 (SD 14.2) **Comparator** Baseline: mean = 87.0 (SD 13.2); 6-month follow-up: mean = 86.8 (SD 11.8); 12-month follow-up: mean = 88.0 (SD 10.8)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Barcs, 2000[70] **Related publications** NRR[389] **Country** Multinational **Source** Literature search **Aim** To evaluate the safety and efficacy of a broad OXC dosage range as adjunctive therapy for uncontrolled partial seizures **Type of publication** Full paper (final analysis) **Funding** Novartis Pharmaceuticals, Basel, Switzerland **Trial ID** OT/PE1 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The study consisted of an 8-week baseline phase during which patients had to have an	**Number of participants** 694 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 692): 34.5 years (SDs not reported); OXC 600 mg/day (n = 168): 34.6 years; OXC 1200 mg/day (n = 177): 33.8 years; OXC 2400 mg/day (n = 174): 35.2 years; placebo (n = 173): 34.3 years; Total (n = 692): 15–66 years; OXC 600 mg/day (n = 168): 15–65 years; OXC 1200 mg/day (n = 177): 16–64 years; OXC 2400 mg/day (n = 174): 15–66 years; placebo (n = 173): 15–65 years **Gender** Total (n = 692): men = 341, women = 351; OXC 600 mg/day (n = 168): men = 86, women = 82; OXC 1200 mg/day (n = 177): men = 80, women = 97; OXC 2400 mg/day (n = 174): men = 98, women = 76; placebo (n = 173): men = 77, women = 96 **Age at onset of seizures** Not stated **Pretrial medication** CBZ, VPA, PHT, PB, VGB, LTG, CLB, CZP, PRM	**Intervention 1** OXC; 600 mg/day; 28 weeks No. randomised: 169 No. completed: 130 **Intervention 2** OXC; 1200 mg/day; 28 weeks No. randomised: 178 No. completed: 97 **Intervention 3** OXC; 2400 mg/day; 28 weeks No. randomised: 174 No. completed: 46 **Comparator** Placebo; 28 weeks No. randomised: 173 No. completed: 124	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** OXC 600 mg/day n = 1 and OXC 1200 mg/day n = 1; both prematurely discontinued (reasons not stated) before taking any trial medication. OXC 600 mg/day (n = 168): premature discontinuation owing to AEs 11.9%, death (n = 3); OXC 1200 mg/day (n = 177): premature discontinuation due to adverse events 36.2%, death (n = 0) OXC 2400 mg/day (n = 174): premature discontinuation due to AEs 66.7%, death (n = 1); placebo (n = 173): premature discontinuation due to AEs 8.7%, death (n = 2) **Adverse events** **Intervention 1** 141/168 patients reported an AE (incidence 83.9%). Serious AEs occurred in 12/168 patients. Deaths 3/168 (1 traumatic shock, 1 cerebral haemorrhage, 1 sudden death after grand mal seizure), dizziness 42/168, headache 54/168, somnolence 33/168, ataxia 16/168, nystagmus 11/168 **Intervention 2** 160/177 patients reported an AE (incidence 90.4%). Serious AEs	**Authors' conclusions** OXC is safe and effective as adjunctive therapy in patients with uncontrolled partial seizures. The minimum effective dose was 600 mg/day. Effectiveness increased with dose, but rapid and fixed titration to high doses was associated with an increased risk of AEs. **Comments** The extensive list of exclusion criteria might limit generalisability of the findings beyond an ideal population most likely to respond with minimum AEs. It is not clear whether the end of the treatment phase for data collection was week 26 or 28 Following the observation of a large number of discontinuations due to AEs, a protocol amendment was made to allow for a blinded reduction to 1800 mg/day OXC in the 2400 mg/day group, either directly after randomisation or on the occurrence of tolerability problems or AEs. No distinction was made in the analysis between 1800 and 2400 mg/day ITT population included all patients who entered the double-blind treatment phase, started trial medication and had a valid seizure count at baseline and at

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
average of at least 4 partial seizures per month (while maintained on 1–3 concomitant AEDs) before randomisation to a 28-week double-blind treatment phase (2-week titration period of either 600 mg/day reached at 2 days, 1200 mg/day reached at 6 days or 2400 mg/day reached at 14 days, and a 24-week maintenance period). There was an optional 2-week tapering period (or continuation of treatment in an open-label extension phase) **ITT analysis performed/method** Authors state yes; not stated **Sample size calculations** Not stated **Analysis methods** Pairwise Wilcoxon rank-sum tests were used to compare percentage change in seizure frequency (the primary outcome) of each dose of OXC versus placebo. A sequentially rejective Bonferroni–Holm procedure was used to adjust for multiple testing. The secondary outcome (response) compared treatment groups using logistic regression. Explanatory variables were dose, country, baseline seizure frequency, sex, age group. Secondarily generalised seizure frequency was analysed using a Wilcoxon rank-sum test **Length of trial/frequency of follow-up** 28 weeks; 12 visits but timing not stated	The majority were taking 2 AEDs (OXC 600 mg/day 64/168; OXC 1200 mg/day 91/177; OXC 2400 mg/day 82/174; placebo 91/173) or 3 AEDs (OXC 600 mg/day 51/168; OXC 1200 mg/day 44/177; OXC 2400 mg/day 49/174; placebo 36/173) More than 70% in each group were taking CBZ (OXC 600 mg/day 122/168; OXC 1200 mg/day 130/177; OXC 2400 mg/day 135/174; placebo 123/173) **Ongoing concurrent medication** See pretrial medication **Co-morbidities** Not stated **Baseline seizure frequency** Median 28-day baseline partial seizure frequency: total (n = 692): not stated; OXC 600 mg/day (n = 168): 9.6; OXC 1200 mg/day (n = 177): 9.8; OXC 2400 mg/day (n = 174): 10.0; placebo (n = 173): 8.6 Median 28-day baseline secondarily generalised seizure frequency: total (n = 228): not stated; OXC 600 mg/day (n = 49): 3.5; OXC 1200 mg/day (n = 68): 2.0; OXC 2400 mg/day (n = 60): 2.4; placebo (n = 51): 3.5		occurred in 9/177 patients. Deaths 0, dizziness 56/177, headache 48/177, somnolence 48/177, ataxia 31/177, nystagmus 36/177 **Intervention 3** 170/174 patients reported an AE (incidence 97.7%). Serious AEs occurred in 18/174 patients. Deaths 1/174 (pulmonary embolism), dizziness 74/174, headache 40/174, somnolence 56/174, ataxia 56/174, nystagmus 41/174 **Comparator** 132/173 patients reported an AE (incidence 76.3%). Serious AEs occurred in 9/173 patients. Deaths 2/173 (1 related to seizure, 1 sudden death), dizziness 22/173, headache 41/173, somnolence 20/173, ataxia 9/173, nystagmus 7/173	least one visit during double-blind treatment Analysis of the primary outcome (reduction in partial seizure frequency) excluding the 43 patients in the 2400 mg/day group who took 1800 mg/day from the start of the double-blind phase (4 others were reduced during the treatment phase) did not change the findings (reduction 52%, $p < 0.0001$ compared with placebo) Analysis of the primary outcome (reduction in partial seizure frequency) in only patients who used CBZ at baseline showed 22, 40 and 50% reduction for 600, 1200 and 2400 mg/day, respectively, compared with 6.8% with placebo. Analysis excluding patients who were taking PHT at baseline showed 25, 43 and 49% reduction for 600, 1200 and 2400 mg/day, respectively Treatment response (secondary outcome) in the 2400 mg/day group excluding the 74% of patients who discontinued prematurely was 67% (n = 31/46) Safety was evaluated by comparing baseline data with data collected during the trial; none of the deaths was considered to be related to the trial drug. Data are

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
	Other characteristics Not stated **Inclusion/exclusion criteria** Inclusion: men and women aged 15–65 years with partial seizures (simple, complex or partial evolving to secondarily generalised; ILAE) were eligible Exclusion: pregnant/nursing women and women trying to conceive; evidence or history of generalised status epilepticus in preceding 24 months; seizures of metabolic, neoplastic or infectious origin; non-compliance; cardiovascular, respiratory, hepatic, renal, gastrointestinal, haematological, oncological, psychiatric or progressive neurological disorder; attempted suicide; substance abuse; hypersensitivity to CBZ; history of OXC treatment; laboratory abnormalities; monoamine oxidase inhibitor treatment in previous 15 days; concomitant ethosuximide and felbamate; or concomitant hormonal contraceptives			also reported for abnormal gait, tremor, vomiting, nausea, abdominal pain, diplopia, abnormal vision, vertigo, fatigue and viral infection Pharmacokinetic data are also reported

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; percentage reduction in partial seizure frequency per 28 days during the double-blind treatment phase relative to baseline **Intervention 1** Median reduction 26.45% (n = 168, ITT); p = 0.0001 versus placebo Median reduction 29.67% (n = 130, completers); p = 0.0006 versus placebo **Intervention 2** Median reduction 40.22% (n = 177, ITT); p = 0.0001 versus placebo Median reduction 43.20% (n = 97, completers); p = 0.0001 versus placebo **Intervention 3** Median reduction 49.95% (n = 174, ITT); p = 0.0001 versus placebo Median reduction 63.85% (n = 46, completers); p = 0.0001 versus placebo **Comparator** Median reduction 7.59% (n = 173, ITT) Median reduction 12.49% (n = 124, completers)	**Outcome** Proportion of responders; percentage of patients who had at least a 50% reduction in partial seizure frequency (responders) in the double-blind treatment phase relative to baseline **Intervention 1** 26.8% (n = 45/168, ITT), p = 0.0008 versus placebo **Intervention 2** 41.2% (n = 73/177, ITT), p = 0.0001 versus placebo **Intervention 3** 50.0% (n = 87/174, ITT), p = 0.0001 versus placebo **Comparator** 12.7% (n = 22/173, ITT)	**Outcome** Proportion of seizure-free patients; not defined **Intervention 1** 3% (n not stated) **Intervention 2** 10% (n not stated) **Intervention 3** 22% (n not stated) **Comparator** 0.6% (n not stated)	**Outcome** Median percentage reduction from baseline in frequency of secondarily generalised seizures per 28 days **Intervention 1** 71% **Intervention 2** 86% **Intervention 3** 94% **Comparator** 12.5% All p = 0.0001. This was calculated for patients who experienced secondarily generalised seizures during the baseline phase (600 mg/day n = 49; 1200 mg/day n = 68; 2400 mg/day n = 60; placebo n = 51)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Bill, 1997[124] **Related publications** None **Country** Multinational **Source** Literature search **Aim** To investigate the use of OXC monotherapy in adults with newly diagnosed epilepsy in a double-blind, randomised, parallel group comparison with PHT **Type of publication** Full paper (final analysis) **Funding** Ciba-Geigy and Novartis Pharma. **Trial ID** OT/F02 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** There was a retrospective baseline phase which began with the patient's initial seizure and included medical and seizure history,	**Number of participants** 287 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** OXC (n = 143): 27.1 years; PHT (n = 144): 26.6 years (SD not stated); OXC (n = 143): 16–63 years; PHT (n = 144): 15–91 years **Gender** OXC (n = 143): men = 82, women = 61; PHT (n = 144): men = 92, women = 52 **Age at onset of seizures** Duration since onset: OXC (n = 143): mean = 94.6 weeks (range = 0.4–1144); PHT (n = 144): mean = 89.4 weeks (range = 0.8–1300) **Pretrial medication** No previous AED treatment was allowed except for emergency treatment of seizures for a maximum of 3 weeks prior to trial entry **Ongoing concurrent medication** No concurrent AEDs were allowed **Co-morbidities** Not stated	**Intervention 1** OXC; 600–2100 mg/day; 48 weeks No. randomised: 143 No. completed: 87 **Comparator** PHT; 100–650 mg/day; 48 weeks No. randomised: 144 No. completed: 83	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** OXC (n = 143): protocol violation (n = 16), non-compliance (n = 13), adverse experiences (n = 5), lost to follow-up (n = 9), administrative reasons (n = 10), unsatisfactory therapeutic effect (n = 1), concomitant illness (n = 2); PHT (n = 144): protocol violation (n = 10), non-compliance (n = 10), adverse experiences (n = 16), lost to follow-up (n = 12), administrative reasons (n = 5), unsatisfactory therapeutic effect (n = 1), death (n = 2) (one patient stopped treatment and died in status epilepticus and one died due to political violence), concomitant illness (n = 4); abnormal laboratory value (HIV positive) (n = 1) **Adverse events** **Intervention 1** OXC (n = 136): AEs experienced by ≥ 5% of participants which were assessed by the investigator as being related to the trial treatment: somnolence 30.1%, headache 14.7%, dizziness 13.2%, nausea 9.6%, rash 8.8%, gum hyperplasia 1.5%, tremor 2.9%, diplopia 0.7%, acne 5.9%,	**Authors' conclusions** This trial provides further support for the efficacy and safety of OXC as first-line treatment in adults with partial seizures and GTC seizures without partial onset. In addition, the results show that OXC has significant advantages over PHT in terms of tolerability **Comments** There was also a long-term open extension to the trial which is not reported in the paper The 48-week treatment period did not include the 8-week titration period. OXC mean dose = 1028.4 mg/day; PHT mean dose 313.4 mg/day. The usual dose of PHT is 200–500 mg (although higher doses may be used). The dose range used in the trial extended beyond both upper and lower limits The authors do not specify how seizure frequency data were gathered for the retrospective phase. If the authors were relying on retrospective records or patient recall (although they do not state this) then this could be an unreliable baseline estimate of seizure frequency The authors also report data from the laboratory tests carried out

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
physical examinations, laboratory evaluations, ECG, EEG and an optional cranial CT to rule out any progressive neurological disorder. After qualifying for trial entry in the baseline phase, patients were randomised and entered the double-blind treatment phase. There was a titration phase of 8 weeks followed by a 48-week maintenance period. The titration period commenced with 300 mg/day of OXC or 100 mg/day of PHT and then gradually increased biweekly based on clinical response over the 8-week period. The titration schedule was not fixed. Patients were to be treated with a daily OXC or PHT dose (administered 3 times/day) of 450–2400 and 150–800 mg, respectively. Dose adjustments within this range were allowed in the maintenance phase based on clinical response **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculations** The authors report that the sample size was chosen to detect a significant difference at the 5% level (two-sided) with a power of 80%. Assuming seizure freedom rates of 50 and 70% for PHT and OXC, respectively, 182 patients in the maintenance period would be needed for the primary analysis **Analysis methods** The primary efficacy variable was the proportion of seizure-free patients who had at least one seizure assessment during the maintenance period. The proportion of seizure-free patients was analysed by logistic regression and a Poisson regression	**Baseline seizure frequency** Partial seizures with/without secondarily generalised seizures: OXC: $n = 84$; PHT: $n = 98$ Generalised seizures without partial onset: OXC: $n = 58$; PHT: $n = 46$ (No main type of seizure indicated $n = 1$) Total number of seizures: OXC: mean = 17.5, median = 4; PHT: mean = 20.0, median = 5 Seizure frequency per week: OXC: mean = 0.98, median = 0.20; PHT: mean = 0.84, median = 0.23 Number of patients at baseline with up to 2 seizures: OXC: $n = 34$; PHT: $n = 33$ Number of patients at baseline with 3–10 seizures: OXC: $n = 68$; PHT: $n = 71$ Number of patients at baseline with 11–99 seizures: OXC: $n = 35$; PHT: $n = 35$ Number of patients at baseline with ≥ 100 seizures: OXC: $n = 6$; PHT: $n = 5$ **Other characteristics** Race: OXC ($n = 143$): white ($n = 92$), black ($n = 22$), other ($n = 49$); PHT ($n = 144$): white ($n = 68$), black ($n = 23$), other ($n = 53$) **Inclusion/exclusion criteria** Inclusion: aged 15–65 years; newly diagnosed epilepsy with partial seizures or GTC seizures; a minimum of two seizures separated by at least 48 hours within the 6 months		nervousness 1.5%, nystagmus 2.2% Proportion of participants experiencing at least one adverse reaction (regardless of relationship to trial drug): 114/136 **Comparator** PHT ($n = 142$): AEs experienced by ≥ 5% of participants which were assessed by the investigator as being related to the trial treatment: somnolence 28.9%, headache 19.0%, dizziness 15.5%, nausea 11.3%, rash 11.3%, gum hyperplasia 12.7%, tremor 2.9%, diplopia 7.0%, acne 7.7%, nervousness 6.3%, nystagmus 5.6% Proportion of participants experiencing at least one adverse reaction (regardless of relationship to trial drug): 122/142	but these have not been extracted. Out of the 238 participants who reached the maintenance period, 237 (OXC $n = 118$; PHT $n = 119$), who had at least one seizure assessment during this period, were included in the efficacy analysis There were no significant differences between the treatment groups in the efficacy analysis

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
was used for the analysis of seizure counts. Both models accounted for duration of treatment, baseline seizure frequency, baseline seizure type, sex, age and country differences. The primary tolerability analysis was a comparison of patients who prematurely discontinued the trial because of adverse experiences. A log-rank test for treatment group differences in the time to premature discontinuation due to adverse experiences was used in the statistical analysis. Patients with premature discontinuations due to other reasons were regarded as censored in this analysis. Clinical utility was assessed by comparing treatment retention, i.e. the rate of premature discontinuations due to any reason, and was analysed using a logistic regression model **Length of trial/frequency of follow-up** 56 weeks; return visits were scheduled every 2 weeks during the titration period and every 8 weeks during the maintenance period	preceding trial entry; no previous AED treatment was allowed except for emergency treatment of seizures for a maximum of 3 weeks prior to trial entry Exclusion: pregnancy or risk of becoming pregnant; history of status epilepticus; severe psychiatric illness or severe mental retardation; progressive neurological disorder; alcoholism; drug abuse; any significant organic disease			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of seizure-free patients; the number of patients who were seizure free during the maintenance period of the trial **Intervention 1** OXC: 70/118 (59.3%) OXC/PHT seizure freedom OR calculated from the logistic regression model was 0.90 (95% CI: 0.52 to 1.57)	**Outcome** Seizure frequency; reported as the mean and median seizure frequency per week and total number of seizures during maintenance period **Intervention 1** Seizure frequency/week (n = 118): mean = 0.08 (SD 0.26), median = 0	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; physicians' and patients' overall evaluation of therapeutic effect on a 4-point scale **Intervention 1** Physician evaluation: Mann–Whitney–Wilcoxon; p = 0.19	**Outcome** Time to exit/withdrawal; defined as the time to premature discontinuation **Intervention 1** The log-rank test on time to premature discontinuation showed a statistically significant difference between the treatment groups (p = 0.02) in favour of OXC (data not reported)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Proportion of seizure-free patients with partial seizures (with or without secondarily generalised seizures): 56% Proportion of seizure-free patients with generalised seizures (without partial onset): 64% The proportion of seizure-free patients with secondarily generalised seizures as their main seizure type (OXC, *n* = 18; VPA, *n* = 16) differed between the treatment groups (OXC, 28%; VPA, 63%) **Comparator** PHT: 69/119 (58%) Proportion of seizure-free patients with partial seizures (with or without secondarily generalised seizures): 53% Proportion of seizure-free patients with generalised seizures (without partial onset): 68%	Number of seizures (*n* = 118): mean = 3.57, median = 0 OXC/PHT seizure frequency OR calculated from the Poisson regression model was 1.92 (95% CI: 0.91 to 4.03) **Comparator** Seizure frequency/week (*n* = 119): mean = 0.06 (SD 0.15), median = 0 Number of seizures (*n* = 106): mean = 2.13, median = 0	Patient evaluation: Mann–Whitney–Wilcoxon; *p* = 0.62 (data not reported) **Comparator** Not reported	**Comparator** Not reported

Outcome 5
Outcome Physicians' and patients' overall evaluation of tolerability on a 4-point scale **Intervention 1** OXC (*n* = 118) Physician assessment of excellent or good: 86.5% (*p* = 0.032) Patient assessment of excellent or good: 79.7% (*p* = 0.026) **Comparator** PHT (*n* = 119) Physician assessment of excellent or good: 74.8% Patient assessment of excellent or good: 67.2%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Christe, 1997[123] **Related publications** None **Country** European **Source** Literature search **Aim** To investigate the use of OXC as monotherapy in adults with newly diagnosed epilepsy in a double-blind, randomised, parallel group comparison with VPA **Type of publication** Full paper (final analysis) **Funding** Ciba-Geigy **Trial ID** OT/F01 **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a retrospective baseline phase which began with the patient's initial seizure and included medical and seizure history, physical	**Number of participants** 249 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** OXC (n = 128): 32.45 years; VPA (n = 121): 32.47 years (SD not stated); OXC (n = 128): 15–65 years; VPA (n = 121): 15–64 years **Gender** OXC (n = 128): men = 60, women = 68; VPA (n = 121): men = 67, women = 54 **Age at onset of seizures** Duration since onset: OXC (n = 128): mean = 178 weeks (range = 0.4–1560); VPA (n = 121): mean = 181 weeks (range = 4–2496) **Pretrial medication** No previous AED treatment was allowed except for emergency treatment of seizures for a maximum of 3 weeks prior to trial entry **Ongoing concurrent medication** No concurrent AEDs were allowed	**Intervention 1** OXC; 600–2400 mg/day; 48 weeks No. randomised: 128 No. completed: 76 **Comparator** VPA; 600–2700 mg/day; 48 weeks No. randomised: 121 No. completed: 80	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** OXC: adverse experiences (n = 15), non-compliance (n = 14), unsatisfactory therapeutic effect (n = 6); lost to follow-up (n = 4), protocol violation (n = 7), administrative reasons (n = 3), concomitant illness (n = 2), death (n = 1) VPA: adverse experiences (n = 10), non-compliance (n = 7), unsatisfactory therapeutic effect (n = 6), lost to follow-up (n = 7), protocol violation (n = 3), administrative reasons (n = 5), concomitant illness (n = 2), abnormal laboratory values (n = 1) **Adverse events** **Intervention 1** AEs with a frequency of at least 5% in a treatment group: somnolence 14.8%, weight increase 12.5%, fatigue 12.5%, headache 10.2%, alopecia 8.6%, dizziness 10.2%, nausea 8.6%, tremor 3.9%, abdominal pain 6.3%, impaired concentration 5.5%, increased appetite 1.6%, diarrhoea 2.3%, death due to road traffic accident (n = 1) Proportion of participants experiencing at least one adverse	**Authors' conclusions** There was no statistically significant difference between the treatment groups with respect to the total number of premature discontinuations or those due to adverse experiences. This trial provides support for the efficacy and safety of OXC as first-line treatment on adults with partial seizures and GTC seizures **Comments** There was also a long-term open extension to the trial which is not reported in the paper The length of treatment was 48 weeks excluding an 8-week titration phase Three patients on OXC and five patients on VPA took a daily dose <900 mg for at least a part of the maintenance treatment. Three patients on VPA took a daily dose >2400 mg for at least part of the maintenance treatment Mean OXC dose at the start of the maintenance period was 1052.8 mg (range = 600–2400 mg). Median daily dose of OXC was 900 mg; mean dose of VPA was 1146.2 mg (range = 600–2700). Median daily dose of VPA was 900 mg Out of the 214 participants who reached the maintenance period,

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
examinations, laboratory evaluations, ECG, EEG and an optional cranial CT to rule out any progressive neurological disorder. After qualifying for trial entry in the baseline phase, patients were randomised and entered the double-blind treatment phase. There was a titration phase of 8 weeks followed by a 48-week maintenance period. The titration period commenced with 300 mg of OXC or VPA and then gradually increased biweekly based on clinical response over the 8-week period. The titration schedule was not fixed. Patients were to be treated with OXC or VPA (administered 3 times per day) of 900–2400 mg/day. Dose adjustments within this range were allowed in the maintenance phase based on clinical response **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculations** The authors state that the protocol specified that OXC would be regarded to be at least as effective as VPA if the 95% CI for the OXC/VPA seizure freedom OR was >0.4286. This arbitrary criterion used for the sample size calculation corresponds to an OXC seizure freedom rate of ≥ 50% if the observed rate for VPA is 70%. The sample size was chosen to detect a significant difference at the two-sided 5% level with a power of 80%. The authors state that assuming seizure freedom rates of 70 and 50% for VPA and OXC, respectively, 182 patients would be needed in the maintenance period for the primary analysis **Analysis methods** The primary efficacy variable was the proportion of seizure-free patients who had at least one	**Co-morbidities** Not stated **Baseline seizure frequency** Partial seizures with/without secondarily generalised seizures: OXC: $n = 76$; VPA: $n = 78$ Generalised seizures without partial onset: OXC: $n = 52$; VPA: $n = 43$ Total number of seizures: OXC: mean = 26.3, median = 5; VPA: mean = 157.9, median = 9 Seizure frequency per week: OXC: mean = 0.58, median = 0.13; VPA: mean = 1.09, median = 0.25 Number of patients at baseline with up to 2 seizures: OXC: $n = 28$; VPA: $n = 21$ Number of patients at baseline with 3–10 seizures: OXC: $n = 59$; VPA: $n = 45$ Number of patients at baseline with 11–99 seizures: OXC: $n = 31$; VPA: $n = 32$ Number of patients at baseline with ≥ 100 seizures: OXC: $n = 10$; VPA: $n = 23$ **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: 15–65 years; newly diagnosed epilepsy with partial seizures or GTC seizures without partial onset; a minimum of two seizures separated by at least 48 hours		reaction (regardless of relationship to trial drug): (115/128) **Comparator** Somnolence 19.8%, weight increase 21.5%, fatigue 15.7%, headache 17.4%, alopecia 17.4, dizziness 11.6%, nausea 11.6%, tremor 15.7%, abdominal pain 7.4%, impaired concentration 4.1%, increased appetite 6.6%, diarrhoea 5.0% Proportion of participants experiencing at least one adverse reaction (regardless of relationship to trial drug): (106/121)	212 (OXC $n = 106$; VPA $n = 106$) who had at least one seizure assessment during this period were included in the efficacy analysis There were no significant differences between the treatment groups in the efficacy or tolerability analysis The authors also report laboratory tests data but these have not been extracted

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
seizure assessment during the maintenance period. The proportion of seizure-free patients was analysed by logistic regression and a Poisson regression was used for the analysis of seizure counts. Both models accounted for duration of treatment, baseline seizure frequency, baseline seizure type, sex, age and country differences. The primary tolerability variable was a comparison of patients who prematurely discontinued the trial because of adverse experiences. A log-rank test for treatment group differences in the time to premature discontinuation due to adverse experiences was used in the statistical analysis. Patients with premature discontinuations due to other reasons were regarded as censored in this analysis. Clinical utility was assessed by comparing treatment retention, that is, the rate of premature discontinuations due to any reason, and was analysed using a logistic regression model **Length of trial/frequency of follow-up** 56 weeks; return visits were scheduled every 2 weeks during the titration period and every 8 weeks during maintenance	within the 6 months preceding trial entry; no previous AED treatment was allowed except for emergency treatment of seizures for a maximum of 3 weeks prior to trial entry Exclusion: pregnancy or risk of becoming pregnant; history of status epilepticus; severe psychiatric illness or severe mental retardation; progressive neurological disorder; alcoholism; drug abuse; any significant organic disease			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of seizure-free patients; seizure free during maintenance period **Intervention 1** OXC: 60/106 (56.6%) Patients with 0 seizures (n = 60); patients with 1 seizure (n = 16); patients with 2–15 seizures (n = 24); patients with >15 seizures (n = 6)	**Outcome** Seizure frequency; seizure frequency per week and total number of seizures during maintenance period **Intervention 1** Seizure frequency/week: OXC (n = 106): mean = 0.17 (SD 0.81), median = 0	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; reported as physicians' and patients' overall evaluation of therapeutic effect on a 4-point scale	**Outcome** Time to exit/withdrawal; defined as time to premature discontinuation **Intervention 1** The log-rank test on time to premature discontinuation showed no difference between the treatment groups (p = 0.33) (data not reported)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
OXC/VPA seizure freedom OR calculated from the logistic regression model was 0.80 (95% CI: 0.44 to 1.50) Proportion of seizure-free patients with partial seizures (with or without secondarily generalised seizures): 46% Proportion of seizure-free patients with generalised seizures (without partial onset): 72% The proportion of seizure-free patients with secondarily generalised seizures as their main seizure type (OXC, $n = 18$; VPA, $n = 16$) differed between the treatment groups (OXC, 28%; VPA, 63%) **Comparator** VPA ($n = 106$): 57/106 (53.8%) Patients with 1 seizure ($n = 7$); patients with 2–15 seizures ($n = 30$); patients with >15 seizures ($n = 12$) Proportion of seizure-free patients with partial seizures (with or without secondarily generalised seizures): 48% Proportion of seizure-free patients with generalised seizures (without partial onset): 62%	Number of seizures: OXC ($n = 106$): mean = 3.57, median = 0 OXC/VPA seizure frequency OR calculated from the Poisson regression model was 0.93 (95% CI: 0.38 to 2.29) **Comparator** Seizure frequency/week: VPA ($n = 106$): mean = 0.40 (SD 1.95), median = 0 Number of seizures: VPA ($n = 106$): mean = 10.96, median = 0	**Intervention 1** Physician evaluation: Mann–Whitney–Wilcoxon; $p = 0.96$ Patient evaluation: Mann–Whitney–Wilcoxon; $p = 0.28$ (data not reported) **Comparator** Not reported	**Comparator** Not reported
Outcome 5			
Outcome Physicians' and patients' overall evaluation of tolerability on a 4-point scale **Intervention 1** OXC ($n = 106$) Physician assessment of excellent or good: 86.8% Patient assessment of excellent or good: 80.2% **Comparator** VPA ($n = 106$) Physician assessment of excellent or good: 77.4% Patient assessment of excellent or good: 73.6%			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Dam, 1989[125] **Related publications** None **Country** Multinational **Source** Literature search **Aim** To assess treatment with either OXC or CBZ in patients with newly diagnosed epilepsy, using a double-blind multi-centre study **Type of publication** Full paper (final analysis) **Funding** Ciba-Geigy **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** Patients were randomly allocated to treatment with OXC or CBZ. There was a	**Number of participants** 235 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** OXC (n = 94): median = 32.5 years; CBZ (n = 100): median = 33.0 years; OXC (n = 94): 14–63 years; CBZ (n = 100): 15–63 years **Gender** OXC (n = 94): men = 45, women = 49; CBZ (n = 100): men = 51, women = 49 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** None stated **Co-morbidities** Not stated **Baseline seizure frequency** See the outcome for change in seizure frequency **Other characteristics** Not stated	**Intervention 1** OXC; 300–1800 mg/day; 48 weeks No. randomised: 94 No. completed: 79 **Comparator** CBZ; 300–1400 mg/day; 48 weeks No. randomised: 100 No. completed: 73	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** 42 patients discontinued the trial for reasons judged not related to the treatment; however, the information is not provided for each patient group Total: protocol violations (n = 7), poor compliance (n = 10), administrative reasons (n = 24) OXC: insufficient efficacy (n = 2), poor tolerability (n = 13); CBZ: insufficient efficacy (n = 2), poor tolerability (n = 25) **Adverse events** **Intervention 1** OXC (n = 92): number of patients with side-effects: n = 63; number of side-effects: n = 175; mean number of side-effects per patient with side-effects: 2.8; severe side-effects: n = 13 (p = 0.04) AEs necessitating withdrawal of trial medication: allergy (n = 9), dizziness (n = 2), tiredness/fatigue (n = 1), psychic lability (n = 1) **Comparator** CBZ (n = 98): number of patients with side-effects: n = 73; number of side-effects: n = 252; mean number of side-effects per patient with side-effects: 3.5; severe side-effects: n = 25	**Authors' conclusions** The authors consider OXC to be a valuable alternative to CBZ, particularly in patients who develop side-effects which prevent optimal seizure control **Comments** The authors do not specify how data on seizure frequency were gathered Although the inclusion criterion was 15–65 years, the lower limit of the age range for the OXC group was 14 years The 48-week treatment period does not include the titration phase. The authors do not specify how many of the 235 patients were randomised to each of the two treatment groups The lowest dose of CBZ of 300 mg/day was less than the usual recommended lowest dose of 800 mg/day. The lowest dose of OXC was less than the lowest usual recommended dose of 600 mg/day The authors did not specify a minimum number of seizures for entry into the trial. The lower range for number of seizures at baseline was zero with 16% of participants in each group seizure free at baseline (note, however, that the median number of seizures at baseline was 1).

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
4-week baseline before the start of the trial during which seizures were recorded (it is not clear whether this was before or after randomisation). This was followed by a titration period of 4–8 weeks with a starting dose of 300 mg/day for OXC and 200 mg/day for CBZ. The daily dose was then adjusted individually at weekly intervals in order to obtain, in the opinion of the investigator, the best possible therapeutic effect associated with satisfactory tolerability. When the optimal dose was achieved, treatment was continued using that dose for a 12-week maintenance period (maintenance period I). This was followed by a further 36-week maintenance period (maintenance period II) for patients who were well controlled and willing to continue the study **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculations** Not stated **Analysis methods** For comparison of frequencies, the Fisher's exact test or the χ^2 test was used. Treatment groups were compared by the Wilcoxon 2-sample test, on the assumption that variables were continuously distributed. Changes with treatment groups were tested by the Wilcoxon matched-pair signed rank test. All tests were two-tailed and the 5% significance level was used **Length of trial/frequency of follow-up** 56 weeks; every week during titration; every second week during the first month	**Inclusion/exclusion criteria** Inclusion: aged 15–65 years; newly diagnosed and previously untreated epilepsy; primary generalised and partial seizures with or without secondary generalisation (as defined by the ICS) Exclusion: pregnancy or trying to become pregnant; patients with known heart, liver, kidney and thyroid disorders; patients with abnormally low leucocyte and/or platelet counts; inoperable tumours; known hypersensitivity to CBZ or tricyclic antidepressants; patients who were being treated with drugs known to interact with CBZ		AEs necessitating withdrawal of trial medication: allergy (n = 16), visual disturbances (n = 1), headache (n = 1), tiredness/ fatigue (n = 3), nausea (n = 1), diarrhoea (n = 2), loss of hair (n = 2), leucopenia (n = 1), liver parameters increased (n = 1)	Therefore, it would not have been possible to detect an improvement of number of seizures in 32% of the total sample Changes in EEG tracing with regard to epileptiform activity between baseline and the end of each maintenance period found no correlation between the therapeutic effect and EEG changes, nor were there any differences between the two drugs in these respects. There were no significant differences between the two treatment groups on any of the efficacy measures

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
of the maintenance period and thereafter monthly for maintenance period I; every third month for maintenance period II				
Results				

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure frequency; reported as the mean and median number of seizures per month at baseline and during treatment **Intervention 1** OXC (n = 83) Baseline: mean = 2.9 (SD 7.0), median = 1 (range, 0–60) Follow-up: mean = 0.4 (SD 3.0), median = 0 (range, 0–27) **Comparator** CBZ (n = 82) Baseline: mean = 5.8 (SD 14.7), median = 1 (range, 0–99) Follow-up: mean = 0.3 (SD 1.4), median = 0 (range, 0–12)	**Outcome** Proportion of seizure-free patients; number of seizure-free patients at baseline and follow-up **Intervention 1** Baseline: n = 13/83 Follow-up: n = 43/83 **Comparator** Baseline: n = 13/82 Follow-up: n = 49/82	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; global evaluation of therapeutic efficacy by the investigator at the end of each maintenance period **Intervention 1** OXC (n = 80) Efficacy: none: 3%; minimal: 1%; good: 41%; excellent: 55% **Comparator** CBZ (n = 71) Efficacy: none: 3%; minimal: 0%; good: 38%; excellent: 59%	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; physician global evaluation of tolerability at the end of the maintenance phases **Intervention 1** Very good or good: n = 76 (84%) Poor or very poor: n = 15 (10%) **Comparator** Very good or good: n = 69 (73%) Poor or very poor: n = 26 (27%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Loiseau, 1998[72] [Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Reinikainen, 1987[115] **Related publications** Preliminary paper[391] **Country** Finland **Source** Literature search **Aim** The antiepileptic efficacy and side-effects of OXC, a new CBZ derivative, were evaluated in a double-blind study **Type of publication** Full paper (final analysis) **Funding** Ciba-Geigy **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient (1 inpatient) **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** Patients currently receiving PHT monotherapy were randomised to receive OXC or CBZ. There was a 6–12 week titration phase during which the CBZ dose	**Number of participants** 40 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** The authors provide mean age by gender group but not by treatment group. Males: mean age = 40 years; females: mean age = 38 years; total (n = 40): 18–76 years **Gender** Total (n = 40): men = 21, women = 19 (not stated for each treatment group) **Age at onset of seizures** Duration of epilepsy: mean = 12 years (range 2–40 years) (not stated for each treatment group) **Pretrial medication** PHT: mean dose = 296 mg/day (SD 91) (range 200–600 mg/day); mean duration of therapy = 8 years (range 2–20 years) **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Seizure frequency not stated	**Intervention 1** OXC; 600–900 mg/day; 56–58 weeks No. randomised: NS No. completed: 16 **Comparator** CBZ; 400–800 mg/day; 48–50 weeks No. randomised: NS No. completed: 18	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Increased seizure frequency (n = 2, one from each treatment group), poor compliance (n = 2), patient withdrawal (n = 1), inpatient moved to another hospital (n = 1) **Adverse events** **Intervention 1** OXC (n = 19): sedation/drowsiness (n = 6); dizziness or vertigo (n = 1), nystagmus (n = 1) OXC vs CBZ ($p < 0.05$) **Comparator** CBZ (n = 17): sedation/drowsiness (n = 7), dizziness or vertigo (n = 6), headache (n = 1), nystagmus (n = 1), nausea (n = 1), prurigo (n = 1), paraesthesia (n = 1), menstruation disturbance (n = 1), accommodation disturbance (n = 1)	**Authors' conclusions** The seizure frequencies on the trial drugs were not significantly different and the antiepileptic efficacy of OXC was comparable to that of CBZ. The incidence of side-effects during the initiation phase was lower with OXC, suggesting better tolerability of OXC than CBZ **Comments** The authors do not specify how data on seizure frequency were gathered during the maintenance period In addition to including patients with unsatisfactory seizure control, patients with unsatisfactory side-effects on PHT but satisfactory seizure control were included in the study. Five patients in both treatment groups had been seizure free 1 year prior to the trial. This could affect the possibility of detecting a treatment effect Forty patients were randomised to the two treatment groups, but the authors do not specify how many were randomised to each group One inpatient was included in the study

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
was gradually increased from 200 to between 400 and 800 mg/day and OXC from 300 to between 600 and 12 mg/day depending on clinical condition. PHT was then withdrawn gradually at weekly intervals during the next 4–8 weeks. This was followed by a 48–50-week maintenance period. The dosage was increased by 0.5 or 1 tablet (300 mg OXC; 200 mg CBZ) if seizure frequency increased and the dosage was lowered when dictated by AEs. The aim was to reach at least therapeutic effect with the test drug compared with PHT **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculations** Not stated **Analysis methods** For statistical analysis the Wilcoxon non-parametric rank sum test and the Mann–Whitney *U*-test were used **Length of trial/frequency of follow-up** 48–50 weeks; weekly during the titration phase, every second week during the first month of the maintenance phase then monthly during the first 3 months and finally every 3 months of the treatment	Seizure type ($n = 36$) GTC seizures: CBZ ($n = 4$); OXC ($n = 6$) Partial secondarily generalised seizures: CBZ ($n = 7$); OXC ($n = 4$) Simple or complex partial seizures: CBZ ($n = 3$); OXC ($n = 1$) Mixed seizure types: CBZ ($n = 4$); OXC ($n = 5$) Unclassifiable seizures: CBZ ($n = 1$); OXC ($n = 1$) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: adult patients with chronic epilepsy on PHT monotherapy with unsatisfactory seizure control or unwanted side-effects. Patients were supervised by two of the authors for at least 1 year prior to the trial Exclusion criteria: pregnancy or a desire to become pregnant; organic heart disease, especially atrioventricular block, liver, kidney or thyroid disease; abnormally low leucocyte or platelet counts; inoperable tumours; known hypersensitivity to tricyclic antidepressants or CBZ; uncooperative patients; patients being treated concomitantly with oral anticoagulants, propoxyphene and dextropropoxyphene, tetracyclines, clofibrate, monoamine oxidase inhibitors and tricyclic antidepressants			The 48–50-week follow-up period does not include the titration phase The dose of CBZ (400–800 mg/day) received by participants was lower than the usual recommended dose of 800–1200 mg/day The mean seizure frequency for each group excluded participants who entered the trial due to side-effects. These patients were seizure free in the 1 year prior to the trial and remained so during the trial Between the treatment groups there was no statistically significant difference in the seizure frequency The authors report that there was an overall reduction in seizure frequency in both treatment groups compared with PHT monotherapy (the data are not reported); however, seizure frequency during PHT monotherapy was gathered retrospectively AEs are reported for 36 patients, but the number in each treatment group is not specified The authors also report data from laboratory tests, but these have not been extracted

continued

Results
Outcome 1
Outcome Seizure frequency; reported as mean number of seizures during the maintenance phase **Intervention 1** OXC (*n* = 11): mean = 1.6 (SE 0.6) **Comparator** CBZ (*n* = 13): mean = 1.5 (SE 0.5)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sachdeo, 1998[111] **Related publications** Novartis NICE submission[263] **Country** USA **Source** Industry submission **Aim** To evaluate the safety and efficacy of OXC monotherapy versus placebo **Type of publication** Industry trial report **Funding** Novartis Pharmaceuticals UK **Trial ID** 025 **Study design** Monotherapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Sequential numbers; after pretrial period **Details of pretrial period** The trial consisted of an 8-week baseline phase, a 90-day double-blind treatment phase (6 days titration and 84 days maintenance) and a long-term extension phase. Patients randomised to the OXC	**Number of participants** 67 **Type of epilepsy** Newly diagnosed **Type of seizures** Partial onset **Mean age/age range** Total (n = 67): 34.7 years (SD 15.2 years); OXC (n = 32): 32.7 years (SD 15.6 years); placebo (n = 35): 36.5 years (SD 14.7 years); total (n = 67): 8–69 years; OXC (n = 32): 8–63 years; placebo (n = 35): 10–69 years **Gender** Total (n = 67): men = 33, women = 34; OXC (n = 32): men = 16, women = 16; placebo (n = 35): men = 17, women = 18 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Reported by at least 10% of patients in either treatment group during the double-blind treatment phase: OXC (n = 32): fluoxetine (n = 1), ibuprofen (n = 6), multivitamins (n = 6), naproxen (n = 1), omeprazole (n = 1), paracetamol (n = 8); placebo (n = 35): fluoxetine (n = 6), ibuprofen (n = 8),	**Intervention 1** OXC; 1200 mg/day; 90 days No. randomised: 32 No. completed: 17 **Comparator** Placebo; 90 days No. randomised: 35 No. completed: 18	**Withdrawals prerandomisation** Not stated. **Withdrawals postrandomisation** OXC: AEs (n = 3), other (n = 7), entered open-label phase before completing visit 6 (n = 5); placebo: AEs (n = 2), other (n = 2), entered open-label phase before completing visit 6 (n = 13) **Adverse events** **Intervention 1** 25/32 (78%) of patients reported ≥ 1 AE Incidence of AEs reported during the double-blind treatment phase by 3 or more patients in either treatment group: OXC (n = 32): dizziness (25%), fatigue (22%), headache (16%), nausea (13%), upper respiratory infection (13%), viral infection (12%), somnolence (2%), vomiting (1%) Severe AEs: severe personality disorder (n = 1) **Comparator** 30/35 (86%) reported ≥ 1 AE Incidence of AEs reported during the double-blind treatment phase by 3 or more patients in either treatment group: placebo (n = 35): dizziness (2.9%) headache (11.4%), somnolence	**Authors' conclusions** The results of this trial support the efficacy of OXC monotherapy in previously untreated patients with recent-onset partial seizures which includes the seizure subtypes of simple, complex and partial seizures evolving to secondarily generalised seizures **Comments** Data extracted from original trial data Patients unable to tolerate the 1200 mg/day OXC dose were allowed to have their dosage decreased to 900 mg/day at visit 3. Thereafter the dose of the trial drug was to remain stable throughout the maintenance period No significant relationship was observed between plasma concentrations of the 10-monohydroxy metabolite (MHD) of oxcarbazepine and the primary efficacy variable, time to first seizure, or the incidence of the most common adverse experiences reported in this trial

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
group were started on an initial OXC dose of 600 mg/day on days 1 and 2, and were titrated to 900 mg/day on days 3 and 4 and 1200 mg/day on days 5 and 6. To qualify, patients had at least 2 documented seizures per month during the baseline phase. Patients who completed the trial or who had one seizure were classed as completers and were eligible to enter the long-term extension phase **ITT analysis performed/method** Authors state yes; not stated **Sample size calculations** The sample size was calculated based on the time to first seizure for detecting a 35% difference between the OXC and placebo treatment groups in the percentage of patients who were seizure free during the double-blind treatment phase, assuming a seizure-free rate during the double-blind treatment phase of 50 and 15% in the OXC and placebo groups, respectively. Using a 2-sided log-rank test with a significance level of 0.05 and a statistical power of 85%, it was determined that approximately 32 patients per treatment group were necessary **Analysis methods** A log-rank test was used to analyse the primary efficacy variable (time to first seizure) and Kaplan–Meier survival curves were computed. Secondary statistical analyses were performed using Cox's proportional hazards regression model, with treatment, centre and baseline seizure frequency per 28 days as explanatory	multivitamins (n = 7), naproxen (n = 5), omeprazole (n = 4), paracetamol (n = 7) **Co-morbidities** Not stated **Baseline seizure frequency** Median seizure frequency per 28 days: total (n = 67): 5.0 (0.5–220.6); OXC (n = 32): 5.0 (2.0–45.6); placebo (n = 35): 5.5 (0.5–220.6) **Other characteristics** Mean weight: total (n = 67): 72.9 kg (SD 20.2 kg), range 26.3–119.0 kg; OXC (n = 32): 69.4 kg (SD 16.9 kg), range 26.3–103.0 kg; placebo (n = 35): 76.1 kg (SD 22.6 kg), range 42.2–119.0kg **Inclusion/exclusion criteria** Inclusion: participants were male or female outpatients, ≥ 10 years, who were seizure free for at least 1 year without therapy prior to the current seizure onset, and who were not treated with a standard AED for at least 90 days prior to randomisation. To qualify, patients had at least 2 documented seizures per month during the baseline phase (56 days) Exclusion: patients with pseudoseizures or other types of treatable seizure, generalised status epilepticus in the past 6 months, cluster seizures, progressive disorders, poor compliance history or		(11.4%), paraesthesia (8.6%), upper respiratory tract infection (n = 2.9%), nausea (17.1%), vomiting (8.6%), increased appetite (8.6%), fatigue (14.3%), viral infections (11.4%) Severe AEs: severe syncope (n = 1), severe dyspepsia (n = 1), severe dry mouth (n = 1), severe arthralgia (n = 1)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
variables, with and without treatment × baseline seizure interaction **Length of trial/frequency of follow-up** 90 days; patient visits were once at screening and on days 0, 7, 35, 63 and 91 of the double-blind period	inability to comply with recordkeeping, significant history of medical disease in the past 2 years, malignancy in the past 5 years, clinically significant ECG abnormalities, history of suicide or mental disorders in the past 6 months, alcohol or drug abuse, use of various other drugs, recent blood donation (within the past 30 days). Female patients of childbearing potential not practising reliable contraception, nursing, or pregnant, were excluded			

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Time to first seizure; median time to first seizure (time at which 50% of the patients had their first seizure) from first dose of medication **Intervention 1** OXB: 11.67days, log-rank test $p = 0.0457$ (OXC vs placebo) **Comparator** Placebo: 3.23 days	**Outcome** Change in seizure frequency; mean (SD) percentage change from baseline in the number of seizures per 28 days **Intervention 1** OXC ($n = 32$): –28.3% (SD 108.8), median = –89.1% Mean difference (mean OXC group minus mean for placebo group) –39.7; $p = 0.033$ **Comparator** Placebo ($n = 35$): 11.4% (SD 127.1), median = –37.4%	**Outcome** Proportion of seizure-free patients; the number of participants who were seizure free during the double-blind treatment phase **Intervention 1** OXC: $n = 11/32$ (34.4%), $p = 0.073$ (OXC vs placebo) **Comparator** Placebo: $n = 5/35$ (14.3%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Schachter, 1999[78] **Related publications** Letter[392] **Country** USA **Source** Literature search **Aim** To evaluate the efficacy and safety of OXC in a placebo-controlled trial **Type of publication** Full paper (final analysis) **Funding** Novartis Pharmaceuticals UK **Trial ID** Novartis 004 **Study design** Monotherapy; new vs placebo; parallel trial; superiority trial **Setting** Inpatient **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** Prior to randomisation, prospective participants underwent inpatient EEG/video monitoring to confirm the presence of partial seizures in addition to physical and neurological examinations during which	**Number of participants** 102 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 102): 33 years; OXC (n = 51): 33 years; placebo (n = 51): 34 years; total (n = 102): 11–62 years (not stated for treatment groups) **Gender** Total (n = 102): men = 56, women = 46; OXC (n = 51): men = 31, women = 20; placebo (n = 51): men = 25, women = 26 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Lorazepam: total (n = 102): n = 92; OXC (n = 51): n = 45; placebo (n = 51): n = 47. Used in the period 48 hours before or 18 hours after randomisation **Co-morbidities** Not stated	**Intervention 1** OXC; 2400 mg/day; 10 days No. randomised: 51 No. completed: 48 **Comparator** Placebo; 10 days No. randomised: 51 No. completed: 49	**Withdrawals prerandomisation** Not applicable **Withdrawals postrandomisation** OXC (n = 51): drop-out [n = 3 due to transient rash (1), post-ictal psychosis (1), administrative reasons (1)]; placebo (n = 51): drop-out (n = 2, all due to administrative reasons) **Adverse events** **Intervention 1** AEs experienced by at least 10% of patients who received OXC: Total number with AEs (n = 38) Nervous system (n = 23): headache (n = 10), dizziness (n = 9), somnolence (n = 8) Gastrointestinal system (n = 21): nausea (n = 10), vomiting (n = 5) Skin (n = 12): pruritus (n = 9) Special senses (n = 8): diplopia (n = 6) Body as a whole (n = 7): fatigue (n = 5) **Comparator** AEs experienced by at least 10% of patients who received placebo: Total number with AEs (n = 29) Nervous system (n = 20): headache (n = 10), dizziness (n = 6), somnolence (n = 0) Gastrointestinal system (n = 9): nausea (n = 3), vomiting (n = 2) Skin (n = 6): pruritus (n = 4): diplopia (n = 0)	**Authors' conclusions** These results demonstrate that OXC given as monotherapy is effective and safe for the treatment of partial seizures in this paradigm **Comments** The authors report that statistical analyses were carried out on the ITT population Included in the 10-day treatment/follow-up phase there was a 1-day titration period. A very short titration period for OXC was used in this study Owing to AEs, seven patients received an OXC dose below the maximum target dose: two received 1200 mg/day; four received 1800 mg/day; the daily dose for one patient was increased again to 2400 mg without recurrence of AEs This study was carried out on patients who were being evaluated for possible surgery for their seizures. These may not be typical epilepsy patients, therefore the applicability of the findings may be limited

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
time other AEDs were discontinued. All AEDs were discontinued at least 48 hours before randomisation, except for lorazepam, which could be administered in dosages up to 8 mg/day if necessary to maintain seizure frequency in a safe range as defined by each investigator. Patients still meeting the eligibility criteria (see below) were randomised to OXC or placebo for a maximum of 10 days. Doses were taken every 12 hours. Patients randomised to OXC received 1500 mg on day 1 and 2400 mg/day days 2–10. If a patient experienced intolerable AEs, the dose was reduced by 1800 mg or 1200 mg daily. Participants exited the trial by completing the 10-day double-blind treatment phase or by experiencing one of the following: four partial seizures (including simple partial); two new-onset secondarily generalised seizures, serial seizures or status epilepticus **ITT analysis performed/method** Authors state yes; drop-outs treated as censored observations (i.e. if the time to meeting one of the exit criteria was unknown then the end-point was imputed based on the time that the patient terminated from the double-blind treatment phase) **Sample size calculations** Sample size was based on the secondary efficacy variable as relevant information for the calculation based on the primary efficacy variable for the patient population under trial was not available. It was calculated with respect to the ability to detect a 30% difference between the OXC and placebo treatment groups for the	**Baseline seizure frequency** Partial seizure frequency: total (n = 102): 4.6; OXC (n = 51): 4.9; placebo (n = 51): 4.4 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: must have 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 11–65 years; weight >45 kg; no AEDs within 48 hours of randomisation (except for lorazepam up to 8 mg/day); normal routine clinical laboratory values; subtherapeutic plasma concentrations of AEDs prior to randomisation; CT scan or MRI within the past 5 years that excluded a progressive cerebral lesion; normal ECG; capability of satisfying protocol requirements; ability to provide informed consent; women of childbearing potential were only included if not pregnant or lactating and were using a barrier method of contraception Exclusion criteria: history of status epilepticus in the 3 months preceding randomisation; ingestion of benzodiazepines or barbiturates within 15 days of hospitalisation		Special senses (n = 1) Body as a whole (n = 5): fatigue (n = 1)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
percentage of patients meeting one of the exit criteria. This difference assumed that 85% of the placebo-treated patients met one of the exit criteria. Given a two-sided *Z*-test with a significance level of 0.05 and statistical power of 0.85, it was determined that ~47 completed patients per treatment group were necessary **Analysis methods** The primary efficacy variable was time to meeting one of the exit criteria and was analysed using the log-rank test. Kaplan–Meier survival curves were also calculated. A Cox's proportional hazards regression model was also performed using the variable treatment, trial site, sex, age and total partial seizure frequency (all partial seizures with or without secondary generalisation) during the 48 hours before randomisation. A secondary efficacy variable was total partial seizure frequency per 9 days during the double-blind period. This was calculated by multiplying the daily average seizure rate of the double-blind period for each patient by 9 days. Total partial seizures evolving to secondarily generalised seizures per 9 days were evaluated by treatment group **Length of trial/frequency of follow-up** 10 days; seizure frequency was monitored continuously	(other than lorazepam); cardiac, hepatic, endocrine, gastrointestinal, renal, haematological, oncological or progressive neurological disorders; seizures of metabolic, neoplastic or active infectious origin; second- or third-degree atrioventricular block if not adequately treated with a cardiac pacemaker; non-epileptic 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 OXC or its metabolites, lorazepam or CBZ; treatment with felbamate within 30 days of randomisation; history of OXC therapy; history of non-compliance			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Time to exit/withdrawal; time to achieving one of the following exit criteria: experiencing four partial seizures (including simple partial), two new onset secondarily generalised seizures, serial seizures or status epilepticus **Intervention 1** Log-rank test significantly in favour of OXC ($p = 0.0001$) Cox's proportional hazards regression model also showed significance in favour of OXC ($p = 0.0001$) **Comparator** Not stated	**Outcome** Exit/withdrawal rate; the number of patients who fulfilled one of the following exit criteria: experiencing four partial seizures (including simple partial), two new onset secondarily generalised seizures, serial seizures or status epilepticus **Intervention 1** OXC: $n = 4/51$ (47%) ($p < 0.0001$) **Comparator** Placebo: $n = 43/51$ (84%) RR = 0.20 (95% CI: 0.11 to 0.38) (risk of meeting one of the exit criteria) OR = 7.24 (95% CI: 2.58 to 20.43) (odds of meeting one of the exit criteria computed from the logistic regression model)	**Outcome** Seizure frequency; the median total partial seizure frequency per 9 days **Intervention 1** OXC: median = 2 (range, 0–296) ($p = 0.0001$) **Comparator** Placebo: median = 31 (range, 0–150)	**Outcome** Proportion of seizure-free patients; the number of participants who were seizure free on day 2 (first day on full dose of OXC) **Intervention 1** OXC: $n = 13/51$ (25%) **Comparator** Placebo: $n = 1/51$ (2%)
Outcome 5			
Outcome Proportion of participants experiencing secondarily generalised seizures Measured over a 9-day period **Intervention 1** OXC: 4/51 (8%), $p = 0.0006$ **Comparator** Placebo 24/51 (47%)			

Tiagabine (licensed use)

Crossover studies (*n* = 3)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Crawford, 2001[147] **Related publications** Industry trial report[395] **Country** European **Source** Literature search **Aim** To assess the efficacy and safety of TGB, a new AED, as add-on therapy in patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** Novo Nordisk and Abbott Laboratories **Trial ID** TIA103 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 88 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total 34.3 years (SD 9.2); TGB/placebo 35.0 years (SD 9.4); placebo/TGB 33.3 years (SD 9.1) (based only on those participants entering the double-blind phase of the trial); total 20–56 years; TGB/placebo 20–56 years; placebo/TGB 20–51 years (based only on those participants entering the double-blind phase of the trial) **Gender** Total: men = 34, women = 10; TGB/placebo: men = 18, women = 8; placebo/TGB: men = 16, women = 2 (based only on those participants entering the double-blind phase of the trial) **Age at onset of seizures** Not stated **Pretrial medication** Number of AEDs ever taken: total mean 7.4 (SD 3.18, range 1–19); TGB/placebo mean 7.6 (SD 2.91, range 1–14); placebo/TGB mean 7.1 (SD 3.60, range 2–19) (based only on those participants entering the double-blind phase of the trial)	**Intervention 1** TGB/placebo; mean 46.4 mg/day, 16–64 mg/day; 6 weeks No. randomised: 26 No. completed: 22 **Comparator** Placebo/TGB; NA; 6 weeks No. randomised: 18 No. completed: 11	**Withdrawals prerandomisation** Total (*n* = 44) From screening phase: AEs (*n* = 15), lack of efficacy (*n* = 3), protocol violations (*n* = 1) Prior to randomisation: no 25% reduction in seizures (*n* = 22), AEs (*n* = 1), other (*n* = 2) **Withdrawals postrandomisation** TGB/placebo: AE during placebo phase (*n* = 1), AE during TGB phase (*n* = 1), protocol violation during TGB phase (*n* = 1), lack of efficacy during placebo phase (*n* = 1) Placebo/TGB: prematurely crossed over to TGB because of lack of efficacy of placebo phase (*n* = 1), prematurely crossed over to TGB because of lack of efficacy before placebo phase (*n* = 2), discontinued prematurely before placebo phase owing to protocol violation (*n* = 2), discontinued prematurely during placebo phase owing to protocol violation (*n* = 1), discontinued prematurely during crossover owing to AE (*n* = 1)	**Authors' conclusions** TGB was significantly better than placebo in terms of seizure rate reduction and was generally well tolerated in patients with difficult to control seizures **Comments** Authors claim to have used an ITT analysis; however, this analysis did not include 8 participants (*n* = 2 TGB/placebo, *n* = 6 placebo/TGB) who did not complete the double-blind phase of the trial. Therefore, the authors failed to carry out a true ITT analysis. A further 3 participants who did not complete the double-blind phase did provide partial data which were included in the ITT analysis Assuming TGB to be between 10 and 25% more efficacious than VPA (based on previous studies), 50 patients would be needed to complete both portions of the double-blind phase to achieve a power of between 0.84 (for the 10% assumption) and 0.93 (for the 25% assumption) at a significance level of 5%. However, only 44 participants were finally randomised, so the sample size was smaller than that estimated to be required

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period The pretrial period consisted of an 8-week baseline period (baseline assessments), a maximum 8-week titration period (TGB dose increased gradually from 12 mg/day until therapeutically optimal dose achieved, max. = 64 mg/day) and a 4-week stabilisation period. To proceed to the double-blind phase patients had to achieve at least a 25% decrease in seizure frequency in the titration phase relative to the baseline phase, have no change in total daily dose of concomitant AED and tolerate TGB adequately during the screening period. The double-blind phase consisted of a 3-week run-in period, two 6-week treatment phases with a 3-week washout period between phases and a final 3-week termination dose tapering phase **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Determined using previous conventional studies of VPA. Assuming TGB to be between 10 and 25% more efficacious than VPA, it was calculated that 50 participants were needed to complete both portions of the double-blind phase to achieve a power of between 0.84 (for the 10% assumption) and 0.93 (for the 25% assumption) at a significance level of 5%	**Ongoing concurrent medication** On average, participants were taking 1.9 concomitant AEDs during the baseline period and this did not change during the double-blind period. The most common AED was CBZ alone (25%) or in combination with one or two other AEDs (47%). CLB and VPA were each taken as mono- or polytherapy by 23% of participants and PHT and VGB by 20% of participants **Co-morbidities** Not stated **Baseline seizure frequency** Median weekly seizure rate in baseline period: all partial (n = 69) 2.7; complex partial (n = 56) 2.0; simple partial (n = 39) 2.1; SGTC (n = 32) 0.9 Mean (SD) weekly seizure rates in baseline period: all partial (n = 69) 4.3 (5.1); complex partial (n = 56) 3.3 (4.4); simple partial (n = 39) 3.6 (4.2); SGTC (n = 32) 1.5 (1.4) **Other characteristics** Years with epilepsy: total mean 23.9 (SD 12.1, range 3.2–52.4); TGB/placebo mean 23.9 (SD 12.8, range 3.2–52.4); placebo/TGB mean 23.9 (SD 11.4, range 4.4–49.4) (based only on those participants entering the double-blind phase of the trial) Number of AEDs ever taken: total mean 7.4 (SD = 3.18, range 1–19); TGB/placebo mean 7.6 (SD = 2.91, range 1–14); placebo/TGB mean 7.1 (SD = 3.60, range 2–19)		**Adverse events** **Intervention 1** 8/36 (22.2%) of participants receiving TGB in the double-blind phase of the trial reported AEs. Dizziness and uncoordination were the most common AE (n = 2), the remaining events were each reported by only one participant. Hospitalisation for events thought to be related to treatment included migraine and dizziness (n = 1) and amnesia and confusion after prolonged seizure after taking two doses simultaneously during titration phase (n = 1) In addition, the following AEs were reported by at least 5% of participants during the pretrial phase (baseline, titration and stabilisation of TGB): dizziness (28/88, 31.8%), somnolence (26/88, 29.5%), asthenia (17/88, 19.3%), headache (15/88, 17.0%), nervousness (8/88, 9.1%), thinking abnormal (poor concentration) (8/88, 9.1%), insomnia (7/88, 8.0%), amblyopia (6/88, 6.8%), accidental injury (6/88, 6.8%), ataxia (5/88, 5.7%) **Comparator** 10/36 (27.8%) of participants receiving placebo in the double-blind phase of the trial reported AEs. Accidental injury was the most commonly reported AE	Dose of intervention 1: individually titrated to optimal therapeutic dose, mean = 46.4 mg/day (range 16–64) or 0.60 mg/kg There was no evidence to suggest that there were any statistically significant period or sequence effects in terms of the outcome data It is not possible to include the data in this trial in either the effectiveness or the AEs analyses owing to the response conditional study design used in this trial The reporting of AEs during the double-blind phase of the study is poor and it is difficult to identify the events that occurred and how many participants were involved

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods Seizure rates were analysed using parametric and non-parametric methods. The primary method was a van Elteren generalisation of Koch's non-parametric method for two-period crossover trials (including tests for crossover interactions). The secondary method was full crossover ANOVA model containing terms for crossover interactions, combined across investigators (performed on square root transformed partial seizure rate). All hypothesis tests were two-tailed and *p*-values ≤ 0.05 were considered statistically significant **Length of trial/frequency of follow-up** 35; weekly in titration phase, twice weekly in stabilisation phase and every 3–4 weeks in double-blind phase	**Inclusion/exclusion criteria** Inclusion: aged 18–65 years; with at least 6 partial seizures in 8-week baseline period while receiving stable regimen of 1–3 AEDs (AZM, CBZ, CLB, CZP, PB, PHT, PRM, VPA, VGB, FNR, LTG, OXC, DZP); a clinical diagnosis of partial seizures supported by ictal EEG, interictal EEG, CT or MRI; women of childbearing age were not pregnant and had to be using an approved form of birth control Exclusion: history of pseudoseizures; non-compliance with medication or medical advice; alcohol/drug abuse; significant psychiatric illness; clinically significant psychological/behavioral problems; clinically significant illness in previous 3 months, clinically significant laboratory abnormality other than that attributable to AEDs; any medical condition which could confound the study results; participants taking AEDs for which plasma concentrations could not be measured; administration of another investigational drug within last 3 months		(*n* = 3). Others included dizziness (*n* = 1)	

Results

Outcome 1	Outcome 2	Outcome 3
Outcome Seizure frequency; median and mean weekly seizure rates **Intervention 1** TGB Weekly seizure rate: All partial seizures (*n* = 36): median = 1.5, mean = 2.4 (SD 3.5) CPSs (*n* = 28): median = 0.9, mean = 1.5 (SD 1.8)	**Outcome** Proportion of seizure-free patients **Intervention 1** All partial seizures *n* = 3/36 CPSs *n* = 2/28 SPSs *n* = 4/21 SGTC *n* = 4/18 **Comparator** All partial seizures *n* = 1/36	**Outcome** Proportion of responders; the number of participants experiencing the specified seizure reduction in the tiagabine treatment period compared with the placebo period were reported **Intervention 1** At least 50% reduction in seizure frequency: All partial seizures *n* = 12/36

continued

Outcome 1	Outcome 2	Outcome 3
SPSs (n = 21): median = 1.3, mean = 2.5 (SD 4.3) SGTC (n = 18): median = 0.6, mean = 0.7 (SD 0.8) Treatment difference (TGB vs placebo): All partial seizures (n = 36): median = –0.6, mean = –1.2 (SD 2.3), $p < 0.01$ CPSs (n = 28): median = –0.7, mean = –1.1 (SD 2.0), $p < 0.001$ SPSs (n = 21): median = –0.4, mean = –1.0 (SD 2.4), $p = 0.339$ SGTC (n = 18): median = –0.4, mean = –0.6 (SD 1.3), $p < 0.05$ Median reduction (TGB vs placebo): All partial seizures (n = 36): 29.0% CPSs (n = 28): 42.9% SPSs (n = 21): 10.7% SGTC (n = 18): 42.9% **Comparator** Placebo: Weekly seizure rate: All partial seizures (n = 36): median = 2.3, mean = 3.7 (SD 4.0) CPSs (n = 28): median = 1.9, mean = 2.6 (SD 2.7) SPSs (n = 21): median = 2.3, mean = 3.5 (SD 4.6) SGTC (n = 18): median = 0.8, mean = 1.3 (SD 1.4)	CPSs n = 0/28 SPSs n = 1/21 SGTC n = 1/18	CPSs n = 13/28 SPSs n = 7/21 SGTC n = 9/18 <50% reduction in seizure frequency: All partial seizures n = 18/36 CPSs n = 11/28 SPSs n = 8/21 SGTC n = 6/18 Increase in seizure frequency; All partial seizures n = 6/36 CPSs n = 4/28 SPS n = 6/21 SGTC n = 3/18 **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Richens, 1995[146] **Related publications** Industry trial report[400] **Country** UK and Denmark **Source** Literature search **Aim** To undertake a Phase II multicentre study of the safety and efficacy of TGB as adjunctive therapy for complex partial seizures. A secondary objective was to study the effect of the drug in patients with SGTC seizures and single partial seizures **Type of publication** Full paper (final analysis) **Funding** Novo Nordisk and Abbott Laboratories **Trial ID** TIA101 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The pretrial period consisted of a screening	**Number of participants** 94 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (for all participants originally recruited): 36.7 years (SD not stated). Mean ages for the two crossover groups are not presented separately; total (for all participants originally recruited): 19–71 years. Age ranges for the two crossover groups are not presented separately **Gender** Total (for all participants originally recruited): men = 61 (65%), women = 33 (35%) Gender data for the two crossover groups are not presented separately **Age at onset of seizures** Mean duration of epilepsy (for all participants originally recruited): 23 years (SD not stated). Mean durations for the two crossover groups are not presented separately **Pretrial medication** On average, each patient had been exposed to 7 AEDs prior to enrolment into the trial	**Intervention 1** TGB/placebo; 12–52 mg/day; 7 weeks No. randomised: 25 No. completed: not stated **Comparator** Placebo/TGB; NA; 7 weeks No. randomised: 21 No. completed: not stated	**Withdrawals prerandomisation** TGB pretrial titration and fixed-dose period: withdrew (n = 20, including n = 16 in titration phase and n = 4 in fixed-dose period). Reasons for withdrawal include: AEs (n = 14), lack of efficacy (n = 4), protocol violation (n = 1) and personal reasons not stated (n = 1) Prior to randomisation: no 25% reduction in seizures (n = 28) **Withdrawals postrandomisation** In the double-blind treatment phase, 7/46 (15%) withdrew. Of these withdrawals, 5/7 (71%) were due to AEs (TGB n = 4 and placebo n = 3) **Adverse events** **Intervention 1** 90/94 (95.7%) of the participants who were originally enrolled in the trial reported AEs. Most were mild/moderate. Of the severe events, the majority occurred as the result of accidental injuries such as falls (n = 26, 28%). The most common AEs were tiredness (40%), dizziness (36%) and headache (27%) During the screening phase of the trial 14 participants withdrew owing to AEs, of which 10 were believed to be associated with TGB. During the double-blind	**Authors' conclusions** The authors conclude that this first trial of a GABA-reuptake inhibitor shows that TGB has antiepileptic effects in human epilepsy. It is currently undergoing further trials **Comments** The study was based on a response-dependent design (i.e. participants had to achieve at least a 25% reduction in seizures during the pretrial titration period before they were allowed to enter the double-blind phase of the trial) and therefore maximises the chance of showing a difference between TGB and placebo. Trials of this design do not give information on the population response to the drug and therefore the results of this study cannot be compared with those of a more conventional design. It is not possible to include the data in this trial in either the effectiveness or the AE analyses owing to the response conditional study design used in this trial 94 participants started the trial, 46 were randomised and 42 completed the study. The 46 participants randomised were those who responded to treatment in the screening treatment phase. The numbers randomised to each initial treatment arm are stated, but

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
phase with an open titration period of up to 8 weeks followed by a 4-week fixed-dose period. The screening phase allowed for a gross assessment of any interaction between TGB and concomitant AEs, and also individualisation of TGB dose used in the double-blind phase of the trial. Participants were only allowed to proceed to randomisation and entry into the double-blind crossover phase of the trial if they fulfilled all of the following criteria: (1) reduction in seizure frequency of at least 25% during the fixed dose pretrial period; (2) no dose changes needed in concomitant AEDs; and (3) tolerated TGB adequately. The double-blind phase lasted 23 weeks (3-week run-in period, 7-week assessment, 3-week crossover, final 7-week assessment, 3-week termination) **ITT analysis performed/method** Authors state no; not stated **Sample size calculation** Power calculations were based on data from previous trials of VPA. It was assumed that TGB would be 5–25% more effective than VPA in the treatment of complex partial seizures. To detect such TGB effects with placebo as an add-on treatment, 50 randomised patients were planned and a power of 0.84 was expected for the 5% assumption and 0.93 for the 25% assumption at a significance level of 0.05 **Analysis methods** For each seizure type, 4-week seizure frequencies were calculated for each 7-week treatment period. Seizure frequencies as a square-root transformed scale, and the percentage change in plasma concentration of	**Ongoing concurrent medication** CBZ (77%), VGB (28%), PHT (20%) and VPA (20%) in various combinations. The average number of drugs received as concurrent medication prior to and unchanged throughout the study was 1.7 **Co-morbidities** Not stated **Baseline seizure frequency** In the 8 weeks before entry into the trial all participants had 6 or more complex partial seizures; in addition, 54% had SGTC seizures, and 26% had simple partial seizures. At entry the seizure frequency was as follows: CPS (n = 74): mean = 18.6 (SD 22.6), median = 8.8 SPS (n = 20): mean = 23.1 (SD 42.7), median = 6.8 SGTC (n = 42): mean = 7.9 (SD 15.3), median = 3.8 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 18–65 years; experienced at least 6 CPSs in the last 8 weeks while on a stable regimen of three or less AEDs; clinical diagnosis of partial seizures supported by one or more of the		treatment phase of the trial, 4 participants failed to complete the trial owing to AEs while on TGB. AEs were reported by 21 patients (50%) in total during the double-blind treatment phase while on TGB (no further details reported) **Comparator** AEs were reported by 26 participants (62%) while taking placebo	only 5 of the 7 withdrawals are accounted for by treatment arm so it is not possible to state the number of completers by study arm. Three of the participants who did not complete the double-blind treatment phase contributed some data to the final analysis, hence the overall final number of 42/46 completers Participants were randomised in a 1:1 ratio at each of the five study centres to one of the two treatment sequences: TGB–placebo or placebo–TGB The predetermined sample size estimated in the power calculations was 50 randomised patients. However, only 46 patients were finally randomised and so the sample size was smaller than estimated Dose of intervention 1: individually titrated. Mean daily dose was 33.4 mg (range 12–52 mg) or 0.48 mg/kg The plasma concentrations of concomitant AEDs were not altered significantly from the levels measured during the fixed-dose period of the screening phase of the study, based on a crossover ANOVA model. No significant differences were observed in clinical laboratory data (full blood count, biochemical

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
concomitant AEDs, were analysed using a crossover ANOVA model, with the addition of centre and centre interaction effects. The percentage difference in seizure frequency between placebo and TGB periods was tested with the Wilcoxon signed rank test for each seizure type. A van Elteren generalisation of Koch's non-parametric method for two-period crossover trials suitable for multicentre studies was used to analyse clinical laboratory data **Length of trial/frequency of follow-up** 20 weeks; every week during the titration period, every 2 weeks during the fixed-dose period of the screening phase and every 3–4 weeks during the double-blind phase	following: ictal or interictal EEG, CT or MRI Exclusion: presence of neurological disorders or medical problems requiring frequent changes in medication; major psychiatric disorders; and in women a risk of pregnancy			screen and urinalysis) or vital signs between TGB and placebo periods. It is not clear how many of the participants who were seizure free during the TGB treatment phase were also seizure free during the placebo phase

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure frequency; measured over a 4-week period in the double-blind treatment phase of the trial and reported as mean and median values **Intervention 1** CPS (n = 42): mean = 13.5 (SD 19.3), median = 6.3, p = 0.002 SPS (n = 13): mean = 23.3 (SD 60.2), median = 3.4, p = 0.199 SGTC (n = 27): mean = 3.7 (SD 8.3), median = 1.1, p = 0.009 **Comparator** CPS (n = 42): mean = 16.6 (SD 24.0), median = 9.1 SPS (n = 13): mean = 22.6, median = 9.6, (SD 37.2) SGTC (n = 27): mean = 7.9 (SD 19.6), median = 2.3	**Outcome** Proportion of seizure-free patients; also includes participants who were seizure free in the placebo period (data not presented) **Intervention 1** CPS: n = 1/42 SPS: n = 2/13 SGTC: n = 10/27	**Outcome** Proportion of responders (at least 50% or other specified criteria); reported as the number of participants with at least a 50% reduction in seizure rate over a 4-week period **Intervention 1** TGB: CPS n = 11/42 SPS n = 7/13 SGTC n = 17/27	**Outcome** Change in seizure frequency; reported as median percentage reduction in seizure frequency over the 4-week period of treatment with TGB **Intervention 1** TGB: CPS (n = 42) median = 32.6% SPS (n = 13) median = 66.0% SGTC (n = 27) median = 61.0%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sveinbjornsdottir, 1994[39] **Related publications** Effectiveness data for all of the centres participating in trial TIA101146 **Country** UK (1 centre) **Source** Literature search **Aim** The neuropsychological effects of the GABA-reuptake blocker TGB HCl were tested in an open trial of 22 adult patients with refractory partial epilepsy followed by a double-blind placebo-controlled crossover trial in 12 subjects **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories and Novonordisk supplied TGB and provided support during the study **Trial ID** TIA101 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 22 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: median = 30 years; total: 19–49 years **Gender** Total: men = 17, women = 5 **Age at onset of seizures** Duration of epilepsy: median = 23 years **Pretrial medication** One AED: *n* = 5 Two AEDs: *n* = 10 Three AEDs: *n* = 7 CBZ: *n* = 20 VPA: *n* = 6 CLB: *n* = 8 PHT: *n* = 5 PRM: *n* = 4 VGB: *n* = 2 PB: *n* = 1 **Ongoing concurrent medication** See medications used before enrolment **Co-morbidities** Not stated	**Intervention 1** TTG/placebo; median 24 mg/day, 20–40 mg/day; 7 weeks No. randomised: not stated No. completed: not stated **Comparator** Placebo/TGB; NA; 7 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Two participants were withdrawn because of AEs (aggression) experienced during the titration (*n* = 1) and fixed dose (*n* = 1) periods **Withdrawals postrandomisation** TGB: aggressive behaviour (*n* = 1); worsening seizures (*n* = 1) **Adverse events** **Intervention 1** Titration and fixed-dose period (*n* = 19): Lethargy (*n* = 8), aggression/ irritability (*n* = 8), drowsiness (*n* = 8), depression (*n* = 9), headache (*n* = 6), dizziness (*n* = 5), shakiness (*n* = 5), unsteadiness (*n* = 3), confusion (*n* = 3), loss of grip (*n* = 3), nausea (*n* = 2), other (lack of concentration, puffy/red eyes, strange taste, blurred vision, cramps in hands/feet, cold hands/feet) (*n* = 6) Double-blind TGB (*n* = 11): Lethargy (*n* = 4); aggression/ irritability (*n* = 3), drowsiness (*n* = 1), depression (*n* = 1), headache (*n* = 3), unsteadiness (*n* = 1), other (lack of concentration, puffy/red eyes, strange taste, blurred vision,	**Authors' conclusions** Neuropsychological evaluation did not show any significant effect on cognitive function in the open or double-blind phases. In this group of patients, no statistically significant difference in the frequency of the total number of seizures or CPSs was found in the open or double-blind stages. Seizure severity was significantly less in the open fixed dose than in the baseline period, but was not significantly different between the two double-blind periods. Reported side-effects were transient, most commonly aggression/irritability, lethargy, headache and drowsiness. No significant EEG changes were observed **Comments** Additional information on randomisation was obtained from the authors. This was linked to trial TIA101, but was only based on data collected at one of the five participating centres The reported inclusion/exclusion criteria are very limited, therefore it is possible that participants may have had concomitant conditions which may have had a confounding effect on the findings 12 patients entered the double-blind phase of the trial; however, it is not stated how many were

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a baseline period of 8 weeks followed by an open titration period during which TGB was added to existing antiepileptic therapy in increasing dosage over a period of 6–9 weeks up to a maximum tolerated dose. This was followed by a 4-week fixed-dose period during which participants had to meet criteria for entry to the double-blind phase of the trial. Entry criteria were >25% reduction in seizure frequency during the fixed-dose period, no dosage changes of concomitant AEDs and acceptable tolerance of TGB. There was a run-in period of 3 weeks for the double-blind placebo-controlled phase and each treatment period lasted 7 weeks separated by a 3-week washout period. TGB was administered 4 times/day **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The authors state that 11 patients completing the double-blind cross-over study gives 90% power to detect an effect size of 1 at $p < 0.05$ **Analysis methods** Neuropsychological test data were analysed using Wilcoxon signed rank sum and Mann–Whitney *U*-tests. Pairwise comparisons of numbers of seizures and seizure severity in the baseline and open fixed dose and the double-blind periods were made with Wilcoxon signed rank sum Test **Length of trial/frequency of follow-up** 20 weeks; at study entry, the end of the baseline period, the fixed-dose period and each double-blind period	**Baseline seizure frequency** See seizure frequency outcome **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: patients with refractory epilepsy. No further criteria were reported		cramps in hands/feet, cold hands/feet) ($n = 1$) **Comparator** Placebo ($n = 11$): Lethargy ($n = 1$), depression ($n = 2$), headache ($n = 1$), confusion ($n = 1$), loss of grip ($n = 1$), nausea ($n = 1$)	randomised to each sequence group. The authors state that 10 patients had >25% reduction in the number of CPSs and continued into the double-blind phase of the study. They also refer to 2 patients who had a marked reduction in seizure severity and who were also included in the double-blind phase. It is unclear whether these 2 patients actually met the preset criteria Intervention 1 dose: median 32 mg/day (range, 16–52 mg/day) during the fixed-dose period and 24 mg/day (range, 20–40 mg/day) during the double-blind period Seizure severity appears to have been assessed across seizure types rather than by patient. The table indicates $n = 30$ for the open phase and $n = 16$ for the double-blind phase, referring to the number of seizure types which were assessed reliably rather than the number of patients. It is unclear what proportion of seizures could not be reliably assessed The data for the neuropsychological tests are not reported; however, the authors report that there was no significant difference between the neuropsychological test scores obtained in the placebo and the

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
				double-blind placebo phase (verbal learning, Stroop test, semantic processing, information processing speed, finger tapping, bimanual hand movements, simple reaction time, choice reaction time, tapping rate, verbal memory). There were also no significant differences between the treatment periods with regards to mood or behavioural rating scales. There were also no significant differences in the EEG measures between placebo and TGB The authors do not report the testing protocol for the neuropsychological assessment; therefore, it is unclear how they dealt with possible order effects or time of day effects on performance

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Seizure frequency; median number of seizures in 4 weeks **Intervention 1** All seizures: Open baseline (n = 19): median = 11.5 (range, 4–175) Open fixed dose (n = 19): median = 15 (range, 1–179) Double-blind TGB (n = 11): median = 6.3 (range, 0.57–219.7) Complex partial seizures: Open baseline (n = 16): median = 9.75 (range, 0–60.5) Open fixed dose (n = 16): median = 6.5 (range, 1–179) Double-blind TGB (n = 10): median = 5.4 (range, 0–68.6) **Comparator** All seizures: Double-blind placebo (n = 11): median = 7.7 (range, 1.1–99.9) Complex partial seizures: Double-blind placebo (n = 10): median = 5.7 (range, 0–35)	**Outcome** Change in seizure severity; not stated how seizure severity defined. Reported as median values with ranges **Intervention 1** (See notes below regarding denominator) Open baseline: median = 38 (range, 1–124) Open fixed dose: median = 30 (range, 1–146) Double-blind TGB: median = 33 (3–124) **Comparator** Double-blind placebo: median = 28 (range, 1–142)	**Outcome** Epilepsy activity index (EAI); expressed as severity × seizure frequency in a 4-week period **Intervention 1** Open baseline (n = 16): median = 384 (range, 110–1577) Open fixed dose (n = 16): median = 198.5 (range, 55–2148) Double-blind TGB (n = 9): median = 218 (range, 16–1652) **Comparator** Double-blind placebo (n = 9): median = 287 (range, 48–1290)

Parallel studies (*n* = 8)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Cramer, 2001[65] **Related publications** Cognitive data,[57] industry trial report M92-825[129] **Country** USA and Canada **Source** Literature search **Aim** To evaluate the efficacy and safety of TGB compared with CBZ or PHT in the treatment of CPS when added to a standard AED **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories **Trial ID** M92-825 **Study design** Add-on therapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after enrolment **Details of pretrial period** There was an 8-week baseline period (which	**Number of participants** 349 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** TGB (CBZ baseline) (*n* = 105): 37 years; PHT (CBZ baseline) (*n* = 101): 33 years; TGB (PHT baseline) (*n* = 67) 41 years; CBZ (PHT baseline) (*n* = 76): 41 years; not stated **Gender** TGB (CBZ baseline) (*n* = 105): men = 45%, women = 55%; PHT (CBZ baseline) (*n* = 101): men = 35%, women = 65%; (PHT baseline) (*n* = 67) men = 46%, women = 54%; (PHT baseline) (*n* = 76): men = 55%, women = 45% **Age at onset of seizures** Mean duration of epilepsy: TGB (CBZ baseline) (*n* = 105): 25 years; PHT (CBZ baseline) (*n* = 101): 20 years; (PHT baseline) (*n* = 67) 23 years; (PHT baseline) (*n* = 76): 21 years **Pretrial medication** CBZ, PHT	**Intervention 1** TGB (CBZ baseline); max. 80 mg/day; 16 weeks No. randomised: 105 No. completed: 73 **Intervention 2** PHT (CBZ baseline); max. 600 mg/day; 16 weeks No. randomised: 101 No. completed: 73 **Intervention 3** TGB (PHT baseline); max. 80 mg/day; 16 weeks No. randomised: 67 No. completed: 51 **Comparator** CBZ (PHT baseline); max. 2000 mg/day; 16 weeks No. randomised: 76 No. completed: 60	**Withdrawals prerandomisation** None stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Intervention 2** Not stated **Intervention 3** Not stated **Comparator** Not stated	**Authors' conclusions** These exploratory analyses suggest a possible early positive effect of TGB on patient-perceived cognitive domains using the QOLIE-89. These findings are limited by the small sample size and could be related to reduction in seizures **Comments** The neuropsychological study is based on a subgroup of patients who were randomised in a clinical trial (Ref. 404, abstract). Only adults who were able to be tested and who provided complete test results were included. The authors state that the original trial inclusion criteria excluded patients with other conditions which would possibly interfere with the purposes of the study, but no details are given. The paper does not state whether tests were administered in a standard order and time of day is not mentioned. Baseline intelligence was measured using the WAIS-R administered once during the baseline period Information on drug dosages is not provided, therefore it is not possible to determine if the drugs were used according to their licensed use with regard to drug

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
included a screening visit), a 16-week double-blind treatment phase and a 4-week termination phase for patients on TGB not continuing into the open-label TGB extension study (M91-604). Patients were randomised on enrolment to TGB (max. 80 mg/day) or PHT (max. 600 mg/day) if already taking CBZ, or TGB (max. 80 mg/day) or CBZ (max. 2000 mg/day) if already taking PHT. Thus, all patients were maintained on their baseline AED with the addition of a second drug. Patients who had at least 4 CPSs with or without secondary generalisation, with at least one such seizure in each of the two 4-week periods of the 8-week baseline phase, were advanced to the double-blind phase **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Comparisons were made for QOLIE-89 subscales and total scores comparing pairs of groups within each trial and between trials by χ^2 tests. ANOVA tests also compared subscale and total scores for demographic characteristics **Length of trial/frequency of follow-up** 24 weeks; baseline, the start of the double-blind phase (week 0) and at the end of the double-blind phase (after up to 16 weeks) or when the patient withdrew from the study	**Ongoing concurrent medication** Either CBZ or PHT **Co-morbidities** Not stated **Baseline seizure frequency** Mean CPS frequency (seizures/28 days): TGB (CBZ baseline) (n = 104): 13 (SD 28); PHT (CBZ baseline) (n = 100): 22 (SD 66); (PHT baseline) (n = 66) 29 (SD 82); (PHT baseline) (n = 76): 15 (SD 30) **Other characteristics** Baseline years of education and employment status showed no statistical difference. Baseline QOLIE-89 total score: TGB (CBZ baseline) (n = 66): 62.0 (SD 16); PHT (CBZ baseline) (n = 58): 63.0 (SD 17); (PHT baseline) (n = 47) 61.0 (SD 19); (PHT baseline) (n = 55): 60.2 (SD 18) **Inclusion/exclusion criteria** Inclusion: patients on CBZ or PHT monotherapy with poorly controlled seizures (i.e. four or more CPSs per month) Exclusion: patients with WAIS IQ < 75 were not asked to complete the questionnaire. Data were excluded for patients who had difficulty responding independently			dosages Additional data relating to changes in subscale scores among responders for each treatment group are available in the paper. Additional information taken from industry trial report

continued

Results	
Outcome 1	**Outcome 2**
Outcome Change in patient-related QoL; measured using the QOLIE-89 assessment **Intervention 1** TGB (CBZ baseline): all patients (n = 73): seizure worry improved; ≤0% seizure reduction (n = 19) overall, physical function, work, energy, emotional well-being, health discouragement worsened; >0% seizure reduction (n = 54) seizure worry improved; <50% seizure reduction (n = 50) seizure worry improved; ≥50% seizure reduction (n = 23) seizure worry improved **Intervention 2** PHT (CBZ baseline): all patients (n = 64): seizure worry improved; ≤0% seizure reduction (n = 18) memory, language improved; energy worsened; >0% seizure reduction (n = 46) seizure worry improved; <50% seizure reduction (n = 43) pain, energy worsened; ≥50% seizure reduction (n = 21) seizure worry improved **Intervention 3** TGB (PHT baseline): all patients (n = 51): seizure worry improved, role physical, role emotional, energy worsened; ≤0% seizure reduction (n = 15) role physical worsened; >0% seizure reduction (n = 36) seizure worry, social isolation improved; <50% seizure reduction (n = 37) role physical, role emotional, energy worsened; ≥50% seizure reduction (n = 14) seizure worry, attention/concentration, memory, language improved **Comparator** CBZ (PHT baseline): all patients (n = 60): seizure worry, pain, work, health discouragement improved; ≤0% seizure reduction (n = 10) emotional well-being worsened; >0% seizure reduction (n = 50) seizure worry, pain, work, health discouragement improved; <50% seizure reduction (n = 27) no changes reported; ≥50% seizure reduction (n = 33) seizure worry, work improved	**Outcome** Proportion of responders (at least 50% or other specified criteria); responders were defined as having at least a 50% reduction in seizure frequency **Intervention 1** TGB (CBZ baseline) (n = 73): 23 (22%) **Intervention 2** PHT (CBZ baseline) (n = 64): 28 (28%) **Intervention 3** TGB (PHT baseline) (n = 51): 14 (21%) **Comparator** CBZ (PHT baseline) (n = 60): 33 (43%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Dodrill, 1997[167] **Related publications** Abstracts,[396,397] effectiveness data,[163] industry trial report[398] **Country** USA **Source** Literature search **Aim** To evaluate the cognitive and quality of life effects of TGB in a double-blind, add-on, placebo-controlled, parallel, multicentre, dose–response efficacy study in patients with focal epilepsy whose complex partial seizures were difficult to control **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories **Trial ID** TIA106 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 322 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 162) 35.62 years (SD = 11.44); total (n = 162) 16–77 years **Gender** Total (n = 162): men = 95, women = 67 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Total (n = 162): number of CPSs per 28 days during the baseline period, mean = 7.58 (95% CI 11.5 to 23.6), range 3–401 **Other characteristics** Full-scale IQ (WAIS-R) for total (n = 162), mean = 89.08 (SD = 12.23), range 65–129	**Intervention 1** TGB; 16 mg/day; 20 weeks No. randomised: 61 No. completed: 34 **Intervention 2** TGB; 32 mg/day; 20 weeks No. randomised: 88 No. completed: 45 **Intervention 3** TGB; 56 mg/day; 20 weeks No. randomised: 57 No. completed: 26 **Comparator** Placebo; NA; 20 weeks No. randomised: 91 No. completed: 57	**Withdrawals prerandomisation** None stated **Withdrawals postrandomisation** None stated **Adverse events** None stated	**Authors' conclusions** Results showed no clinically important changes with the addition of TGB on the test battery. Although this is an encouraging finding, it remains for future investigations to determine the cognitive and behavioural effects of TGB either as monotherapy or in relation to other AEDs **Comments** Additional information received from trial authors There was no significant difference in age or IQ across the groups. There were relatively more men in the placebo and 56 mg/day groups Randomisation poor/poorly described No element of dose titration was described for the placebo group. A total of 297 patients were randomised. Of these, 247 were considered for neuropsychological evaluation and 51 of these did not complete either the drug treatment period neuropsychological testing or the neuropsychological testing at the end of the study. Since results are reported for only 162 patients, there are 34 randomised patients unaccounted for in the report. There is some ambiguity around

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 12-week baseline phase, followed by a 20-week treatment phase (4-week dose titration phase, 12-week fixed-dose treatment phase and 4-week taper down phase). Patients were required to experience at least eight CPSs during the baseline period (with at least one having occurred in at least two of the three 4-week blocks). After the baseline period, patients were randomised to placebo or one of three treatment groups: TGB 16 mg/day, TGB 32 mg/day, TGB 56 mg/day. Patients in the TGB groups were titrated to their preassigned doses before entering the fixed-dose period. Randomisation followed a 3:2:3:2 patient allocation plan. Neurophysiological tests were administered initially at the end of the baseline period and again at the the end of the fixed-dose period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The sample size calculation was based on the preliminary analysis from the open phase of study M90-481 (TIA-101). Signal-to-noise ratios (S/N) were calculated for different power levels. S/N is the ratio of expected treatment difference divided by the standard deviation. S/N for the placebo vs TGB (32 and 56 mg/day combined) comparison was assumed to be between 0.41 and 0.76 depending on the assumption of placebo response. Using a 0.05 false-positive rate in the ANOVA and a sample size of 60 for the placebo group and 100 for the TGB group, the power range for	**Inclusion/exclusion criteria** Inclusion: patients with focal epilepsy whose CPSs were difficult to control who had reported at least six CPSs occurring alone or in combination with any other seizure types during the 8 weeks before the screening visit; each 4-week segment within the 8-week period was to have contained at least one CPS; patients were required to be on a stable regimen of one hepatic enzyme-inducing AED Exclusion: a history of progressive neurological disorder; frequent episodes of status epilepticus; ongoing or unstable psychiatric disorder; or any other condition that may have had an impact on the results of the study; patients under 16 years; and those with an IQ of <65			the length of the baseline and treatment phases as they are variously quoted as 8 and 12 weeks at different points in the paper

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
0.41–0.76 was 70%–>99%. The approximate placebo responses of mean seizure rate reduction in the untransformed scale that correspond to the above table range from 15 to 0% **Analysis methods** Changes from baseline testing to testing at the end of the treatment period were compared between the placebo group and the combined higher dose (32 and 56 mg) TGB groups. This was done for each psychological test variable individually by evaluating the interaction effect (group × time) arising from repeated measures ANOVA. Changes in scores during the treatment period, across all patient groups, were evaluated for trend using a linear regression model. Patients were also grouped based on whether or not they had experienced significant seizure reduction (defined as at least 50% reduction in seizure frequency during the fixed-dose period as compared with the baseline period); the interaction between this seizure relief variable and the time effect was evaluated by repeated measures ANOVA **Length of trial/frequency of follow-up** 20 weeks; at the end of the baseline period and once at the end of the fixed-dose period				

continued

Results

Outcome 1

Baseline and treatment performances across the four patient groups on tests of abilities.

	Placebo (n = 57)		16 mg/day TGB (n = 34)	
Test/variable	**Baseline mean (SD)**	**Treatment mean (SD)**	**Baseline mean (SD)**	**Treatment mean (SD)**
Lafayette Grooved Pegboard				
Preferred hand (sc)	88.00 (20.45)	85.02 (20.32)	77.00 (17.36)	77.24 (16.25)
Non-preferred hand (sc)	95.21 (20.41)	92.75 (22.14)	85.64 (18.57)	83.82 (17.04)
Stroop Test				
Reading speed (sc)	58.00 (23.23)	61.02 (28.50)	55.36 (16.93)	59.00 (17.61)
Reading speed (errors)	0.96 (1.14)	0.87 (1.11)	0.82 (1.28)	0.97 (1.79)
Interference (sc)	140.08 (54.78)	139.19 (61.94)	137.70 (53.20)	135.18 (54.47)
Interference (errors)	6.42 (4.75)	5.54 (4.82)	5.76 (4.42)	5.18 (4.77)
Benton Visual Retention				
Form F (number correct)	11.44 (2.76)	12.22 (2.18)	12.00 (2.08)	12.15 (2.27)
Form G (number correct)	13.04 (2.53)	13.36 (2.33)	13.70 (1.90)	14.15 (1.79)
Controlled Oral Word				
Total number right	26.85 (11.03)	27.00 (10.86)	26.55 (13.45)	25.52 (11.07)
Symbol Digit Modalities				
Number right (written)	38.21 (12.57)	39.61 (13.57)	42.06 (10.50)	43.39 (11.94)
Auditory Verbal Learning				
Trial 1–5, first list recall	42.93 (10.35)	42.33 (11.73)	45.21 (10.76)	47.70 (10.94)
Trial 6, second list recall	5.09 (1.95)	4.96 (1.64)	5.33 (2.26)	5.58 (2.54)
Trial 7, first list recall	8.26 (3.05)	7.81 (3.54)	8.33 (3.83)	9.67 (3.39)
Trial 8, first delay recall	7.56 (3.54)	7.51 (3.66)	8.36 (4.00)	8.79 (4.19)
Trial 9, first delay recognition	12.95 (2.84)	12.93 (2.37)	13.21 (2.52)	13.79 (1.65)
Wonderlic Personnel Test				
Items correct	13.51 (6.96)	13.98 (7.33)	13.94 (8.65)	13.70 (7.37)
Items wrong	7.84 (4.49)	7.98 (4.66)	6.78 (4.23)	7.15 (3.73)
Digit Cancellation				
Number right	134.75 (42.20)	136.05 (51.55)	136.15 (44.04)	134.76 (40.00)
Number omitted	4.25 (6.33)	5.14 (7.76)	2.76 (2.88)	2.67 (3.16)

continued

Outcome 1

Test/variable	32 mg/day TGB (n = 45)		56 mg/day TGB (n = 26)	
	Baseline mean (SD)	Treatment mean (SD)	Baseline mean (SD)	Treatment mean (SD)
Lafayette Grooved Pegboard				
Preferred hand (sc)	85.36 (20.65)	81.44 (18.08)	88.42 (20.23)	85.19 (18.48)
Non-preferred hand (sc)	90.53 (20.25)	88.56 (20.30)	93.40 (18.65)	92.08 (18.21)
Stroop Test				
Reading speed (sc)	58.74 (19.46)	56.36 (17.12)	59.96 (27.04)	60.75 (23.92)
Reading speed (errors)	1.43 (1.79)	0.95 (1.29)	1.42 (2.22)	0.96 (1.04)
Interference (sc)	142.26 (56.99)	136.60 (54.19)	151.96 (65.89)	158.33 (69.46)
Interference (errors)	5.55 (4.24)	5.67 (5.57)	6.17 (3.96)	5.17 (3.00)
Benton Visual Retention				
Form F (number correct)	11.98 (2.12)	11.81 (2.13)	10.76 (1.74)	10.80 (2.60)
Form G (number correct)	13.42 (2.29)	13.35 (2.62)	13.28 (2.17)	13.00 (2.40)
Controlled Oral Word				
Total number right	27.26 (10.40)	27.23 (11.49)	24.23 (8.11)	24.85 (9.85)
Symbol Digit Modalities				
Number right (written)	39.67 (11.10)	40.13 (11.63)	40.12 (12.02)	38.62 (13.11)
Auditory Verbal Learning				
Trial 1–5, first list recall	44.38 (8.41)	43.71 (10.04)	44.72 (7.28)	44.28 (9.97)
Trial 6, second list recall	4.87 (1.60)	4.82 (2.19)	4.84 (1.70)	5.20 (1.83)
Trial 7, first list recall	7.73 (2.96)	7.78 (3.78)	7.84 (2.93)	7.68 (2.84)
Trial 8, first delay recall	7.20 (3.75)	7.20 (4.05)	7.32 (2.70)	7.32 (3.48)
Trial 9, first delay recognition	12.91 (2.59)	12.87 (3.04)	13.20 (1.85)	13.00 (2.50)
Wonderlic Personnel Test				
Items correct	13.07 (6.12)	14.32 (6.27)	13.15 (7.89)	14.27 (7.87)
Items wrong	7.36 (5.12)	7.43 (5.60)	6.80 (4.40)	7.88 (5.30)
Digit Cancellation				
Number right	143.02 (39.42)	141.42 (39.74)	132.32 (49.79)	128.95 (5.51)
Number omitted	6.00 (8.04)	7.00 (7.48)	11.28 (26.50)	6.12 (9.10)

continued

Outcome 1

Test/variable	Placebo vs 32- and 56-mg group: significance for group × time interaction	Four groups: significance for trend
Lafayette Grooved Pegboard		
Preferred hand (sc)	0.729	0.648
Non-preferred hand (sc)	0.704	0.658
Stroop Test		
Reading speed (sc)	0.139	0.252
Reading speed (errors)	0.241	0.205
Interference (sc)	0.937	0.512
Interference (errors)	0.424	0.741
Benton Visual Retention		
Form F (number correct)	0.021	0.049
Form G (number correct)	0.099	0.051
Controlled Oral Word		
Total number right	0.954	0.739
Symbol Digit Modalities		
Number right (written)	0.141	0.051
Auditory Verbal Learning		
Trial 1–5, first list recall	0.936	0.889
Trial 6, second list recall	0.569	0.457
Trial 7, first list recall	0.364	0.773
Trial 8, first delay recall	0.915	0.992
Trial 9, first delay recognition	0.849	0.650
Wonderlic Personnel Test		
Items correct	0.305	0.286
Items wrong	0.708	0.479
Digit Cancellation		
Number right	0.462	0.455
Number omitted	0.652	0.534

continued

Outcome 1

Baseline and treatment performances across the four patient groups on tests of mood and adjustment

Test/variable	Placebo (n = 57)		16 mg/day TGB (n = 34)	
	Baseline mean (SD)	Treatment mean (SD)	Baseline mean (SD)	Treatment mean (SD)
POMS				
Tension–anxiety	9.47 (5.85)	10.91 (6.58)	11.88 (5.95)	11.71 (7.34)
Depression–dejection	9.51 (7.27)	11.60 (8.57)	12.68 (10.62)	11.47 (11.56)
Anger–hostility	9.75 (7.83)	9.54 (8.71)	10.06 (8.32)	9.41 (9.37)
Vigour–activity	17.25 (6.03)	15.89 (6.44)	16.32 (5.34)	16.71 (5.40)
Fatigue–inertia	9.25 (6.04)	8.72 (5.95)	9.26 (5.70)	9.18 (5.15)
Confusion–bewilderment	8.72 (5.26)	8.49 (4.61)	9.15 (4.22)	9.03 (4.55)
Total mood disturbance	29.46 (29.71)	33.37 (32.59)	36.71 (29.86)	34.09 (35.67)
Mood Rating Scale				
Average score	63.65 (16.00)	60.13 (17.92)	60.65 (13.58)	58.74 (18.30)
WPSI				
Family background	1.85 (1.56)	2.25 (2.34)	2.48 (2.20)	2.58 (1.95)
Emotional adjustment	10.85 (4.87)	11.22 (5.58)	12.27 (7.36)	12.15 (7.42)
Interpersonal adjustment	4.73 (3.41)	4.95 (3.61)	6.24 (4.76)	6.30 (4.80)
Vocational adjustment	6.09 (3.10)	6.51 (2.94)	6.30 (3.17)	6.09 (3.45)
Financial status	2.00 (1.93)	2.11 (2.05)	2.52 (2.24)	2.33 (2.45)
Adjustment to seizures	4.98 (3.26)	5.29 (3.67)	4.85 (3.68)	5.03 (4.07)
Medicine and medical management	1.53 (1.03)	1.42 (1.20)	1.91 (1.44)	1.85 (1.66)
Overall functioning	16.71 (8.40)	17.51 (9.28)	18.52 (11.88)	18.67 (12.13)
Lie	2.29 (1.66)	2.44 (2.01)	2.28 (1.94)	2.16 (1.78)
Rare items	1.25 (1.17)	1.54 (1.38)	1.66 (1.31)	1.75 (1.59)

continued

Outcome 1

Test/variable	32 mg/day TGB (*n* = 45)		56 mg/day TGB (*n* = 26)	
	Baseline mean (SD)	**Treatment mean (SD)**	**Baseline mean (SD)**	**Treatment mean (SD)**
POMS				
Tension–anxiety	12.14 (7.08)	14.34 (7.68)	10.92 (5.41)	13.36 (7.66)
Depression–dejection	14.48 (12.30)	16.93 (13.16)	11.52 (7.88)	12.84 (10.63)
Anger–hostility	11.00 (8.49)	11.57 (9.73)	7.40 (5.94)	10.08 (8.36)
Vigour–activity	15.66 (5.50)	15.27 (6.59)	17.00 (5.03)	15.48 (6.10)
Fatigue–inertia	9.98 (5.97)	10.39 (6.51)	7.84 (4.91)	9.08 (5.53)
Confusion–bewilderment	9.84 (5.84)	10.57 (5.80)	8.36 (4.97)	9.84 (5.44)
Total mood disturbance	41.77 (35.44)	48.52 (40.36)	28.96 (23.65)	39.72 (37.33)
Mood Rating Scale				
Average score	52.38 (15.33)	55.80 (19.31)	62.88 (18.01)	54.72 (19.17)
WPSI				
Family background	2.19 (1.87)	2.30 (1.98)	2.28 (1.49)	2.36 (1.29)
Emotional adjustment	13.23 (7.22)	13.49 (7.49)	12.44 (5.05)	13.20 (6.73)
Interpersonal adjustment	6.26 (4.60)	6.40 (5.14)	5.92 (4.21)	7.08 (4.10)
Vocational adjustment	6.63 (3.41)	6.63 (3.66)	7.08 (2.80)	7.76 (3.18)
Financial status	2.44 (2.38)	2.72 (2.29)	2.48 (1.98)	2.44 (1.98)
Adjustment to seizures	6.16 (3.99)	5.58 (4.07)	5.48 (3.37)	6.40 (3.50)
Medicine and medical management	2.02 (1.55)	1.70 (1.37)	1.44 (1.00)	1.68 (1.38)
Overall functioning	20.35 (11.51)	19.60 (10.55)	19.84 (7.62)	20.92 (9.66)
Lie	2.31 (1.84)	2.05 (1.77)	1.62 (2.08)	1.96 (2.53)
Rare items	1.05 (0.96)	1.14 (1.34)	1.33 (2.01)	1.46 (1.82)

continued

Outcome 1

Test/variable	Placebo vs 32- and 56-mg group: significance for group × time interaction	Four groups: significance for trend
POMS		
Tension–anxiety	0.470	0.330
Depression–dejection	0.978	0.978
Anger–hostility	0.323	0.152
Vigour–activity	0.619	0.978
Fatigue–inertia	0.214	0.157
Confusion–bewilderment	0.156	0.099
Total mood disturbance	0.397	0.214
Mood Rating Scale		
Average score	0.350	0.752
WPSI		
Family background	0.273	0.323
Emotional adjustment	0.920	0.718
Interpersonal adjustment	0.613	0.277
Vocational adjustment	0.718	0.817
Financial status	0.878	0.995
Adjustment to seizures	0.433	0.811
Medicine and medical management	0.967	0.498
Overall functioning	0.441	0.810
Lie	0.469	0.976
Rare items	0.430	0.541

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Dodrill, 2000[57] **Related publications** Industry trial report M92-825,[129] QoL data,[65] effectiveness, abstract[404] **Country** USA and Canada **Source** Literature search **Aim** To evaluate the efficacy and safety of TGB compared with CBZ or PHT in the treatment of CPSs when added to a standard AED **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories **Trial ID** M92-825/TIA128 **Study design** Add-on therapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** The study consisted of 3 phases: an 8-week baseline period (which included a screening	**Number of participants** 349 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: not stated; TGB (CBZ baseline): 37.07 years (SD 11.13); PHT (CBZ baseline): 33.34 years (SD 13.11); TGB (PHT baseline): 39.41 years (SD 13.48); CBZ (PHT baseline): 40.42 years (SD 12.19); not stated **Gender** Total men = 125, women = 152; TGB (CBZ baseline): men = 37, women = 45; PHT (CBZ baseline): men = 24, women = 47; TGB (PHT baseline): men = 27, women = 31; CBZ (PHT baseline): men = 37, women = 29 **Age at onset of seizures** Mean age at seizure onset: total not stated; TGB (CBZ baseline): 12.23 years (SD 10.40); PHT (CBZ baseline): 12.73 years (SD 10.78); TGB (PHT baseline): 16.38 years (SD 12.93); CBZ (PHT baseline): 20.45 years (SD 15.84) **Pretrial medication** Carbamazepine, phenytoin	**Intervention 1** TGB (CBZ baseline); 80 mg/day max.; 16 weeks No. randomised: 106 No. completed: 82 **Intervention 2** PHT (CBZ baseline); max. 600 mg/day; 16 weeks No. randomised: 100 No. completed: 71 **Intervention 3** TGB (PHT baseline); max. 80 mg/day; 16 weeks No. randomised: 68 No. completed: 58 **Comparator** CBZ (PHT baseline); max. 2000 mg/day; 16 weeks No. randomised: 75 No. completed: 66	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Neuropsychological outcomes: see inclusion criteria for details of patients excluded (72/349) Clinical outcomes (reported only in the abstract of Ref. 404), discontinuation due to AEs: TGB add-on to CBZ 11/106; PHT add-on to CBZ 17/100; TGB add-on to PHT 10/68; CBZ add-on to PHT 13/75 **Adverse events** **Intervention 1** Not stated **Intervention 2** Not stated **Intervention 3** Not stated **Comparator** Not stated	**Authors' conclusions** The results did not show any convincing evidence for differences between add-on TGB and the add-on of the standard drugs CBZ and PHT, either with respect to cognitive abilities or adjustment and mood. The abstract (Ref. 404) concluded that add-on TGB appears better tolerated than, and has similar efficacy to, add-on CBZ or PHT **Comments** Additional information taken from trial report The neuropsychological study is based on a subgroup of 277/349 patients who were randomised in a clinical trial (Ref. 404, abstract). Only adults who were able to be tested and who provided complete test results were included. The authors state that the original trial inclusion criteria excluded patients with other conditions which would possibly interfere with the purposes of the study, but no details are given. The paper does not state whether tests were administered in a standard order and time of day is not mentioned. Baseline intelligence was measured using the WAIS-R administered once during the baseline period

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
visit), a 16-week double-blind treatment phase, and a 4-week termination phase for patients on TGB not continuing into the open-label TGB extension study (M91-604). Patients were randomised on enrolment to one of two treatment comparisons: TGB (max. 80 mg/day) or PHT (max. 600 mg/day) if already taking CBZ, or TGB (max. 80 mg/day) or CBZ (max. 2000 mg/day) if already taking PHT. Thus, all patients were maintained on their baseline AED with the addition of a second drug. Patients who experienced at least 4 CPSs with or without secondary generalisation, with at least one such seizure in each of the two 4-week periods of the 8-week baseline phase, were advanced to the double-blind phase. Duration of titration not stated **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Neuropsychological outcomes: in the primary analysis difference scores were calculated for each patient (baseline period test score minus double-blind period score) for each of the 37 test variables. The average difference scores were compared for CBZ add-on TGB vs CBZ add-on PHT, and for PHT add-on TGB vs PHT add-on CBZ, using the Student *t*-statistic. One variable (digit cancellation) used the Mann–Whitney *U*-statistic owing to lack of homogeneity of variance. A secondary analysis used the same methods to compare	**Ongoing concurrent medication** Either CBZ or PHT **Co-morbidities** Not stated **Baseline seizure frequency** Baseline CPS frequency (seizures 28 days) Total not stated; TGB (CBZ baseline): 81 (median 6); PHT (CBZ baseline): 70 (7); TGB (PHT baseline): 57 (7); CBZ (PHT baseline): 66 (6) Baseline total partial seizure frequency (seizures 28 days) Total not stated; TGB (CBZ baseline): 81 (median 7); PHT (CBZ baseline): 70 (10); TGB (PHT baseline): 58 (9); CBZ (PHT baseline): 66 (8) Baseline GTC seizures (seizures 28 days) Total not stated; TGB (CBZ baseline): 24 (median 2); PHT (CBZ baseline): 23 (2); TGB (PHT baseline): 22 (1); CBZ (PHT baseline): 20 (2) **Other characteristics** Baseline years of education and employment status are also reported and showed no statistical difference **Inclusion/exclusion criteria** Inclusion: adult patients with uncontrolled CPSs taking only CBZ or PHT as monotherapy at entry into the study			Add-on CBZ and add-on PHT are separate comparators to add-on TGB. Patients were treated with the drug dose judged by the investigator to bring maximum benefit. The maximum tolerated dose of TGB used (80 mg/day) exceeds the recommended maintenance maximum of 45 mg/day; the dose of PHT used (600 or 1000 mg/day) exceeds the recommended maximum of 500 mg/day Statistical analysis does not appear to have taken multiple testing into account (at the 0.05 level used, 1 in 20 comparisons may be expected to be statistically significant by chance) The full paper reports neuropsychological outcomes only. Scores for each neuropsychological test are tabulated in detail in the paper. A reported comparison of all add-on TGB patients versus all the add-on CBZ and PHT patients together appears to ignore that these groups were created by two separate randomisations. The findings from the investigation of the impact of significant seizure relief (at least 50% reduction) on test scores are reported as being within the realm of chance The abstract (Ref. 404) reports clinical outcomes only; analysis of

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
changes in test scores of patients with ≥ 50% reduction in partial complex seizure frequency with those of patients with <50% reduction. Clinical outcomes (Ref. 404, abstract): not stated **Length of trial/frequency of follow-up** 24 weeks; midway through the 8-week baseline period and again after 12 weeks of the double-blind treatment period (or at discontinuation)	Exclusion: postrandomisation exclusionso from the neuropsychological evaluation were <16 years of age, invalid testing conditions, and testing not accomplished			reduction in seizure rates (primary efficacy outcome) showed no statistically significant difference between treatments for any partial seizure type. There is insufficient information in the abstract to support the conclusions on efficacy and tolerability The data on discontinuation due to AEs reported in the abstract for the CBZ add-on to PHT group (13/75) is at odds with the number of patients included in the neuropsychological study ($n = 66$)

Results

Outcome 1	Outcome 2
Outcome Measures of abilities; includes various cognitive skills (Stroop Test, Benton Visual Retention Test, Controlled Oral Word Association Test, Symbol Digit Modalities Test, Rey Auditory Verbal Learning Test, Wonderlic Personnel Test, Digit Cancellation) **Intervention 1** TGB add-on to CBZ ($n = 82$) vs PHT add-on to CBZ ($n = 71$): no statistically significant differences between interventions. All p-values >0.05 **Intervention 2** See Intervention 1 data, PHT add-on to CBZ is the comparator **Intervention 3** Statistically significant differences found for verbal fluency (Controlled Oral Word Association Test, $p = 0.014$) and perceptual/motor speed (Digit Cancellation, number of items correct variable, $p = 0.009$) showing improvement for TGB add-on to PHT ($n = 58$) versus worsening for CBZ add-on to PHT ($n = 66$) **Comparator** See Intervention 3 data, CBZ add-on to PHT is the comparator	**Outcome** Measures of adjustment and mood; includes emotional adjustment, QoL, psychosocial variables (POMs, WPSI) **Intervention 1** TGB add-on to CBZ ($n = 82$) vs PHT add-on to CBZ ($n = 71$): no statistically significant differences between. All p-values >0.05 **Intervention 2** See Intervention 1 data, PHT add-on to CBZ is the comparator **Intervention 3** Statistically significant differences found for overall mood (Mood Rating Scale, total, $p = 0.029$) and financial concern (WPSI, financial status variable, $p = 0.017$) showing improvement for TGB add-on to PHT ($n = 58$) versus worsening for CBZ add-on to PHT ($n = 66$) **Comparator** See Intervention 3 data, CBZ add-on to PHT is the comparator

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Kälviäinen, 1996[43] **Related publications** Paper,[164] and abstract[399] **Country** Finland **Source** Literature search **Aim** The aim of the present study was to evaluate cognitive functioning and EEG findings before and during TGB add-on treatment in chronic patients with partial epilepsy **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories **Trial ID** TIA107 (M92-775) **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The pretrial period consisted of a 12-week baseline period where cognitive testing and	**Number of participants** 43 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** TGB (n = 17): 37 years (SD 9); placebo (n = 20): 40 years (SD 14); not stated **Gender** TGB (n = 17): men = 7, women = 10; placebo (n = 20): men = 10, women = 10 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Participants were described as being on optimal doses of 1–3 approved drugs, but the authors give no further details **Co-morbidities** Not stated **Baseline seizure frequency** TGB (n = 17): median/month = 23 (range 4–73); placebo (n = 20): median/month = 15 (range 3–48). The two groups significantly differed ($p < 0.05$) in terms of this baseline	**Intervention 1** TGB; 30 mg/day; 12 weeks No. randomised: not stated No. completed: 17 **Comparator** Placebo; 12 weeks No. randomised: not stated No. completed: 20	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** 6/43 (14%) of the participants entering the double-blind phase of the trial withdrew postrandomisation for the following reasons: seizures (n = 3), non-compliance (n = 2), nausea (n = 1). No further details in terms of the individual study groups are presented **Adverse events** **Intervention 1** Not stated. Reported in another report published by the Northern European Tiagabine Study Group[164] **Comparator** Not stated (see above)	**Authors' conclusions** In the present study population, the short-term TGB treatment had no cognitive or EEG AEs at low doses (30 mg/day) compared with placebo **Comments** Not stated how many participants were initially recruited to the trial and took part in the baseline (pretrial period). Also not stated how many participants randomised to each group The authors also do not state for how many years the participants had experienced seizure or what other medications including AEDs they were taking. These are important factors which may have varied between the intervention groups at baseline and possibly confounded the final results. This is particularly important considering the fact that the authors did find significant differences at baseline in terms of the seizure frequency of participants in the two treatment groups. However, seizure frequency was used as a covariate in the MANOVA and no significant interactions were identified It is not stated how many participants achieved the target dose of 30 mg/day or what the mean target dose achieved was

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
an EEG were performed on all patients. This was followed by a 12-week fixed-dose period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Continuous variables were presented as means (±SD). Medians (range) were used for continuous measurements which had an asymmetric distribution. Categorised variables were presented as frequency estimates. The difference between two group means was analysed by Student's two-tailed *t*-test. When the continuous variables had an asymmetric distribution, the Mann–Whitney rank-sum test was used. The χ^2 test with Yates' correction or Fisher's exact test for independent observations were used for comparing frequencies. Follow-up cognitive data were analysed by MANOVA for repeated measures with time as within-participants factor and the drug as between-participants factor using age, IQ and changes in seizure frequency as covariates. Descriptive EEG data were compared. A probability level of $p < 0.05$ was considered to be of statistical significance **Length of trial/frequency of follow-up** 12 weeks; once during pretrial baseline period and then once at the end of the double-blind treatment period (12 weeks)	characteristic and this was entered as a covariate in the MANOVA **Other characteristics** Full-scale IQ: TGB ($n = 17$): mean = 82 (SD 18); placebo ($n = 20$): mean = 88 (SD 20) **Inclusion/exclusion criteria** Inclusion: aged 18–75 years; partial seizures with or without secondary generalisation; incomplete seizure control, i.e. at least 6 partial seizures in the 8 weeks preceding enrolment, despite optimal doses of 1–3 approved AED			Efficacy and AE data are reported in another publication by the Northern European Tiagabine Study Group[164] This publication also reports data from a long-term open label uncontrolled study (25 of the participants went on to participate in an open uncontrolled follow-up study for up to 2 years) which has not been reported here. This part of the study used a much higher dose of tiagabine (up to 80 mg/day) than is normally used

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Results	
Outcome 1	**Outcome 2**
Outcome Cognitive tests; tests included Full-scale Intelligence Quotient (FIQ) calculated on the basis of 6 subtests of the Wechsler Adult Intelligence Scale, Modification of the Controlled Oral Word Association Test, Logical Prose Story A from the Wechsler Memory Scale, List Learning Test, Forward Digit Span, Corsi Block Span, Alternating S-task, Letter Cancellation Task, Stroop Test, Modified Finger Tapping Test, WMS Visual Reproduction Subtest, Auditory and Visual Reaction Times and Binary Choice Reaction Time **Intervention 1** There were no significant differences across the cognitive tests from baseline to follow-up comparing TGB and placebo Baseline data: Controlled Oral Word Association Test Total no. right: mean = 29.9 (SD 9.9) Logical Prose Story A Immediate recall: mean = 8.2 (SD 4.2) Delayed recall: mean = 6.0 (SD 3.7) % retention: mean = 70.3 (SD 24.3) List Learning Test Immediate recall: mean = 24.4 (SD 7.6) Delayed recall: mean = 3.7 (SD 2.2) % retention: mean = 36.9 (SD 32.8) Delayed recognition: mean = 11.1 (SD 1.9) Visual Reproduction Subtest Immediate recall: mean = 7.9 (SD 2.3) Delayed recall: mean = 5.3 (SD 3.7) % retention: mean = 65.5 (SD 3.3) Forward Digit Span: mean = 5.0 (SD 1.3) Corsi Block Span: mean = 4.6 (SD 1.0) Alternating S-task: mean = 32.4 (SD 18.6) Letter Cancellation task: mean = 24.1 (SD 9.0) Stroop Test, Part C: mean = 102.0 (SD 51.1) Auditory Reaction Time: mean = 322.2 (SD 148.5) Visual Reaction Time: mean = 394.4 (SD 243.2)	**Outcome** EEG recordings **Intervention 1** There were no significant changes between baseline and follow-up comparing TGB with placebo **Comparator** See above

continued

Outcome 1	Outcome 2
Binary Choice Reaction Time: mean = 540.1 (SD 214.3) Modified Finger Tapping Test: mean = 40.5 (SD 9.7) Follow-up data (12 weeks): Controlled Oral Word Association Test Total no. right: mean = 31.1 (SD 11.7) Logical Prose Story A Immediate recall: mean = 7.4 (SD 3.1) Delayed recall: mean = 5.2 (SD 3.2) % retention: mean = 62.6 (SD 32.6) List Learning Test Immediate recall: mean = 23.3 (SD 7.4) Delayed recall: mean = 3.5 (SD 2.7) % retention: mean = 34.4 (SD 31.1) Delayed recognition: mean = 11.7 (SD 1.7) Visual Reproduction Subtest Immediate recall: mean = 8.8 (SD 3.3) Delayed recall: mean = 5.0 (SD 3.9) % retention: mean = 49.2 (SD 30.2) Forward Digit Span: mean = 4.8 (SD 1.2) Corsi Block Span: mean = 4.8 (SD 1.0) Alternating S-task: mean = 32.6 (SD 18.5) Letter Cancellation Task: mean = 22.2 (SD 7.8) Stroop Test, Part C: mean = 112.0 (SD 70.7) Auditory Reaction Time: mean = 315.7 (SD 144.6) Visual Reaction Time: mean = 388.2 (SD 239.0) Binary Choice Reaction Time: mean = 532.6 (SD 184.9) Modified Finger Tapping Test: mean = 42.1 (SD 9.4) **Comparator** Baseline data: Controlled Oral Word Association Test Total no. right: mean = 30.5 (SD 11.7) Logical Prose Story A Immediate recall: mean = 7.9 (SD 3.9)	

continued

Outcome 1	Outcome 2
Delayed recall: mean = 6.0 (SD 3.5) % retention: mean = 65.5 (SD 22.7) List Learning Test Immediate recall: mean = 25.0 (SD 7.3) Delayed recall: mean = 2.8 (SD 2.7) % retention: mean = 48.7 (SD 27.3) Delayed recognition: mean = 10.1 (SD 3.4) Visual Reproduction Subtest Immediate recall: mean = 9.6 (SD 2.6) Delayed recall: mean = 7.3 (SD 3.2) % retention: mean = 74.5 (SD 25.7) Forward Digit Span: mean = 4.9 (SD 1.1) Corsi Block Span: mean = 4.6 (SD 1.1) Alternating S-task: mean = 41.0 (SD 22.2) Letter Cancellation Task: mean = 23.9 (SD 8.6) Stroop Test, Part C: mean = 96.9 (SD 68.9) Auditory Reaction Time: mean = 419.1 (SD 283.0) Visual Reaction Time: mean = 327.5 (SD 73.9) Binary Choice Reaction Time: mean = 553.7 (SD 262.1) Modified Finger Tapping Test: mean = 40.9 (SD 6.4) Follow-up data (12 weeks): Controlled Oral Word Association Test Total no. right: mean = 29.7 (SD 9.8) Logical Prose Story A Immediate recall: mean = 6.9 (SD 3.4) Delayed recall: mean = 4.6 (SD 3.5) % retention: mean = 69.1 (SD 26.7) List Learning Test Immediate recall: mean = 24.0 (SD 6.6) Delayed recall: mean = 2.8 (SD 2.4) % retention: mean = 36.8 (SD 28.3) Delayed recognition: mean = 11.2 (SD 2.8)	

continued

Outcome 1	Outcome 2
Visual Reproduction Subtest Immediate recall: mean = 9.0 (SD 2.9) Delayed recall: mean = 6.4 (SD 3.5) % retention: mean = 70.6 (SD 26.8) Forward Digit Span: mean = 4.8 (SD 1.1) Corsi Block Span: mean = 4.6 (SD 1.0) Alternating S-task: mean = 42.4 (SD 25.2) Letter Cancellation Task: mean = 23.2 (SD 7.2) Stroop Test, Part C: mean = 90.8 (SD 59.7) Auditory Reaction Time: mean = 369.7 (SD 276.3) Visual Reaction Time: mean = 319.9 (SD 90.2) Binary Choice Reaction Time: mean = 519.7 (SD 212.3) Modified Finger Tapping Test: mean = 42.7 (SD 6.8)	

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Kälviäinen, 1998[164] **Related publications** Papers[43,399] **Country** Finland and UK **Source** Literature search **Aim** To evaluate the effectiveness and tolerability of a three-times daily regimen of TGB compared with placebo as add-on therapy in adult patients with refractory partial seizures **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories and the Northern European Tiagabine Study Group **Trial ID** TIA107 (M92-775) **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** The study consisted of a 12-week baseline phase during which existing medication remained	**Number of participants** 177 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 154): 36.2 years; TGB (n = 77): 36.4 years; placebo (n = 77): 36.0 years (SDs not stated); total (n = 154): 17.9–71.3 years; TGB (n = 77): 18.7–59.7 years; placebo (n = 77): 17.9–71.3 years **Gender** Total (n = 154): men = 90, women = 64; TGB (n = 77): men = 43 (56%), women = 34 (44%); placebo (n = 77): men = 47 (61%), women = 30 (39%) **Age at onset of seizures** Mean period with epilepsy: TGB (n = 77): 24.9 years (range 2–52); placebo (n = 77): 23.0 years (range 1–49) **Pretrial medication** Not stated **Ongoing concurrent medication** CBZ: TGB n = 62 (81%), placebo n = 59 (77%); CZP:	**Intervention 1** TGB; 30 mg/day; 22 weeks No. randomised: 77 No. completed: 56 **Comparator** Placebo; 22 weeks No. randomised: 77 No. completed: 69	**Withdrawals prerandomisation** Total: not randomised (n = 23) **Withdrawals postrandomisation** TGB (n = 77): AEs (n = 17, 22%), lack of efficacy (n = 2, 3%), non-compliance (n = 1, 1%); placebo (n = 77): AEs (n = 2, 3%), lack of efficacy (n = 1, 1%), personal reasons (n = 1, 1%), loss to follow-up (n = 1, 1%), other (n = 3, 4%) **Adverse events** **Intervention 1** Number experiencing at least 1 treatment-emergent AE: 73 (95%) AEs reported by >5% of patients in either treatment group during the double-blind phase. TGB (n = 77): dizziness (n = 22), asthenia (n = 16), headache (n = 15), somnolence (n = 11), infection (n = 11), nausea (n = 9), injury (n = 6), pharyngitis (n = 6), pain (n = 5), vomiting (n = 5), diplopia (n = 5), confusion (n = 5), rash (n = 5), insomnia (n = 5), gastroenteritis (n = 4), flu syndrome (n = 3) Dizziness was the only AE that occurred significantly more often in TGB-treated patients than placebo-treated patients ($p \leq 0.01$)	**Authors' conclusions** TGB, administered at a dose of 10 mg three times daily, was well tolerated and demonstrated efficacy for the add-on treatment of partial seizures. The daily dosage used in this study has subsequently been shown to be at the lower end of the recommended effective dose range (30–50 mg/day TGB base) **Comments** It is not clear what happened to patients opting to enter the open-label extension phase The 22-week follow-up period included a 6-week titration phase and a 4-week termination period. Therefore, participants were not receiving the full dose for the entire follow-up period The mean TGB HCl dosage for the fixed-dose period was 27.5 mg/day. Based on drug accountability information, the proportion of prescribed doses taken during the fixed dose period was 85% (±12%) for TGB and 88% (±6%) for placebo Mean changes in plasma concentrations of concomitant AEs were small and similar in the intervention and comparator groups. No consistent changes suggestive of an interaction

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
unchanged, followed by a 22-week double-blind phase. The double-blind phase comprised a 6-week titration period, followed by a 12-week fixed-dose period and a 4-week termination period. At the end of the fixed-dose period patients had the option to enter an open-label extension phase Patients were randomised at the start of the double-blind phase. During the first 2 weeks of the titration period, TGB HCl treatment was initiated at a dosage of 12 mg/day. This was titrated up to 18 mg/day in the third week and to the full dose of 30 mg/day at the start of week 5. This dosage was then maintained throughout the 12-week fixed-dose period unless a patient experienced problems of tolerance, in which case the dosage could be reduced to 24 mg/day. To be eligible for randomisation, patients were required to have experienced at least 8 partial seizures, alone or in combination with any other seizure type, during the 12-week baseline period while on a stable regimen of one to three AEDs. Patients must not have experienced a seizure-free interval of more than 4 weeks during the baseline phase. AED dosage adjustment during the baseline period disqualified patients from entering the double-blind phase, and were permitted during the the double-blind phase only if clinically significant and consistent change in plasma drug levels occurred **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Sample size calculations were based on the results of a previous study.[146] It was estimated that 80% of enrolled patients would complete the study, and that 35% and 10% of the TGB	TGB $n = 10$ (13%), placebo $n = 10$ (13%); PHT: TGB $n = 10$ (13%), placebo $n = 14$ (18%); VPA: TGB $n = 23$ (30%), placebo $n = 19$ (25%); VGB: TGB $n = 15$ (19%), placebo $n = 14$ (18%) **Co-morbidities** None stated **Baseline seizure frequency** Baseline median 4-weekly seizure rate: All partial: TGB ($n = 77$) 12.2; placebo ($n = 77$) 10.5. Complex partial: TGB ($n = 77$) 7.0; placebo ($n = 77$) 7.7 Simple partial: TGB ($n = 77$) 10.9; placebo ($n = 77$) 12.5 SGTC: TGB ($n = 77$) 2.0; placebo ($n = 77$) 1.3 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: male and female patients aged 16–75 years were enrolled in the study if they had a documented history of partial seizures (six in the previous 8 weeks) supported by one of the following findings: an ictal EEG demonstrating a focal abnormality; an interictal EEG demonstrating unilateral or bilateral asynchronous activity; or evidence of a focal CNS lesion by CT or MRI. Female		**Comparator** Number experiencing at least 1 treatment-emergent AE: 66 (86%) AEs reported by >5% of patients in either treatment group during the double-blind phase: placebo ($n = 77$): dizziness ($n = 8$), asthenia ($n = 12$), headache ($n = 13$), somnolence ($n = 12$), infection ($n = 11$), nausea ($n = 8$), injury ($n = 10$), pharyngitis ($n = 1$), pain ($n = 2$), vomiting ($n = 1$), diplopia ($n = 5$), confusion ($n = 0$), rash ($n = 3$), insomnia ($n = 4$), gastroenteritis ($n = 6$), flu syndrome ($n = 8$)	between TGB and any of the other drugs were detected. There were no clinically significant changes or statistically significant between-group differences for any of the clinical laboratory tests or vital sign measurements, including body weight changes

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
and placebo groups, respectively, would achieve a reduction of at least 50% in partial seizure rate. Using a 5% level of significance, it was calculated that at least 60 patients were required in each treatment group to achieve a minimum statistical power of 80% **Analysis methods** Efficacy analyses were performed on an ITT basis in patients who provided at least one seizure evaluation during the double-blind phase. All 154 patients who entered the double-blind phase were included in the ITT analysis. Baseline 4-weekly seizure rates and demographic data for the two patient groups were compared using a two-sample *t*-test, Fisher's exact test and the Mann–Whitney *U*-test, as appropriate. Baseline medical and neurological history and evaluations were compared descriptively. Percentages of responders, stratified by centre, were compared using the Mantel–Haenszel test. An exact test to determine whether the common OR was unity was performed and a CI for the common odds ratio was calculated. An exact test for homogeneity of the odds ratios (Zelen's test) was also performed. The median percentage reduction in seizure rate and the change in number of seizure-free days were analysed (by treatment group and centre) using the van Elteren test and Hodges–Lehmann estimates. The number of patients reporting adverse events, classified by the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART), was examined for treatment group differences using Fisher's exact test. Changes in vital signs and clinical laboratory variables were analysed by the two-sample Wilcoxon tests. *p*-Values of ≤ 0.05 were considered statistically significant	patients were required to be post-menopausal or practising an acceptable method of birth control Exclusion: a history of pseudoseizures; any active progressive disease of the CNS; any significant illness within the previous 3 months; any medical or neurological disorder requiring frequent changes in medication or dosage which might confound interpretation of the results; clinically significant laboratory abnormalities; a history of drug or alcohol abuse; or poor compliance with past medication or medical advice			

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Length of trial/frequency of follow-up 22 weeks; patients were assessed at 14-day intervals during the titration and termination phases and every 28 days during the baseline phase and fixed-dose period				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**		
Outcome Proportion of responders; reported percentage of patients experiencing at least a 50% seizure reduction in the 4-weekly seizure rate **Intervention 1** TGB (n = 77): All partial seizures n = 11/77 (14%) CPSs n = 15/73 (21%) SPSs n = 11/53 (21%), $p < 0.01$ (TGB vs placebo) SGTC seizures n = 12/38 (32%) **Comparator** Placebo (n = 77): All partial seizures n = 5/77 (6%) CPSs n = 11/75 (15%) SPSs n = 3/50 (6%) SGTC seizures n = 9/35 (26%)	**Outcome** Change in seizure frequency; median percentage reduction (from baseline) in the 4-weekly seizure rate **Intervention 1** Tiagabine (n = 77): All partial seizures (n = 77): 12.6%, $p < 0.05$ (TGB vs placebo) CPSs (n = 73): 5.5% SPSs (n = 53): 12.6%, $p < 0.05$ (tiagabine vs placebo) SGTC seizures (n = 38) 21.8% Patients in the intervention group experienced a significantly greater reduction than those in the comparator group for all partial seizures ($p < 0.05$) and for simple partial seizures ($p < 0.05$). There were no significant differences for complex partial seizures or SGTC seizures **Comparator** Placebo (n = 77) All partial seizures (n = 77): 0.0 CPSs (n = 73): 0.0 SPSs (n = 53): 0.0 SGTC seizures (n = 38) 0.0	**Outcome** Proportion of responders; reported as the percentage of patients experiencing an increase of at least 50% in the proportion of seizure-free days **Intervention 1** TGB (n = 77): All partial seizures: 14%, $p < 0.01$ (TGB vs placebo) Non-significant trends in favour of tiagabine were observed for simple partial, complex partial and SGTC seizures **Comparator** Placebo (n = 77): All partial seizures: 4%		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sachdeo, 1997[140] **Related publications** Abstract,[401] industry trial report[402] **Country** USA **Source** Literature search **Aim** To evaluate the efficacy and safety of two regimens (b.d. and q.d.s dosing) of TGB as add-on therapy for patients with CPSs refractory to other treatment **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories **Trial ID** TIA109/M91-605 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The study consisted of an 8-week baseline period for prospective	**Number of participants** 351 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 318): 33.8 years (SD 12.49); TGB 16 mg b.d. (n = 106): 33.4 years (SD); TGB 8 mg q.d.s. (n = 105): 32.6 years (SD 11.36); placebo (n = 107): 35.3 years (SD 12.61); total (n = 318): 12–71 years; TGB 16 mg b.d. (n = 106): 12–67 years; TGB 8 mg q.d.s. (n = 105): 12–66 years; placebo (n = 107): 13–71 years **Gender** Total (n = 318): men = 179, women = 139; TGB 16 mg b.d. (n = 106): men = 65, women = 41; TGB 8 mg q.d.s. (n = 105): men = 60, women = 45; placebo (n = 107): men = 53, women = 54 **Age at onset of seizures** Mean years with seizures: total (n = 318): 22.8 years (SD 12.23); TGB 16 mg b.d. (n = 106): 21.6 years (SD 12.68); TGB 8 mg q.d.s. (n = 105): 22.4 years (SD 10.82); placebo (n = 107): 24.3 years (SD 13.00) Median (range) duration of seizure history: TGB 16 mg b.d. (n = 106): 18 years (3–54 years); TGB 8 mg q.d.s. (n = 105): 22 years (1–45 years); placebo (n = 107): 24 years (2–62 years)	**Intervention 1** TGB; 32 mg/day (16 mg b.d.); 16 weeks No. randomised: 106 No. completed: 90 **Intervention 2** TGB; 32 mg/day (8 mg q.d.s.); 16 weeks No. randomised: 105 No. completed: 84 **Comparator** Placebo; 16 weeks No. randomised: 107 No. completed: 97	**Withdrawals prerandomisation** Total: failure to meet baseline seizure criteria (n = 18); occurrence of AEs (n = 2); changes in concomitant AED administration (n = 3); miscellaneous factors (n = 10) **Withdrawals postrandomisation** Intervention 1: AE (n = 14), lack of efficacy (n = 1), other (includes failure to meet seizure criteria, non-compliance, intercurrent medical events, and personal reasons) (n = 1) Intervention 2: AE (n = 10), lack of efficacy (n = 1), other (n = 10) Comparator: AE (n = 7), lack of efficacy (n = 1), other (n = 2) **Adverse events** **Intervention 1** Nervousness (n = 10), vomiting (n = 10), abdominal pain (n = 8), emotional lability (n = 1), amnesia (n = 7), other pain (n = 10) **Intervention 2** Nervousness (n = 11), vomiting (n = 4), abdominal pain (n = 10), emotional lability (n = 8), amnesia (n = 5), other pain (n = 1) **Comparator** Nervousness (n = 1); vomiting (n = 3); abdominal pain (n = 1); emotional lability (n = 1); amnesia (n = 1); other pain (n = 3)	**Authors' conclusions** TGB administered b.d. and q.d.s. as add-on pharmacotherapy was effective in reducing CPS in patients with epilepsy whose conditions were refractory to treatment with other AEDs, and it was well tolerated. TGB has a therapeutic effect independent of the effects of concomitant AEDs taken by the patient. Evidence suggests that the pharmacodynamic effects of the drug are longer lasting than the half-life would suggest. The tolerability to AEs appears to be satisfactory for >80% of patients treated with either regimen **Comments** Additional information extracted from industry trial report for patient characteristics, randomisation and sample size calculations For pairwise comparisons of changes in vital signs, there were no statistically significant differences among the three groups. No clinically important changes in vital signs were reported. No progressive changes were noted on the ECGs. Abnormal laboratory findings for common haematological and blood chemistry variables were similar among the three groups

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
determination of seizure frequency, followed by a 16-week double-blind period. The double-blind period was divided into a 4-week dose-escalation period, an 8-week fixed-dose period and a 4-week termination period. After the fixed-dose period, patients were offered the option of entering an open-label TGB study Patients were randomised at the start of the double-blind period in a ratio of 1:1:1 in blocks of six per study centre to receive one of the following three regimens: TGB 16 mg 2 times daily (b.d.), TGB 8 mg 4 times daily (q.d.s.), or placebo 4 times daily. All patients took 4 tablets 4 times daily; this was done by dispensing TGB (2 and 4 mg) and placebo as identically appearing tablets **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The sample size calculation was based on the preliminary analysis from the open phase of study M90-481 (TIA-101). S/Ns were calculated for different power levels. S/N is the ratio of expected treatment difference divided by the standard deviation. S/N between 0.50 and 0.60 was suggested by a previous study (94–99% power) with a TGB (q.d.s.) regimen. The efficacy of (b.d.) dosing is unknown and power calculation is not stated	**Pretrial medication** CBZ (69%); VPA (38%); PHT (36%); PB (8%); PRM (8%); clorazepate (7%); AZM (5%) **Ongoing concurrent medication** Not stated **Co-morbidities** No numbers are reported for co-morbidities: 'Approximately 80% of patients had abnormal neurological histories. The most common reported conditions were chronic headaches, mental retardation, memory impairment, and dizziness. About one-third of patients had a history of psychiatric illness, including depression, anxiety, mood swings, and behaviour disorders. These patients were allowed into the study if their condition was well controlled or not active' **Baseline seizure frequency** Baseline 4-week CPS median frequency: TGB 16 mg b.d. (n = 106): 8.4; TGB 8 mg q.d.s. (n = 105): 7.9; placebo (n = 107): 8.0. Baseline 4-week SPS median frequency: TGB 16 mg b.d. (n = 106): 8.5; TGB 8 mg q.d.s. (n = 105): 9.2; placebo (n = 107): 8.0 **Other characteristics** Mean weight (range): total (n = 318): 71 kg (41–118 kg); TGB 16 mg b.d. (n = 106): 76 kg (37–162 kg); TGB 8 mg q.d.s. (n = 105): 75 kg (33–133 kg); placebo (n = 107): 71 kg (41–118 kg) Race: total (n = 318): white 86%, black 7%, other 6%; TGB 16 mg b.d. (n = 106): white 84%, black 9%, other 7%; TGB			Patients in all three groups had similar changes in the plasma concentrations of CBZ, PHT and PB. However, in patients who were taking concomitant VPA, more TGB-treated patients than placebo-treated patients had increases of >20% in the plasma VPA concentrations: 20% of the TGB b.d. group and 40% of the TGB q.d.s. group vs 12% of the placebo group by the end of the fixed-dose period

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods The primary method of analysis was Van Eltern's method of linearly combining Wilcoxon rank sum test results from individual study sites. Pairwise comparisons between each of the two intervention groups and the placebo group were performed. The proportions of patients experiencing a reduction of 50% or more in their CPS frequency were compared among the three groups using the Cochran–Mantel–Haenszel test with study sites as the strata SPSs and SGTC seizures were analysed similarly, except that the study sites were not incorporated into the statistical models, and only patients in whom that seizure type occurred during the baseline period were included in the analysis All tests were 2-tailed, with significance set at $p \leq 0.05$. **Length of trial/frequency of follow-up** 16 weeks; not stated	8 mg q.d.s. ($n = 105$): white 90%, black 5%, other 6%; placebo ($n = 107$): white 86%, black 7%, other 7% The most common causes of epilepsy were idiopathic origin (52%), trauma (28%), infection (21%), genetic propensity (18%) and antenatal or perinatal injury (16%) **Inclusion/exclusion criteria** Inclusion: aged 12–75 years; weighing at least 45 kg (100 lb); female patients of childbearing age had to be using an approved method of birth control; the diagnosis of a CPS with or without secondary generalisation had to be established by reliable clinical observations and the diagnosis had to be supported by a defined focal abnormality on an ictal or intraictal ECG. Patients had to have experienced at least six CPSs (either alone or in combination with any other seizure type) during the 8-week period before screening, with at least one CPS occurring within each of the two 4-week segments. All patients had to be treated with a stable regimen of 1–3 marketed AEDs, at least one of which had to be a hepatic enzyme inducer. A CT or MRI scan had to have been performed since the diagnosis of epilepsy was made Exclusion: a history of pseudoseizures; any active disease of the CNS; a history of drug abuse or addiction (including alcohol); or unstable or severe psychiatric illness; abnormal laboratory findings that were not attributable to their concomitant AEDs; if they had used any investigational drug within 30 days before the screening visit. Pregnant or lactating females were excluded			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; median reduction in 4-week seizure frequency from baseline **Intervention 1** CPS (n = 106): 1.6 (p = 0.18 vs placebo) SPS (n = 57): 1.4 (no p-value given) SGTC (n = 43): 0.8 (p = 0.69 vs placebo) Combined partial seizure rates (n = 106): 1.6 **Intervention 2** CPS (n = 103): 1.2 (p = 0.02 vs placebo) SPS (n = 42): 2.1 (p = 0.008 vs placebo) SGTC (n = 44): 0.7 (p = 0.48 vs placebo) Combined partial seizure rates (n = 103): 1.2 **Comparator** CPS (n = 105): 0.2 SPS (n = 49): Increase of 0.6 SGTC (n = 37): 0.3 Combined partial seizure rates (n = 105): increase of 0.3	**Outcome** Proportion of responders; reported as the number of patients experiencing at least a 50% reduction in the number of seizures during experimental period compared with baseline **Intervention 1** Combined partial seizures (n = 106): 30 (28%) ($p < 0.001$ vs placebo) CPS (n = 106): 33 (31%), ($p < 0.001$ vs placebo) SPS (n = 57): 21 (37%), (p = 0.03 vs placebo) SGTC (n = 43): 18 (42%) **Intervention 2** Combined partial seizures (n = 103): 24 (23%) ($p < 0.002$ vs placebo) CPS (n = 103): 28 (27%), ($p \leq 0.001$ vs placebo) SPS (n = 42): 30 (29%), (p = 0.21 vs placebo) SGTC (n = 44): 21 (48%) **Comparator** Combined partial seizures (n = 105): 8 (8%) CPS (n = 105): 10 (10%) SPS (n = 49): 8 (16%) Combined partial seizures: 9 (8%) SGTC (n = 37): 11 (30%)		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sommerville, 1998[129] **Related publications** Cognitive data,[57] QoL data,[65] abstracts[403,404] **Country** USA and Canada **Source** Industry submission **Aim** To evaluate the efficacy and safety of TGB compared with CBZ or PHT in the treatment of refractory CPSs when added to a standard AED **Type of publication** Industry trial report **Funding** Abbott Laboratories **Trial ID** M92-825 **Study design** Add-on therapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Randomisation schedule; after pretrial period **Details of pretrial period** The study consisted of 3 phases: an 8-week baseline period (which included a screening visit), a 16-week double-blind treatment phase	**Number of participants** 451 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** TGB (CBZ baseline) (n = 105): 35 years (SD 13); PHT (CBZ baseline) (n = 101): 33 years (SD 13); TGB (PHT baseline) (n = 67) 39 years (SD 14); CBZ (PHT baseline) (n = 76): 40 years (SD 12); TGB (CBZ baseline) (n = 105): 10–65 years; PHT (CBZ baseline) (n = 101): 10–71 years; TGB (PHT baseline) (n = 67) 11–73 years; CBZ (PHT baseline) (n = 76): 19–75 years **Gender** TGB (CBZ baseline) (n = 105): men = 46%, women = 54%; PHT (CBZ baseline) (n = 101): men = 35%, women = 65%; TGB (PHT baseline) (n = 67) men = 45%, women = 55%; CBZ (PHT baseline) (n = 76): men = 55%, women = 45% **Age at onset of seizures** Mean duration of epilepsy: TGB (CBZ baseline) (n = 105): 23 years (SD 12), range 0–62 years; PHT (CBZ baseline) (n = 101): 20 years (SD 14), range 1–57 years; TGB (PHT	**Intervention 1** TGB (CBZ baseline); max. 80 mg/day; 16 weeks No. randomised: 105 No. completed: 82 **Intervention 2** PHT (CBZ baseline); max. 600 mg/day; 16 weeks No. randomised: 101 No. completed: 70 **Intervention 3** TGB (PHT baseline); max. 80 mg/day; 16 weeks No. randomised: 67 No. completed: 50 **Comparator** CBZ (PHT baseline); max. 2000 mg/day; 16 weeks No. randomised: 76 No. completed: 55	**Withdrawals prerandomisation** [Data have been designated commercial-in-confidence and have been removed] **Withdrawals postrandomisation** [Data have been designated commercial-in-confidence and have been removed] **Adverse events** **Intervention 1** [Data have been designated commercial-in-confidence and have been removed] **Intervention 2** [Data have been designated commercial-in-confidence and have been removed] **Intervention 3** [Data have been designated commercial-in-confidence and have been removed] **Comparator** [Data have been designated commercial-in-confidence and have been removed]	**Authors' conclusions** [Data have been designated commercial-in-confidence and have been removed] **Comments** [Data have been designated commercial-in-confidence and have been removed]

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
and a 4-week termination phase for patients on TGB not continuing into the open-label TGB extension study (M91-604). Patients were randomised on enrolment to one of two treatment comparisons: TGB (max. 80 mg/day) or PHT (max. 600 mg/day) if already taking CBZ, or TGB (max. 80 mg/day) or CBZ (max. 2000 mg/day) if already taking PHT. Thus, all patients were maintained on their baseline AED with the addition of a second drug. CPSs with or without secondary generalisation, with at least one such seizure in each of the two 4-week periods of the 8-week baseline phase, were advanced to the double-blind phase **ITT analysis performed/method** [Data have been designated commercial-in-confidence and have been removed] **Sample size calculation** [Data have been designated commercial-in-confidence and have been removed] Analysis methods [Data have been designated commercial-in-confidence and have been removed] **Length of trial/frequency of follow-up** 16 weeks; baseline, the start of the double-blind phase (week 0) and at the end of the double-blind phase (after up to 16 weeks) or when the patient withdrew from the study	baseline) (n = 67) 22 years (SD 14), range 0–60 years; CBZ (PHT baseline) (n = 76): 21 years (SD 15), range 0–59 years **Pretrial medication** [Data have been designated commercial-in-confidence and have been removed] **Ongoing concurrent medication** Either carbamazepine or phenytoin **Co-morbidities** Not stated **Baseline seizure frequency** Mean CPS frequency (seizures/28 days): TGB (CBZ baseline) (n = 104): 13 (SD 28); PHT (CBZ baseline) (n = 100): 22 (SD 66); (PHT baseline) (n = 66) 29 (SD 82); (PHT baseline) (n = 76): 15 (SD 30) **Other characteristics** **Inclusion/exclusion criteria** [Data have been designated commercial-in-confidence and have been removed]			

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome [Data have been designated commercial-in-confidence and have been removed]	**Outcome** [Data have been designated commercial-in-confidence and have been removed]	**Outcome** [Data have been designated commercial-in-confidence and have been removed]

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Uthman, 1998[163] **Related publications** Cognitive results,[167,405,406] industry trial report[398] **Country** USA **Source** Literature search **Aim** To determine the efficacy and tolerability of TGB, a new AED that inhibits GABA uptake, at three dose levels vs placebo as adjunctive therapy in patients with intractable CPSs **Type of publication** Full paper (final analysis) **Funding** Abbott Laboratories **Trial ID** TIA106/M91 603 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 322 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 297): 34.0 years; TGB 16 mg/day (n = 61): 32.5 years; TGB 32 mg/day (n = 88): 34.5 years; TGB 56 mg/day (n = 57): 34.4 years; placebo (n = 91): 34.3 years (SDs not stated); total (n = 297): 12–77 years; TGB 16 mg/day (n = 61): 13–51 years; TGB 32 mg/day (n = 88): 12–72 years; TGB 56 mg/day (n = 57): 13–58 years; placebo (n = 91): 12–77 years **Gender** Total (n = 297): men = 172, women = 125; TGB 16 mg/day (n = 61): men = 31, women = 30; TGB 32 mg/day (n = 88): men = 47, women = 41; TGB 56 mg/day (n = 57): men = 35, women = 22; placebo (n = 91): men = 59, women = 32 **Age at onset of seizures** Years of seizure history, median (range): total (n = 297): 22.9 (1.4–65.8); TGB 16 mg/day (n = 61): 21.5 (3.4–42.8); TGB 32 mg/day (n = 88): 24.6 (1.4–65.8); TGB 56 mg/day (n = 57): 24.5 (5.2–54.5); Placebo (n = 91): 21.1 (1.8–58.6) **Pretrial medication** CBZ as monotherapy 77/297; CBZ in combination with other AED 128/297; PHT as monotherapy 25/297; PHT in	**Intervention 1** TGB; 16 mg/day; 20 weeks No. randomised: 61 No. completed: 55 **Intervention 2** TGB; 32 mg/day; 20 weeks No. randomised: 88 No. completed: 70 **Intervention 3** TGB; 56 mg/day; 20 weeks No. randomised: 57 No. completed: 40 **Comparator** Placebo; 20 weeks No. randomised: 91 No. completed: 78	**Withdrawals prerandomisation** Total: (n = 25): AEs (n = 3), change in concomitant AED (n = 3), did not meet baseline seizure criteria (n = 5), other (n = 14) **Withdrawals postrandomisation** TGB 16 mg/day: AEs (n = 4), lack of efficacy (n = 2), non-compliance (n = 0), lost to follow-up (n = 0), personal (n = 0), other (n = 0) TGB 32 mg/day: AEs (n = 13), lack of efficacy (n = 1), non-compliance (n = 0), lost to follow-up (n = 0), personal (n = 2), other (n = 2) TGB 56 mg/day: AEs (n = 9), lack of efficacy (n = 5), non-compliance (n = 1), lost to follow-up (n = 1), personal (n = 0), other (n = 1) Comparator: AEs (n = 7), lack of efficacy (n = 6), non-compliance (n = 0), lost to follow-up (n = 0), personal (n = 0), other (n = 0) **Adverse events** **Intervention 1** Dizziness (n = 18) (p = 0.71 vs placebo), tremor (n = 6) (p = 0.16 vs placebo), abnormal thinking (n = 2) (p = 0.99 vs placebo), depression (n = 4) (p = 0.02 vs placebo)	**Authors' conclusions** TGB is efficacious and well tolerated as adjunctive therapy for CPS; there is a clear dose–response relationship **Comments** Additional clarifications supplied by the lead author and from the trial report The highest dose comparison exceeds the maximum recommended dose and is therefore noted as an unlicensed comparison The authors state that 'when CPS frequencies were correlated with trough plasma levels of tiagabine, the 4-week CPS frequency was found to decrease with increasing plasma tiagabine concentrations'. The dose–response relationship does not appear to be clearly established from the limited data presented There were no statistically significant changes in serum concentrations of concomitant AEDs between the baseline and the double-blind treatment phases

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period The study lasted for 32 weeks and included a 12-week baseline phase and a 20-week double-blind phase. To be eligible for double-blind treatment, a patient had to have at least eight CPSs during the baseline phase, with at least one occurring during two of the three 4-week periods, either alone or in combination with SPS and/or SGTC seizures. The 20-week double-blind phase comprised a 4-week titration period (sham titration was performed for the placebo group), followed by a 12-week fixed-dose period and a 4-week tapering off period **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The sample size calculation was based on the preliminary analysis from the open phase of study M90-481 (TIA-101). S/Ns were calculated for different power levels. S/N is the ratio of expected treatment difference divided by the standard deviation. S/N for the placebo vs TGB (32 and 56 mg/day combined) comparison was assumed to be between 0.41 and 0.76 depending on the assumption of placebo response. Using a 0.05 false-positive rate in the ANOVA and a sample size of 60 for the placebo group and 100 for the TGB group, the power range for 0.41–0.76 was 70–>99%. The approximate placebo	combination with other AED 69/297; VPA 79/297; PRM 40/297; PB 76/297. Patients taking VPA could enter the study only if taking it in combination with another enzyme-inducing drug **Ongoing concurrent medication** See details of pretrial period **Co-morbidities** None stated **Baseline seizure frequency** Baseline 4-week CPS frequency, median (range): TGB 16 mg/day (n = 61): 8.5 (2.6–170); TGB 32 mg/day (n = 86): 9.6 (2.2–401); TGB 56 mg/day (n = 55): 9.1 (2.1–209); placebo (n = 90): 7.4 (2.8–109) Baseline 4-week SPS frequency, median: TGB 16 mg/day (n = 39) 9.7; TGB 32 mg/day (n = 49) 13.7; TGB 56 mg/day (n = 33) 9.1; placebo (n = 51) 8.6 Baseline 4-week SGTC seizure frequency, median: TGB 16 mg/day 1.6; TGB 32 mg/day 1.8; TGB 56 mg/day 1.5; placebo 2.0 **Other characteristics** The authors state that there were no significant differences between groups on any demographic or medical variable Race: total (n = 297): white (n = 261), black (n = 20), other (Hispanic, Asian, etc.) (n = 16); TGB 16 mg/day (n = 61): white (n = 55), black (n = 5), other (Hispanic, Asian, etc.) (n = 1); TGB 32 mg/day (n = 88): white (n = 79), black (n = 5), other (Hispanic, Asian, etc.) (n = 4); TGB 56 mg/day (n = 57): white (n = 48), black (n = 5), other (Hispanic, Asian, etc.)		**Intervention 2** Dizziness (n = 29) (p = 0.02 vs placebo), tremor (n = 13) (p = 0.008 vs placebo), abnormal thinking (n = 7) (p = 0.21 vs placebo), depression (n = 2) (p = 0.24 vs placebo) **Intervention 3** Dizziness (n = 17) (p = 0.07 vs placebo), tremor (n = 12) (p = 0.001 vs placebo), abnormal thinking (n = 8) (p = 0.02 vs placebo), depression (n = 4) (p = 0.02 vs placebo) **Comparator** Dizziness (n = 15), tremor (n = 3), abnormal thinking (n = 3), depression (n = 0)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
responses of mean seizure rate reduction in the untransformed scale that correspond to the above table range from 15 to 0% **Analysis methods** The primary method of analysis was the van Elteren method of linearly combining Wilcoxon rank sum test results from individual study sites; pairwise comparisons were performed between each TGB group and the placebo group. The proportions of patients with a 50% or greater reduction in CPS frequency were compared using the Cochran–Mantel–Haenszel test with study sites as strata The frequencies of other seizure types were analysed similarly, except that study sites were not incorporated into the models. Only patients reporting these seizure types during baseline or treatment phases were included in these analyses All tests were two-tailed with significance set at $p \leq 0.05$ **Length of trial/frequency of follow-up** 20 weeks; monthly during the baseline and double-blind phases	($n = 4$); placebo ($n = 91$): white ($n = 79$), black ($n = 5$), other (Hispanic, Asian, etc.) ($n = 7$) Median number of AEDs ever taken: total ($n = 297$): 7, range 2–20; TGB 16 mg/day ($n = 61$): 7, range 3–16; TGB 32 mg/day ($n = 88$): 7, range 2–20; TGB 56 mg/day ($n = 57$): 7, range 2–16; placebo ($n = 91$): 6, range 3–18 **Inclusion/exclusion criteria** Inclusion: patients with partial epilepsy, aged 12–77 years, in good health except for epilepsy; an occurrence of at least six CPSs, 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 one CPS); ECG evidence of unilateral or bilateral abnormality consistent with CPS; and the availability of at least one neuroimaging study of the brain to rule out the presence of any progressive lesions; must be receiving a stable regimen of 1–3 hepatic enzyme-inducing AEDs: PHT, CBZ, PB or PRM. VPA could be used in combination with any of the hepatic enzyme-inducing AEDs, but VPA monotherapy was not allowed Exclusion: pregnant or lactating females			

continued

Results	
Outcome 1	**Outcome 2**
Outcome Change in seizure frequency; change in 4-week median seizure frequency from baseline to double-blind treatment phase	**Outcome** Proportion of responders; the number (%) of participants experiencing at least a 50% reduction in seizure frequency
Intervention 1 CPS (n = 61): –0.8 (p = 0.44 vs placebo) SPS (n = 39): –2.3 (p = 0.001 vs placebo)	**Intervention 1** CPS n = 5/61 (8%) (p = 0.42 vs placebo) SPS n = 11/39 (28.2%) (p = 0.03 vs placebo)
Intervention 2 CPS (n = 86): –2.2 (p = 0.03 vs placebo) SPS (n = 49): –1.7 (p = 0.04 vs placebo)	**Intervention 2** CPS n = 17/86 (20%) (p = 0.002 vs placebo) SPS n = 17/49 (34.7%) (p = 0.003 vs placebo)
Intervention 3 CPS (n = 55): –2.8 (p = 0.03 vs placebo) SPS (n = 33): –3.3 (p = 0.003 vs placebo)	**Intervention 3** CPS n = 16/55 (29%) (p = 0.001 vs placebo) SPS n = 12/33 (36.4%) (p = 0.005 vs placebo)
Comparator CPS (n = 90): –0.7 SPS (n = 51) 0.9	**Comparator** CPS n = 4/90 (4%) SPS n = 55/1 (9.8%)

Tiagabine (unlicensed use)

Crossover studies (n = 0)
Parallel studies (n = 3)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Aikia, 1999[52] **Related publications** Abstract[393] **Country** Finland **Source** Literature search **Aim** TGB, a GABA uptake inhibitor, is an effective and well tolerated add-on AED in partial epilepsy. The aim was to evaluate the cognitive effects of TGB monotherapy as initial treatment for adult-onset partial epilepsy **Type of publication** Abstract (final analysis) **Funding** Sanofi **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient	**Number of participants** 67 **Type of epilepsy** Newly diagnosed **Type of seizures** Partial onset **Mean age/age range** Not stated; not stated **Gender** TGB (n = 28): men = 20, women = 8; CBZ (n = 27): men = 15, women = 12 (Information on gender is only provided for the successfully treated participants) **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated	**Intervention 1** TGB; 10–20 mg/day; 6 months No. randomised: 33 No. completed: 28 **Comparator** CBZ; 400–800 mg/day; 6 months No. randomised: 34 No. completed: 27	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** In the present series of patients initial TGB and CBZ monotherapies seemed to be equally successful and caused no cognitive AEs **Comments** TGB is not licensed for use as a monotherapy in the UK. Both treatment drugs (particularly CBZ) were administered at slightly lower than normal recommended doses. The usual dose of CBZ is 800–1200 mg/day. The usual dose of TGB as an adjunctive treatment (with non-enzyme-inducing drugs) is 15–30 mg daily The authors state that 28/33 TGB participants and 27/34 CBZ participants were successfully treated. Unsuccessful treatment has been extracted as study withdrawals This is an abstract and so few details about the trial design and quality are available. Only limited outcome data are reported. The authors state that as a group, the patients with either TGB or CBZ monotherapy showed no

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Method/timing of randomisation Not stated; not stated **Details of pretrial period** Patients with newly diagnosed partial epilepsy were randomised to TGB or CBZ as initial monotherapy. Treatment was for 6 months **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 6 months; 6 months	**Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 15–75 years; newly diagnosed epilepsy; normal intelligence (full IQ >85 years)			significant deterioration in verbal ability, memory performance, attention or reaction times compared with baseline
Results				
Outcome 1				
Outcome Proportion of responders; reported as successful treatment but no further details reported **Intervention 1** TGB: 28/33 (85%) **Comparator** CBZ: 27/34 (79%)				

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Baulac, 2001[329] **Related publications** NRR[394] **Country** Multinational **Source** Industry submission [Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]	[Data have been designated commercial-in-confidence and have been removed]

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome [Data have been designated commercial-in-confidence and have been removed] **Intervention 1** [Data have been designated commercial-in-confidence and have been removed] **Comparator** [Data have been designated commercial-in-confidence and have been removed]			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Schachter, 1995[251] **Related publications** None **Country** UK **Source** Literature search **Aim** To investigate the safety and efficacy of TGB monotherapy for the treatment of CPSs **Type of publication** Full paper (final analysis) from unpublished data **Funding** Abbott Laboratories **Trial ID** Not stated **Study design** Monotherapy; new vs placebo; parallel trial; superiority trial **Setting** Inpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a 4-week baseline period. Participants were then screened (taking medical and neurological histories, physical and neurological examinations, and	**Number of participants** 11 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** See Outcome 1 **Other characteristics** Not stated. **Inclusion/exclusion criteria** Inclusion: diagnosis of epilepsy with at least six complex partial seizures in the 8 weeks preceding screening undergoing evaluation for epilepsy surgery	**Intervention 1** TGB; max. 66 mg/day; 7 days No. randomised: 7 No. completed: 3 Comparator Placebo; NA; 7 days No. randomised: 4 No. completed: 0	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** TGB ($n = 7$): discontinued owing to seizure frequency exceeding the pre-established escape criteria ($n = 2$), AEs ($n = 2$); placebo ($n = 4$): discontinued owing to seizure frequency exceeding the pre-established escape criteria ($n = 4$). **Adverse events** **Intervention 1** TGB ($n = 7$): any AE ($n = 7$, 100%), dizziness ($n = 1$), asthenia ($n = 0$), abnormal thinking ($n = 1$), somnolence ($n = 0$), accidental injury ($n = 0$), insomnia ($n = 0$), nervousness ($n = 0$), paraesthenia ($n = 2$), headache ($n = 1$), amnesia ($n = 1$) **Comparator** Placebo (n = 4): any AE ($n = 2$, 50%), dizziness ($n = 1$), asthenia ($n = 0$), abnormal thinking ($n = 0$), somnolence ($n = 0$), accidental injury ($n = 0$), insomnia ($n = 1$), nervousness ($n = 0$), paraesthenia ($n = 1$), headache ($n = 2$), amnesia ($n = 0$)	**Authors' conclusions** The types of AEs with TGB monotherapy were similar to those observed in add-on trials. These initial trials in difficult-to-treat epilepsy patients indicate that TGB monotherapy may provide a new approach to the treatment of patients with partial seizures refractory to other AEDs **Comments** TGB is not licensed for monotherapy used in the UK. In addition, the maximum dose in this study exceeds the recommended dose. Sample size calculations are not stated for the study, so it is not possible to state that the study had an adequate number of participants to show a statisticaly significant difference between the treatments. The study does not state the method of randomisation and lacks detail regarding the process of randomisation and the blinding of participants and study investigators and evaluators. It is therefore not possible to provide necessary data for a complete quality assessment of this study Safety was assessed by monitoring vital signs, haemotology and clinical chemistry and by recording observed and reported AEs. Of the 3 TGB patients who completed the study, two

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
laboratory tests). Within 4 weeks of screening, eligible patients were hospitalised for the remainder of the study. Current AEDs were discontinued abruptly at randomisation, with the exception of PRM and PB, which were discontinued before enrolment. All patients were randomised to receive double-blind treatment with either TGB or placebo every 4 hours for 7 days. Titration of TGB to the maximum dosage was at the discretion of the investigator, but the final dosage was not to exceed 66 mg/day. After a 1-day washout period, a final evaluation was performed and previous AED treatment was reinstated **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** No formal statistical analyses were performed because too few patients were recruited to the study. Seizure rates during baseline and treatment periods were calculated over 24 hours **Length of trial/frequency of follow-up** 7 days; there was a final evaluation after the 1-day wash-out period				achieved the maximum permitted dosage of 66 mg/day and the third reached a maximum dosage of 42 mg/day

continued

Results

Outcome 1

Outcome
Change in seizure frequency; median 24-hour seizure rates

Intervention 1
TGB: patients who received TGB experienced fewer seizures of all types than the placebo group during the double-blind period

Complex partial (n = 7): baseline = 0.3; double-blind = 1.2; change from baseline = 0.9

Simple partial (n = 5): baseline 0.1; double-blind = 0.3; change from baseline = 0.2

Combined partial (n = 7): baseline = 0.3; double-blind = 1.3; change from baseline = 1.0

SGTC (n = 4): baseline = 0.2; double-blind = 0.7; change from baseline = 0.5

Comparator
Complex partial (n = 4): baseline = 0.1; double-blind = 1.7; change from baseline = 1.6

Simple partial (n = 2): baseline = 0.1; double-blind = 2.7; change from baseline = 2.6

Combined partial (n = 4): baseline = 0.2; double-blind = 2.0; change from baseline = 1.8

SGCT (n = 4): baseline = 0.0; double-blind = 1.6; change from baseline = 1.6

Topiramate (licensed use)

Crossover studies (*n* = 0)
Parallel studies (*n* = 15)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Aldenkamp, 2000[130] **Related publications** Abstract,[407] NRR[408,409] **Country** Multinational **Source** Literature search **Aim** To assess and compare the effects of efficacious doses of TPM and VPA on cognitive function **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** Not stated **Study design** Add-on therapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; not stated	**Number of participants** 59 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total not reported (ITT): TPM 34.7 years (SD 10.2); VPA 39.4 years (SD 11.4); not stated **Gender** Total (ITT) men = 30, women = 23; TPM men = 15, women = 9; VPA men = 15, women = 14 **Age at onset of seizures** Time since first seizure: total not reported; TPM 18.3 years (SD 12.4); VPA 22.7 years (SD 16.0) **Pretrial medication** CBZ (all patients) **Ongoing concurrent medication** CBZ, average daily dose at baseline: TPM 1070.8 mg/day (SD 411.23); VPA 1231.0 (SD 409.79). **Co-morbidities** Not stated	**Intervention 1** TPM; 200–400 mg/day; 20 weeks No. randomised: 29 No. completed: 21 **Comparator** VPA; 1800 mg/day; 20 weeks No. randomised: 30 No. completed: 26	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** TPM: 6/29 drop-outs during titration owing to tiredness, psychomotor slowing, dysarthria, loss of balance (*n* = 1), tiredness (*n* = 1), depression, mood disturbance (*n* = 1), kidney stone (*n* = 1), CBZ non-compliance (*n* = 1), choice (*n* = 1); 2/23 drop-outs during maintenance owing to poor concentration and tiredness (*n* = 1), impaired judgement, confusion, tiredness (*n* = 1) VPA: 1/30 drop-out during titration owing to nausea, insomnia, worsening of headaches (*n* = 1); 3/29 drop-outs during maintenance owing to irritability (*n* = 1), lack of efficacy (*n* = 1), overdose CBZ, ibuprofen, codydramol (*n* = 1) **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** The differences found between the treatments are small. Gradual introduction of TPM can reduce the extent of cognitive impairment **Comments** The extensive list of exclusion criteria could limit generalisability of the findings to the population most likely to respond to treatment with minimal AEs. Cognitive tests were performed between 9 a.m. and 12 noon, at the same hour as the baseline tests, and all tests were performed in a fixed order During the study, plasma levels of TPM ranged from 17.9 to 21.1 mol/l and VPA from 18.7 to 21.5 mol/l The ITT population comprised all randomised patients who entered the add-on phase and provided at least one cognitive function test assessment after baseline All the baseline data and all the analyses are based on 24 patients on TPM and 26 patients on VPA

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Baseline phase of 4 weeks to carry out all baseline procedures immediately followed by a titration period: TPM was titrated to at least 200 mg/day in 25 mg/week increments over 8 weeks, and additional individual titration allowed until week 12 in increments of 50 mg/week up to 400 mg/day or maximum tolerated dose; VPA was titrated over 12 weeks in increments of 150 mg/week to 1800 mg/day or maximum tolerated dose (whichever was less). There was an 8-week maintenance period **ITT analysis performed/method** Authors state yes; last observation carried forward **Sample size calculation** A clinically relevant difference was calculated using an information-processing task for assessing drug-induced mental slowing. Approximately 25 patients per group (ITT) were expected to give a 95% CI of 2 seconds or less for the between-group mean difference in score change assuming a SD of 1.7 seconds in each group. This would allow detection of a statistically significant difference at the 0.05 level **Analysis methods** The difference between TPM and VPA in change scores from baseline to end point and from baseline to titration were estimated by 95% CIs based on the *t*-distribution and pooled estimates of variance. The null hypothesis of no difference between treatment groups was	**Baseline seizure frequency** Total not reported; TPM median 5.9/month; VPA median 5.8/month; mostly CPS or SPS. Secondarily generalised seizures: TPM 0.5/month; VPA 1.0/month **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 18–60 years, with localisation-related epilepsy with POSs (ILAE 1981) with or without secondary generalisation; on steady-state CBZ monotherapy for at least 28 days but epilepsy uncontrolled with CBZ or another AED required for other reasons Exclusion: progressive cerebral lesion; degenerate disorder or malignancy; cognitive impairment that could interfere with testing; women not using reliable contraception; non-epileptic seizures; status epilepticus; unstable medical conditions; drug or alcohol abuse; psychiatric disorders; previous use of TPM; history of poor compliance with antiepileptic treatment; and use of various non-epilepsy-related medications			The two statistically significant ($p = 0.02$ and 0.04) findings among the cognitive functioning tests may be due to multiple testing rather than functional changes, and inconsistency in the patterns of scoring in the two tests adds to the possibility that chance played a role Treatment-emergent AEs are not mentioned in the results, only the information about drop-outs

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
tested. No correction was used for multiple testing (20 change scores were tested) **Length of trial/frequency of follow-up** 24 weeks; cognitive assessment at baseline (up to 2 weeks before titration), after the initial 8 weeks of titration (day 57) and at the end of the maintenance period (day 141). Participants visited the clinic 8 times during the trial when seizures were recorded, vital signs controlled and clinical, laboratory, neurological, physical and treatment-emergent AEs evaluations were performed				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Motor speed/motor fluency; average number of index finger taps for five consecutive trials **Intervention 1** Dominant hand Change in mean score from baseline to endpoint 1.6, Mean difference in change between TPM and VPA groups 2.5 (95% CI: –0.1 to 5.1), $p = 0.06$ Change in mean score from baseline to titration 0.1; mean difference in change between TPM and VPA groups 0.3 (95% CI: –2.4 to 3.0), $p = 0.81$ Non-dominant hand Change in mean score from baseline to endpoint 1.1; mean difference in change between TPM and VPA groups 2.0 (95% CI: –0.6 to 4.6), $p = 0.13$	**Outcome** Alertness/reaction speed; reaction time in msec to a visual computer image **Intervention 1** Dominant hand Change in mean score from baseline to endpoint –19.5; mean difference in change between TPM and VPA groups –45.7 (95% CI: –97.6 to 6.1), $p = 0.08$ Change in mean score from baseline to titration –2.5; mean difference in change between TPM and VPA groups –17.6 (95% CI: –66.7 to 31.5), $p = 0.48$ Non-dominant hand Change in mean score from baseline to end-point –0.5; mean difference in change between TPM and VPA groups –28.3 (95% CI: –63.3 to 6.8), $p = 0.11$	**Outcome** Information processing speed; reaction time in milliseconds in a binary choice reaction test and the total average searching time in seconds in a visual searching task **Intervention 1** Binary choice reaction test Change in mean score from baseline to end-point –15.7; mean difference in change between TPM and VPA groups –67.1 (95% CI: –159.4 to 25.3), $p = 0.15$ Change in mean score from baseline to titration –14.0; mean difference in change between TPM and VPA groups –43.5 (95% CI: –101.4 to 14.4), $p = 0.14$ Computer visual searching task Change in mean score from baseline to end-point 2.0; mean difference in change	**Outcome** Memory; correct recognition of target words/figures score out of 24; correct recall of words using Rey auditory verbal learning test, immediate recall score out of 75, delayed recall score out of 15 **Intervention 1** Recognition of words Change in mean score from baseline to end-point –2.5; mean difference in change between TPM and VPA groups –1.5 (95% CI: –4.0 to 1.0), $p = 0.23$ Change in mean score from baseline to titration –2.4; mean difference in change between TPM and VPA groups –2.2 (95% CI: –4.4 to –0.1), $p = 0.04$ Recognition of figures Change in mean score from baseline to end-point –1.0; mean difference in change

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Outcome 1	Outcome 2	Outcome 3	Outcome 4
Change in mean score from baseline to titration 1.1; mean difference in change between TPM and VPA groups 1.5 (95% CI: –1.3 to 4.4), $p = 0.28$ **Comparator** Dominant hand Change in mean score from baseline to end-point –0.9 Change in mean score from baseline to titration –0.2 Non-dominant hand Change in mean score from baseline to endpoint –0.9 Change in mean score from baseline to titration –0.4	Change in mean score from baseline to titration 16.3; mean difference in change between TPM and VPA groups –10.9 (95% CI: –44.8 to 23.0), $p = 0.52$ **Comparator** Dominant hand Change in mean score from baseline to end-point 26.2 Change in mean score from baseline to titration –15.1 Non-dominant hand Change in mean score from baseline to end-point 27.8 Change in mean score from baseline to titration 16.3	between TPM and VPA groups 1.9 (95% CI: –0.1 to 4.0), $p = 0.06$ Change in mean score from baseline to titration 2.6; mean difference in change between TPM and VPA groups 2.6 (95% CI: –0.1 to 5.3), $p = 0.06$ **Comparator** Binary choice reaction test Change in mean score from baseline to end-point 51.3 Change in mean score from baseline to titration 29.5 Computer visual searching task Change in mean score from baseline to end-point 0.1 Change in mean score from baseline to titration 0.0	between TPM and VPA groups –1.2 (95% CI: –3.4 to 1.0), $p = 0.26$ Change in mean score from baseline to titration –1.1; mean difference in change between TPM and VPA groups –1.0 (95% CI: –2.9 to 0.9), $p = 0.31$ Rey test immediate recall Change in mean score from baseline to end-point –2.7; mean difference in change between TPM and VPA groups –3.7 (95% CI: –7.0 to –0.5), $p = 0.02$ Change in mean score from baseline to titration 0.7; mean difference in change between TPM and VPA groups –2.0 (95% CI: –5.9 to 1.9), $p = 0.31$ Rey test delayed recall Change in mean score from baseline to end-point –0.7; mean difference in change between TPM and VPA groups –0.9 (95% CI: –2.3 to 0.4), $p = 0.17$ Change in mean score from baseline to titration 0.1; mean difference in change between TPM and VPA groups –0.7 (95% CI: –2.0 to 0.5), $p = 0.23$ **Comparator** Recognition of words Change in mean score from baseline to end-point –1.0 Change in mean score from baseline to titration –0.2 Recognition of figures Change in mean score from baseline to end-point 0.3 Change in mean score from baseline to titration 0.1

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Outcome 1	Outcome 2	Outcome 3	Outcome 4
			Rey test immediate recall Change in mean score from baseline to end-point 1.0 Change in mean score from baseline to titration 2.7 Rey test delayed recall Change in mean score from baseline to end-point 0.2 Change in mean score from baseline to titration 0.9
Outcome 5			
Outcome Mood; using the POMs and as subjective complaints on the Neurotoxicity Scale **Intervention 1** TPM: mean reduction in the average monthly seizure rate: 29.6% Differences between TPM and VPA groups from baseline to end-point and from baseline to titration were not statistically significant for any of the mood ratings **Comparator** VPA: mean reduction in the average monthly seizure rate was 22.1%			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Barrett, 1997[76] **Related publications** None **Country** Multinational **Source** Industry submission **Aim** To investigate the efficacy and safety of of TPM as adjunctive therapy for the treatment of PGTC seizures in a randomised, double-blind, placebo-controlled study **Type of publication** Industry trial report **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** RWJ-17021-000 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised (permuted blocks of size 2); after pretrial period	**Number of participants** 87 **Type of epilepsy** Refractory **Type of seizures** Generalised onset **Mean age/age range** Total (n = 80): 29.1 years (SD 10.66 years); TPM (n = 40): 29.2 years (SD 12.44 years); placebo (n = 40): 29.1 years (SD 8.69 years); total (n = 80): 7–60 years; TPM (n = 40): 7–60 years; placebo (n = 40): 12–46 years Age ≤ 16 years: total (n = 80): 11 (14%); TPM (n = 40): 9 (23%); placebo (n = 40): 2 (5%) Age >16 years: total (n = 80): 69 (86%); TPM (n = 40): 31 (77%); placebo (n = 40): 38 (95%) **Gender** Total (n = 80): men = 38, women = 42; TPM (n = 40): men = 17 (43%), women = 23 (57%); placebo (n = 40): men = 21 (52%), women = 19 (48%) **Age at onset of seizures** Not stated **Pretrial medication** Total (n = 80): VPA (n = 45), LTG (n = 29), CBZ (n = 25), PHT (n = 15), GBP (n = 8), lorazepam (n = 7), PB (n = 6), CLB (n = 5), ethosuximide (n = 4), CZP (n = 3), mephobarbital (n = 2), PRM (n = 2), VGB (n = 2), methsuximide (n = 1), DZP (n = 1) TPM (n = 40): VPA (n = 22), LTG (n = 13), CBZ (n = 11), PHT (n = 7), GBP (n = 4), lorazepam (n = 5), PB (n = 5), CLB (n = 4),	**Intervention 1** TPM; 175, 225 or 400 mg/day; 20 weeks No. randomised: 40 No. completed: 31 **Comparator** Placebo; 20 weeks No. randomised: 40 No. completed: 29	**Withdrawals prerandomisation** Total: ineligible (n = 4), administrative exclusions (n = 3) **Withdrawals postrandomisation** TPM: patient choice (n = 2), limiting AE (n = 5), other (n = 2); placebo: limiting AE (n = 7), investigator's discretion (n = 1), other (n = 3) **Adverse events** **Intervention 1** Most common (experienced by ≥ 10% of patients in either treatment group) treatment-emergent AEs: TPM (n = 40): somnolence (n = 9), nervousness (n = 8), anorexia (n = 7), confusion (n = 6), insomnia (n = 5), difficulty with memory (n = 4), aggressive reaction (n = 3), headache (n = 9), dizziness (n = 6), ataxia (n = 3), convulsions (aggravated) (n = 2), fatigue (n = 8), injury (n = 2), nausea (n = 5), diarrhoea (n = 4), upper respiratory tract infection (n = 4), vision abnormal (n = 5), diplopia (n = 2), weight decrease (n = 5), rash (n = 1) **Comparator** Placebo (n = 40): somnolence (n = 7), nervousness (n = 1),	**Authors' conclusions** TPM at dosages up to 400 mg/day was well tolerated in this trial of subjects with PGTC seizures with or without other generalised seizures. TPM was also effective in reducing the rate of occurrence of PGTC seizures. TPM was also effective in reducing seizure severity **Comments** Further data from analyses are available in the industry trial report The 20-week follow-up period consisted of an 8-week titration phase, therefore patients were not receiving the target doses of TPM for the full 20 weeks Number achieving their target dose at some time during the double-blind treatment phase: TPM: 29 (73%); placebo: 30 (75%) Number completing the stabilisation period on their target dose: TPM: 25 (63%); placebo: 24 (60%) Mean duration of double-blind treatment: total (n = 80): 128.8 days (SD 38.22 days); TPM (n = 40): 129.3 days (SD 36.9 days); placebo: 128.4 days (SD 39.97 days) Mean dosage of TPM during the entire double-blind phase: 3.7 (SD 2.17) mg/kg/day; mean dosage of TPM during the stabilisation phase: 5.2 (SD 2.78) mg/kg/day

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was an 8-week baseline phase, followed by a 20-week double-blind phase that consisted of an 8-week titration and a 12-week stabilisation period. The titration period consisted of an initial 4-week interval and two 2-week intervals. Patients were randomised at the start of the double-blind phase if they had experienced 3 or more PGTC seizures during the baseline phase, and at least one PGTC seizure must have occurred in each 4-week period of the baseline phase while receiving a stable concomitant AED regimen. Study medication (TPM or matching placebo) was administered once daily for the first 4 weeks and thereafter was administered twice daily. During the first interval, the initial dosage of TPM was 50 mg/day. During the 2nd and 3rd titration intervals, TPM was titrated to maximum daily dosages of 175, 225 or 400 mg/day, based on patients' weight. Patients were then followed for 12-week stabilisation period on this regimen The target dose (theoretical dosage range based on protocol-defined TPM maximum target dosages of 175, 225 or 400 mg/day) of the 3 weight groups were 5.2–7.0, 5.2–6.6 and ≤ 9.3 mg/kg/day, respectively	ethosuximide (*n* = 3), CZP (*n* = 1), mephobarbital (*n* = 2), PRM (*n* = 0), VGB (*n* = 1), methsuximide (*n* = 0), DZP (*n* = 1) Placebo (*n* = 40): VPA (*n* = 23), LTG (*n* = 16), CBZ (*n* = 14), PHT (*n* = 8), GBP (*n* = 4), lorazepam (*n* = 2), PB (*n* = 1), clobazam (*n* = 1), ethosuximide (*n* = 1), CZP (*n* = 2), mephobarbital (*n* = 0), PRM (*n* = 2), VGB (*n* = 1), methsuximide (*n* = 1), DZP (*n* = 0) Number of concurrent AEDs: total (*n* = 80): 1 AED (*n* = 20), 2 AEDs (*n* = 45), >2 AEDs (*n* = 15); TPM (*n* = 40): 1 AED (*n* = 9), 2 AEDs (*n* = 23), >2 AEDs (*n* = 8); placebo (*n* = 40): 1 AED (*n* = 11), 2 AEDs (*n* = 22), >2 AEDs (*n* = 7) **Ongoing concurrent medication** Listed above. Additional concomitant medications allowed were: TPM: acetaminophen (*n* = 11), multivitamins/acetaminophen (*n* = 5), and medroxyprogesterone acetate (*n* = 4); placebo: acetaminophen (*n* = 13) and ibuprofen (*n* = 4) **Co-morbidities** Not stated **Baseline seizure frequency** Average monthly seizure rate per 28 days: PGTC seizures: total (*n* = 80): 79, mean 10.9, SD 21.38, median 3.7, range 0.5–159.5; TPM (*n* = 40): 39, mean 15.5, SD 28.62, median 5.0, range 0.5–159.5; placebo (*n* = 40): 40, mean 6.5, SD 8.68, median 3.0, range 0.5–34.1. All seizures: total (*n* = 80): mean 513.4, SD 2388, median 20.8, range 1–18 232; TPM (*n* = 40): mean 604.5, SD 2880, median 25.7, range 1.5–18 232; placebo (*n* = 40): mean 422.3, SD 1799, median 15.0, range 1–10 876		anorexia (*n* = 2), confusion (*n* = 4), insomnia (*n* = 3), difficulty with memory (*n* = 2), aggressive reaction (*n* = 4), headache (*n* = 8), dizziness (*n* = 6), ataxia (*n* = 4), convulsions (aggravated) (*n* = 6)	Several of the newer drugs were allowed as concomitant AEDs during the study. This may have affected the study results 31 participants (placebo *n* = 16; TPM *n* = 15) had deviations from inclusion/exclusion criteria or deviations detected during the study: 15 placebo and 11 TPM patients were randomised prior to completing the 56-day baseline phase; 4 placebo and 4 TPM patients were randomised even though they were being maintained on more than two concomitant AEDs; 2 TPM patients were randomised even though they had recently completed another experimental drug regimen; 1 TPM patient was randomised even though he did not have PGTC seizures during baseline; 1 placebo patient was randomised even though she had a history of attempted suicide; 5 TPM patients who were randomised deviated from the dose requirements of the protocol 39 of 40 TPM-treated patients were included in the ITT efficacy analysis for variables based on PGTC seizures as 1 subject did not have PGTC seizures during baseline or double-blind phase Intervention 1 dose: ~6 mg/kg/day

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
If a subject could not tolerate the titration schedule, the investigator was permitted to maintain the subject's dosage at the level the subject was receiving at the time of the dose-limiting AE or to reduce the subject's dosage **ITT analysis performed/method** Authors state yes; seizure data for patients who were withdrawn from the study were averaged for the portion of the double-blind phase completed up to the time of study drug discontinuation **Sample size calculation** A sample of 36 subjects per treatment group was estimated to be adequate to detect a 30% between-group difference in PGTC seizure rate. This assumed a Type I error level of 5%, power of 80% and population SD of 45% **Analysis methods** Analyses were based on data from all randomised patients during the baseline and double-blind phases of the study (i.e. the ITT population). Secondary analyses were performed on patients who completed the double-blind phase. The percentage reduction in seizure rate from baseline during the double-blind phase (for PGTC and all seizures) was analysed using a 2-way ANOVA	**Other characteristics** Race: total (n = 80): white = 79, black = 1; TPM (n = 40): white = 39, black = 1; placebo (n = 40): white = 40, black = 0 Mean weight: total (n = 80): 75.0 kg (SD 21.78 kg, range 25–146 kg); TPM (n = 40): 71.3 kg (SD 23.63 kg, range 25–123 kg); placebo (n = 40): 78.7 kg (SD 19.34 kg, range 33–146 kg) Baseline seizure type: total (n = 80): tonic–clonic (n = 79), absence (n = 33), myclonic (n = 23), tonic (n = 11), atypical absence (n = 9), drop attack (n = 4), clonic (n = 1), other (n = 4), tonic–clonic only (n = 18), tonic–clonic and at least one other type (n = 61); TPM (n = 40): tonic–clonic (n = 39), absence (n = 14), myclonic (n = 13), tonic (n = 6), atypical absence (n = 7), drop attack (n = 1), clonic (n = 1), other (n = 2), tonic–clonic only (n = 9), tonic–clonic and at least one other type (n = 30); placebo (n = 40): tonic–clonic (n = 40), absence (n = 19), myclonic (n = 10), tonic (n = 5), atypical absence (n = 2), drop attack (n = 3), clonic (n = 0), other (n = 2), tonic–clonic only (n = 9), tonic–clonic and at least one other type (n = 31). Individuals may have had more than one seizure type **Inclusion/exclusion criteria** Inclusion: ≥ 4 years of age; weighing >25 kg, and, if female, were premenarchal or postmenopausal or practising an acceptable method of birth control; had a history of PGTC seizures, with or without other generalised seizure types, with the exception of POSs; receiving 1 but not more than 2 standard AEDs, and were being maintained on a stable dosage regimen during the baseline phase. Eligible			The authors state that although the efficacy results of this trial consistently favoured TPM over placebo, the treatment comparisons generally did not achieve statistical significance using standard unadjusted ITT analyses. There were indications that the standard analysis tended to underestimate TPM efficacy in this particular study Pharmacokinetic/pharmaco-dynamic analyses revealed no statistically significant differences between TPM plasma concentrations and clinical efficacy end-points in this study The relationship between duration of exposure to TPM and onset of selected neuropsychiatric AEs was examined using the Kaplan–Meier method. No consistent relationship between the first occurrence of these selected treatment-emergent AEs and duration of exposure to TPM was observed

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
based on ranks using the SAS (Cary, NC, USA) procedure for general linear models, to compare treatment groups. The Cochran–Mantel–Haenszel method was used to analyse differences in percentage responders (those with at least a 50, 75 or 100% reduction from baseline in average monthly rates of PGTC and of all generalised seizures) between treatment groups stratified by centre. All statistical tests were 2-sided. Global evaluation of improvement in seizure severity was analysed using the exact Wilcoxon rank-sum test. Treatment-emergent AEs were tabulated and the cumulative incidence of treatment-emergent AEs over time was estimated using the Kaplan–Meier method **Length of trial/frequency of follow-up** 20 weeks; at 4-week intervals, with the first visit at the start of baseline. An additional visit was scheduled after 6 weeks of the titration period	patients had EEG or CCTV/EEG done prior to the baseline phase with findings consistent with generalised epilepsy. An ECG had to have been done during the baseline phase with no significant findings. A CT or MRI scan done prior to trial entry was required to exclude potentially progressive neurological diseases Exclusion: patients with a treatable cause of seizures (e.g. metabolic disturbance, toxic exposure, active infection or neoplasm); progressive neurological disease; clinically diagnosed Lennox–Gastaut syndrome; multiple seizure types; mental retardation; a history of an EEG with slow spike waves; a history of GTC status epilepticus within the previous 3 months, while receiving appropriate AED therapy; evidence of use of an experimental device within 60 days before enrolment; or treatment with AZM, ZNS, triamterene, vitamin C (>2 g per day), antacids or calcium supplements within 3 months before enrolment (because of an increased possibility of renal stone formation). In addition, patients with a history of any of the following were excluded: seizure occurring only in clustered patterns; significant medical disease (within the previous 2 years); a psychiatric or mood disorder (within the previous 6 months); attempted suicide; nephrolithiasis; malignancy; alcohol or drug abuse; history of poor compliance as judged by the investigator; taking benzodiazepines on more than an occasional basis, unless used as one of the two concomitant AEDs; schizophrenia or history of exhibiting psychotic symptomatology; clinically significant ECG abnormalities; poor compliance or inability to comply; inability to take medication or maintain a seizure calendar independently or with assistance			

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Change in seizure frequency; median percentage reduction from baseline in average monthly seizure rate during the double-blind phase **Intervention 1** PGTC seizures: TPM (n = 39): 57.1%, p = 0.124 All generalised seizures: TPM (n = 40): 26%, p = 0.212 **Comparator** Placebo (n = 40): 33.2% All generalised seizures: placebo (n = 40): 12.1%	**Outcome** Proportion of responders; percentage of patients with ≥ 50% reduction in seizure frequency from baseline in the average monthly rate of seizures **Intervention 1** PGTC seizures: TPM (n = 39): 54%, p = 0.102 TPM (n = 40): 40%, p = 0.061 Proportion of patients with ≥ 75% reduction in seizures: PGTC seizures: TPM (n = 39): 36%, p = 0.040 All generalised seizures: TPM (n = 40): 30%, p = 0.005 Proportion of patients with 100% reduction (seizure free) in seizures: PGTC seizures: TPM (n = 39): 8%, p = not stated All generalised seizures: TPM (n = 40): 3%, p = not stated **Comparator** PGTC seizures: placebo (n = 40): 35% All generalised seizures: placebo (n = 40): 20% Proportion of patients with 75% or more reduction in seizures: PGTC seizures: placebo (n = 40): 15% All generalised seizures: placebo (n = 40): 5% Proportion of patients with 100% reduction (seizure free) in seizures: PGTC seizures: placebo (n = 40): 10% All generalised seizures: placebo (n = 40): 3%	**Outcome** Patients' global evaluation of improvement/efficacy Patients' global evaluation of improvement in seizure severity: 0 = worse, 1 = none, 2 = minimal, 3 = moderate, 4 = marked **Intervention 1** TPM (n = 37): 48% of patients reported improvement (minimal, moderate, or marked); p = 0.026 **Comparator** Placebo (n = 36): 33% of patients reported improvement (minimal, moderate or marked)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Ben-Menachem, 1996[151] **Related publications** Abstracts[410,411] **Country** European **Source** Literature search **Aim** To compare TPM with placebo as add-on therapy in patients with refractory partial epilepsy in a double-blind, randomised, parallel-group trial **Type of publication** Full paper (final analysis) **Funding** R.W. Johnson Pharmaceutical Research Institute **Trial ID** Europe Y3 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** There was an 8-week baseline phase followed by a 13-week double-blind phase (which consisted of a 5-week titration period and an 8-week	**Number of participants** 57 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 56): 37.2 years (SD not stated); total (n = 56): 8–65 years **Gender** Total (n = 56): men = 84%, women = 16% **Age at onset of seizures** Not stated **Pretrial medication** Not stated. 38% were receiving one AED at baseline and 62% were receiving two **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Median monthly seizure rates: TPM (n = 28): 14.2; placebo (n = 28): 11.4	**Intervention 1** TPM; 800 mg/day; 13 weeks No. randomised: 28 No. completed: not stated **Comparator** Placebo; NA; 13 weeks No. randomised: 28 No. completed: not stated	**Withdrawals prerandomisation** Total group (TPM + placebo): withdrawals (n = 1) **Withdrawals postrandomisation** TPM: withdrawals prior to completion of titration period (n = 3), reasons not stated; discontinued treatment owing to an AE (n = 6), but unclear whether this implies withdrawal before or after completion of the study, whether there were others who discontinued treatment for reasons other than an AE and whether this figure includes or is separate from the 3 lost prior to completion of the titration period Placebo: unclear whether there were participants who discontinued treatment for reasons other than an AE **Adverse events** **Intervention 1** Death (n = 0); serious AE (n = 0) AEs observed in ≥ 15% of patients in either treatment group (n = 28): fatigue (n = 22, 79%), headache (n = 6, 21%), concentration impaired (n = 7, 25%), weight loss (n = 7, 25%), dizziness (n = 6, 21%), paraesthesia (n = 5, 18%) AEs observed in 10–14% of patients (numbers or percentages	**Authors' conclusions** The present results support the findings of other controlled trials that have evaluated TPM, in dosages ranging from 200 to 1000 mg, as add-on therapy in resistant partial seizures. The present study further establishes the favourable profile and good benefit/risk ratio of TPM in resistant partial epilepsy **Comments** Other outcomes are reported in the study such as blood chemistry and urinalysis outcomes. Data for these outcomes were collected by clinic assessment There are no details of baseline characteristics (except for median baseline monthly seizure rates) presented separately for each treatment group in order to assess baseline comparability The number of participants who completed the trial for each group out of those who were originally assigned to each group is unclear. All that is stated in the paper is the number of participants who completed the titration period and entered the stabilisation period of the double-blind phase. This was 25 out of 28 for the TPM group and 28 out of 28 for the placebo group

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
stabilisation period). In the titration period, patients were started at a dose of one 100-mg TPM tablet or one placebo tablet daily. The dosage was increased after 1 week to one 100-mg TPM tablet or one placebo tablet twice daily, and titrated weekly thereafter at increments of 200 mg/day either to the target dose of four 100-mg TPM tablets (or the maximum tolerated dose, if lower) or four placebo tablets twice daily. To qualify for entry into the double-blind phase, patients had to have at least 8 partial seizures during the 8-week baseline period while maintained on therapeutic doses and plasma concentrations of one or two appropriate AEDs. During this phase, the longest allowable seizure-free period was 3 weeks, and only one such period was permitted **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** All analyses of efficacy variables were performed on an ITT basis Comparisons of % reduction in seizure rate were made with 2-factor ANOVA on ranks. A similar analysis was used for % reduction in generalised seizure rate. The % responders (50–75%) were stratified by centre and were compared by the Cochran–Mantel–Haenszel method. Investigator's global evaluation of improvement and patient's overall assessment of study medication were analysed by Wilcoxon rank-sum tests stratified by centre	**Other characteristics** Mean body weight: total: 75.2 kg No. of AEDs received at baseline: total: 1 AED = 38%, 2 AEDs = 62% **Inclusion/exclusion criteria** Inclusion: aged 18–65 years; with a history of partial seizures which had not responded to treatment with one or two AEDs. Patients could also have secondary generalised seizures. An EEG taken in the preceding 5 years documenting the presence of a lateralised epileptiform pattern consistent with a diagnosis of localisation-related epilepsy was required. Women were required to be postmenopausal or surgically rendered incapable of having children or to be using an acceptable method of birth control Exclusion: patients with a treatable cause of seizures; progressive neurological disorder; clinically significant baseline laboratory abnormalities; acute or chronic confounding disease; history of alcohol or drug abuse; serious psychiatric disorder; nephrolithiasis; or a history of poor compliance with AED therapy		are not stated): abdominal pain, anorexia, ataxia, diplopia, dry mouth, tremor, upper respiratory infection 6 of 28 (21%) patients discontinued treatment owing to an AE; in 5 of these patients the AE began during the rapid titration phase; in 1 of these patients, the AE occurred during titration and at the 600 mg/day dose level There were no clinically meaningful changes in neurological examinations **Comparator** Death (n = 0); serious AE (n = 0) AEs observed in ≥ 15% of patients in either treatment groups (n = 28): fatigue (n = 10, 36%); headache (n = 10, 36%); concentration impaired (n = 0, 0%); weight loss (n = 0, 0%); dizziness (n = 1, 4%); paraesthesia (n = 1, 4%) AEs observed in 10–14% of patients (numbers or percentages are not stated): accidental injury, diarrhoea, dyspepsia, insomnia, nystagmus, upper respiratory infection 0 (0%) patients discontinued treatment owing to an AE	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Length of trial/frequency of follow-up 13 weeks; neurological examination was carried out at the initial screening visit, and then repeated periodically during the study and at the conclusion of the treatment. Patients were interviewed at each visit to document AEs			There were no clinically meaningful changes in neurological examinations	

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; a negative number denotes an increase in seizure rate (unclear over what time period) **Intervention 1** TPM (n = 28): median = 35.8% (range –554.6 to 100.0%; $p < 0.001$) There were no statistically significant treatment–centre interactions for comparisons of % seizure rate reduction ($p = 0.591$), indicating that the relative differences between TPM and placebo were consistent across study centres **Comparator** Placebo (n = 28): median = –17.8% (range –152.1 to 42.3%)	**Outcome** Proportion of responders; defined as having achieved at least a 50% reduction in seizure frequency from baseline **Intervention 1** ≥ 50% reduction: TPM (n = 28): n = 12 patients (43%); $p = 0.001$ ≥ 75% reduction: TPM (n = 28): n = 10 patients (36%); $p = 0.001$ There were no statistically significant treatment–centre interactions for comparisons of treatment responders ($p = 0.506$), indicating that the relative differences between TPM and placebo were consistent across study centres **Comparator** ≥ 50% reduction: placebo (n = 28): n = 0 patients (0%) ≥ 75% reduction: TPM (n = 28): n = 0 patients (0%); $p = 0.001$	**Outcome** Physician global evaluation of improvement/efficacy; reported as the investigator's global evaluation. Ratings were defined as 5 = marked; 4 = moderate; 3 = minimal; 2 = none; 1 = worse **Intervention 1** TPM (n = 28): mean score = 3.7; $p < 0.001$ 71% of patients showed an improvement over baseline ($p \leq 0.001$) **Comparator** Placebo (n = 28): mean score = 2.3; $p < 0.001$ 22% of patients showed an improvement over baseline	**Outcome** Patient global evaluation of improvement/efficacy; reported as the patient's global evaluation. Ratings were defined as 4 = excellent; 3 = good; 2 = fair; 1 = poor **Intervention 1** TPM (n = 28): mean score = 2.4; $p = 0.009$ 50% of patients rated TPM as good to excellent ($p = 0.009$) **Comparator** Placebo (n = 28): mean score = 1.8 18% of patients rated placebo as good to excellent

continued

Outcome 5
Outcome % reduction in generalised seizure rate **Intervention 1** TPM (n = 11): median = 90.0%; p = 0.044 ≥ 50% reduction = 9 patients (69%) 100% reduction = 6 patients (46%) **Comparator** Placebo (n = 13): median = 18.8%; p = 0.044 ≥ 50% reduction = 3 patients (27%) 100% reduction = 2 patients (18%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Biton, 1999[79] **Related publications** None **Country** USA and Costa Rica **Source** Literature search **Aim** To investigate the efficacy and safety of TPM as adjunctive therapy for the treatment of PGTC seizures in a randomised, double-blind, placebo-controlled study **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** YTC **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised (permuted blocks of size 2); after pretrial period **Details of pretrial period** There was an 8-week baseline phase, followed	**Number of participants** 103 **Type of epilepsy** Refractory **Type of seizures** Generalised onset **Mean age/age range** TPM (n = 39): 26.8 years (SD 12.8 years); placebo (n = 41): 25.6 years (SD 13.4 years); TPM (n = 39): 5-59 years; placebo (n = 41): 3–50 years Age ≤ 16 years: TPM (n = 39): n = 8; placebo (n = 41): n = 13 Age >16 years: TPM (n = 39): n = 31; placebo (n = 41): n = 28 **Gender** TPM (n = 39): men = 24, women = 15; placebo (n = 41): men = 21, women = 20 **Age at onset of seizures** Not stated **Pretrial medication** TPM (n = 39): VPA (n = 19), PHT (n = 12), CBZ (n = 11), LTG (n = 6), PB (n = 8), CZP (n = 6), GBP (n = 5); placebo (n = 41): VPA (n = 20), PHT (n = 13), CBZ (n = 9), LTG (n = 10), PB (n = 3), CZP (n = 6), GBP (n = 3), PRM (n = 6) Number of background AEDs: TPM (n = 39): 1 AED (n = 9),	**Intervention 1** TPM; 175–400 mg/day; 20 weeks No. randomised: 39 No. completed: 34 **Comparator** Placebo; 20 weeks No. randomised: 41 No. completed: 38	**Withdrawals prerandomisation** Total: n = 23 (reasons not stated) **Withdrawals postrandomisation** TPM: patient choice (n = 2), limiting AE: anorexia and weight loss (n = 1), non-compliance (n = 1), inadvertent premature discontinuation (n = 1); placebo: patient choice (n = 1), limiting AE: granulocytopenia and thrombocytopenia (n = 1), lost to follow-up (n = 1) **Adverse events** **Intervention 1** Incidence of most common (experienced by ≥ 10% of patients in the TPM group) treatment-emergent AEs: TPM (n = 39): somnolence (n = 26), anorexia (n = 15), difficulty with memory (n = 13), nervousness (n = 10), psychomotor slowing (n = 10), upper respiratory tract infection (n = 41), pharyngitis (n = 10), fatigue (n = 18), weight loss (n = 15), headache (n = 13), dizziness (n = 10), speech disorders and related speech problems (n = 10), abdominal pain (n = 10) AEs considered to be of marked severity: injury (n = 1) pain (n = 1), abnormal gait (n = 1), speech disorders and related	**Authors' conclusions** Topiramate is well tolerated and effective for the adjunctive treatment of PGTC seizures in children and adults **Comments** Information given on titration and target doses is unclear. The details extracted under 'brief details of study design …' box come from *Table 1* of the paper. However, there is text on p. 1331 of the paper to contradict this, which states that during weeks 5–8 of the titration period 'topiramate (or matching placebo) was titrated to target dosages of 175, 225 or 400 mg/day, in two divided doses. Patients then were maintained on this regimen during the stabilisation period' The 20-week follow-up period consisted of an 8-week titration phase, therefore patients were not receiving the target doses of TPM for the full 20 weeks Number achieving their target dose at some time during the double-blind treatment phase: TPM: 36; placebo: 36 Number completing the stabilisation period on their target dose: TPM: 30; placebo: 34 Mean duration of double-blind treatment: TPM: 139.9 days (SD 25.4 days); placebo: 138.8 days (SD 29.3 days)

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
by randomisation to a 20-week double-blind phase that consisted of an 8-week titration and a 12-week stabilisation period. Patients were required to experience 3 or more PGTC seizures during the baseline phase in order to proceed to the double-blind phase. At least one seizure must have occurred in each 4-week period of the baseline phase Dose of study medication (TPM or matching placebo) was based on patients' weight: patients weighing between 25 and 33.9 kg received 50 mg TPM once daily during titration weeks 1–4, 50 mg TPM twice daily during titration weeks 5–6, 75 mg TPM twice daily during titration weeks 7–8 and 75 mg TPM twice daily during stabilisation weeks 9–20; patients weighing between 34 and 42.9 kg received 50 mg TPM once daily during titration weeks 1–4, 50 mg TPM twice daily during titration weeks 5–6, 75 mg TPM twice daily during titration weeks 7–8 and 100 mg TPM twice daily during stabilisation weeks 9–20; patients weighing ≥ 43 kg received 50 mg TPM once daily during titration weeks 1–4, 75 mg TPM twice daily during titration weeks 5–6, 150 mg TPM twice daily during titration weeks 7–8 and 200 mg TPM twice daily during stabilisation weeks 9–20. The target dose (theoretical dosage range based on protocol-defined TPM maximum target dosages of 175, 225 or 400 mg/day) of the 3 weight groups were 5.2–7.0, 5.2–6.6 and 9.3 mg/kg/day, respectively. This schedule applied unless the dosage was decreased by the investigator because of AEs. If a subject could not tolerate a dose, an adjustment could be made by decreasing the study medication until a maximum tolerated dose was achieved. In addition, titration	2 AEDs (n = 19), >2 AEDs (n = 11); placebo (n = 41): 1 AED (n = 9), 2 AEDs (n = 22), >2 AEDs (n = 10) **Ongoing concurrent medication** Same as before enrolment **Co-morbidities** Not stated **Baseline seizure frequency** Median monthly seizure rate per 28 days: PGTC seizures: TPM (n = 39): 5.0 (range 1–298), placebo (n = 41): 4.5 (range 1–300); All seizures: TPM (n = 39): 15.3 (range 1–1134), placebo (n = 41): 17.5 (range 2–79 109) **Other characteristics** Race: TPM (n = 39): white = 32, black = 6, Hispanic = 1; placebo (n = 41): white = 36, black = 5, Hispanic = 0 Mean weight: TPM (n = 39): 71.8 kg (SD 28.5 kg, range 22–143 kg); placebo (n = 41): 61.3 kg (SD 25.1 kg, range 17–129 kg) Baseline seizure type: TPM (n = 39): tonic–clonic (n = 39), tonic–clonic only (n = 13), absence (n = 16), tonic (n = 9), myclonic (n = 8), drop attack (n = 2), atypical absence (n = 2),		speech problems (n = 1), viral infection (n = 1) Serious treatment-emergent AEs: pneumonia (n = 1), grand mal convulsions (n = 1), tremor, speech disorder (slurred speech), abnormal gait, nervousness (n = 1), thrombophlebitis, micturition disorder, urinary incontinence, prostatic disorder, viral infection (n = 1) **Comparator** Placebo (n = 41): somnolence (n = 15), anorexia (n = 7), psychomotor slowing (n = 2), upper respiratory tract infection (n = 32), pharyngitis (n = 5), fatigue (n = 7), weight loss (n = 2), headache (n = 20), dizziness (n = 15), speech disorders and related speech problems (n = 2), abdominal pain (n = 5) AEs considered to be of marked severity: headache (n = 2), chest pain (n = 1), dyspepsia (n = 1), increased saliva (n = 1), impotence (n = 1), granulocytopenia (n = 1) Serious treatment emergent AEs: abscess (n = 1), chest pain (n = 1)	Mean dosage of TPM during the entire double-blind phase: 3.6 (SD 1.2) mg/kg/day; mean dosage of TPM during the stabilisation phase: 5.0 (SD 1.6) mg/kg/day One patient in the placebo group did not experience PGTC seizures during the baseline phase, as required by the protocol, and was not included in the analyses of PTGC seizures. One patient in the TPM group was considered to have Lennox–Gestaut syndrome; this patient was included in the analyses The newer drugs LTG and GBP were allowed as concomitant AEDs during the study. This may have affected the study results There was no significant correlation between plasma TPM concentration and percentage reduction in average monthly PGTC seizure rate. However, there was a weak correlation between plasma TPM concentration and percentage reduction in average monthly rate of all generalised seizures (p = 0.032) When seizure response rates were evaluated for patients who completed the double-blind phase, results were consistent with those described for the ITT population. Specific results

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
intervals could be adjusted for individual subjects to achieve their maximum tolerated dose. For patients who withdrew early from the study, the dose of study medication was tapered and discontinued **ITT analysis performed/method** Authors state yes; seizure data for patients who were withdrawn from the study were averaged for the portion of the double-blind phase completed up to the time of study drug discontinuation **Sample size calculation** A sample of 36 subjects per treatment group was estimated to be adequate to detect a 30% between-group difference in PGTC seizure rate. This assumed a Type I error level of 5%, power of 80% and population SD of 45% **Analysis methods** Analyses were based on data from all randomised patients during the baseline and double-blind phases of the study. Additional analyses were performed on patients who completed the double-blind phase, but these analyses were considered to be secondary. The percentage reduction in seizure rate from baseline during the double-blind phase (for PGTC and all seizures) was analysed using a 2-way ANOVA based on ranks using the SAS (Cary, NC, USA) procedure for general linear models, to compare treatment groups. The Cochran–Mantel–Haenszel method was used to analyse differences in percentage responders (those with at least a 50, 75 or 100% reduction from baseline in average monthly rates of PGTC and of all generalised seizures) between treatment groups stratified by centre. All statistical tests were 2-sided.	clonic (n = 1), other (n = 1); placebo (n = 41): tonic–clonic (n = 40), tonic–clonic only (n = 13), absence (n = 16), tonic (n = 10), myclonic (n = 8), drop attack (n = 5), atypical absence (n = 4), clonic (n = 1), other (n = 1) **Inclusion/exclusion criteria** Inclusion: patients ≥ 4 years old; weighing >25 kg; and if female, were premenarchal or postmenopausal or practising an acceptable method of birth control; a history of PGTC seizures, with or without other generalised seizure types; receiving 1 or 2 standard AEDs; EEG findings consistent with generalised epilepsy but no other significant findings. Patients were required to give written consent Exclusion: patients with a history of partial onset seizures; a treatable cause of seizures (e.g., metabolic disturbance, toxic exposure, active infection or neoplasm); progressive neurological disease; clinically diagnosed Lennox–Gastaut syndrome; evidence of use of an experimental device within 60 days before enrolment; or treatment with AZM, ZNS, triamterene, vitamin C (>2 g per day), antacids or calcium supplements within 3 months before enrolment (because of an			relating to this can be found in the paper (p. 1334) Mean changes in plasma concentrations of concomitant AEDs during the double-blind phase relative to baseline were small in both the TPM and placebo patients and, except for CBZ (p = 0.009), were not statistically significantly different Dosage reduction due to one or more treatment emergent CNS-related AEs was required in 2 placebo patients and 4 TPM patients Results of an analysis using the Kaplan–Meier method did not show a significantly consistent relation between the first occurrence of treatment-emergent AEs and duration of exposure to TPM There were no clinically significant mean changes in any laboratory test value other than those associated with carbonic anhydrase inhibition. There were no clinically meaningful treatment-emergent changes in vital signs, neurological examination findings, physical examination findings or EEG results. TPM patients had a mean weight decrease of 1.8 kg (–2.2%), whereas placebo patients had a mean increase of 1.1 kg (+2.0%)

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Global evaluation of improvement in seizure severity was analysed using the exact Wilcoxon rank-sum test. Treatment-emergent AEs were tabulated and the cumulative incidence of treatment-emergent AEs over time was estimated using the Kaplan–Meier method. The patients' global evaluations of mental status, clinical laboratory test results, vital signs and EEGs were summarised **Length of trial/frequency of follow-up** 20 weeks; study visits were scheduled at 4-week intervals, with an additional visit after 6 weeks of the titration period	increased possibility of renal stone formation); a history of any of the following were excluded: GTC status epilepticus (within the previous 3 months) while receiving appropriate AED therapy; seizure occurring only in clustered patterns; significant medical disease (within the previous 2 years); a psychiatric or mood disorder (within the previous 6 months); attempted suicide; nephrolithiasis; malignancy; alcohol or drug abuse			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; median percentage reduction from baseline in average monthly seizure rate during the double-blind phase **Intervention 1** PGTC seizures: TPM (n = 30): 56.7%, p = 0.019 All generalised seizures: TPM (n = 39): 42.1%, p = 0.003 >16 years old: PGTC seizures: TPM (n = 31): 57% ≤ 16 years old: PGTC seizures: TPM (n = 8): 50% **Comparator** PGTC seizures: placebo (n = 40): 9.0% All generalised seizures: placebo (n = 41): 0.9%	**Outcome** Proportion of responders; percentage of patients with at least a 50% reduction in seizure frequency from baseline in the average monthly rate of seizures **Intervention 1** PGTC seizures: TPM (n = 39): 56%, p = 0.001 All generalised seizures: TPM (n = 39): 46%, p = 0.003 >16 years old: PGTC seizures: TPM (n = 31): 58% ≤ 16 years old: PGTC seizures: TPM (n = 8): 50% Proportion of patients with 75% or more reduction in seizures: PGTC seizures: TPM (n = 39): 33%, p = 0.037 All generalised seizures: TPM (n = 39): 26%, p = 0.026	**Outcome** Patients' global evaluation of improvement/efficacy; patients' global evaluation of improvement in seizure severity: 0 = worse, 1 = none, 2 = minimal, 3 = moderate, 4 = marked **Intervention 1** This was similar in the TPM and placebo groups **Comparator** Not stated	**Outcome** Patients' global evaluation of improvement/efficacy; patients' global evaluations of improvements in mental status in terms of percentage of patients who evaluated themselves as showing improvement (minimal, moderate or marked) **Intervention 1** TPM (n = 39): level of alertness 46%; level of interaction with environment 49%; ability to perform activities of daily living 41%; responsiveness to verbal requests 41%; 'TPM-treated patients tended to show more improvement than did placebo-treated patients' **Comparator** Placebo (n = 38): level of alertness 39%; level of interaction with environment 29%;

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
>16 years old: PGTC seizures: placebo (n = 28): 25% ≤ 16 years old: PGTC seizures: placebo (n = 12): 4%	Proportion of patients with 100% reduction (seizure free) in seizures: PGTC seizures: TPM (n = 39): 13%, p = 0.225 All generalised seizures: TPM (n = 39): 5%, p = 0.173 **Comparator** PGTC seizures: placebo (n = 40): 20% All generalised seizures: placebo (n = 41): 17% >16 years old: PGTC seizures: placebo (n = 28): 18% ≤ 16 years old: PGTC seizures: placebo (n = 12): 25% Proportion of patients with 75% or more reduction in seizures: PGTC seizures: placebo (n = 40): 13% All generalised seizures: placebo (n = 41): 7% Proportion of patients with 100% reduction (seizure free) in seizures: PGTC seizures: placebo (n = 40): 5% All generalised seizures: placebo (n = 41): 0%		ability to perform activities of daily living 29%; responsiveness to verbal requests 34%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Coles, 1999[60] **Related publications** None **Country** UK **Source** Literature search **Aim** To compare the effect of TPM on seizure severity, psychological health and seizure severity with placebo **Type of publication** Abstract (final analysis) **Funding** Janssen-Cilag **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a 1-month baseline period. Patients were then titrated with TPM (or placebo) over 12 weeks and according to	**Number of participants** 128 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Median age: total (n = 128): 39 years (SD not stated); not stated **Gender** Total (n = 128): men = 66, female = 62 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** No. of patients reporting certain seizure types during baseline: total (n = 128): simple partial seizures = 29; complex partial = 79; secondarily generalised = 41; PGTC either as their seizure type or as one of their seizure types = 12	**Intervention 1** TPM; not stated; 28 weeks No. randomised: not stated No. completed: not stated **Comparator** Placebo; 28 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Total: withdrawals (n = 25) **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** Analysis of the performance of the two seizure severity scales provided a novel insight into the relationship between patient-based and observer-based measures of seizure severity **Comments** This trial is in abstract form only, very few details are available and no outcome data are reported The 28-week follow-up period includes a 12-week stabilisation period. Therefore, participants may not have been receiving the target dose for these 12 weeks Although 103 patients were randomised, the authors do not state how may patients were randomised to each of the intervention groups

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
clinical outcome. There was then a 16-week stabilisation period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 28 weeks; end of baseline, titration and stabilisation or on early termination	No. of seizure types experienced by randomised patients: total (n = 103): 1 seizure type = 43.5%; 2 seizure types = 49.5%; 3 seizure types = 7% **Inclusion/exclusion criteria** Inclusion: patients were required to have a monthly seizure frequency of 3 partial onset seizures or 2 PGTC and current treatment with 1–3 AEDs			
Results				
Outcome 1	**Outcome 2**	**Outcome 3**		
Outcome Change in seizure severity; measured using the Liverpool Seizure Severity Scale (LSSS) and National Hospital Seizure Severity Scale (NHS3) **Intervention 1** Results not stated **Comparator** Results not stated	**Outcome** Psychological health (affect and balance, mastery and anxiety and depression); assessed by questionnaire **Intervention 1** Results not stated **Comparator** Results not stated	**Outcome** Seizure frequency; number of seizures in the previous 4 weeks **Intervention 1** Results not stated **Comparator** Results not stated		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Faught, 1996[67] **Related publications** Abstract[412] **Country** USA **Source** Literature search **Aim** To conduct a randomised double-blind comparison of three doses of the novel AED TPM (200, 400 and 600 mg/day) and placebo as adjunctive therapy in patients with refractory partial onset epilepsy receiving one or two other AEDs at therapeutic concentrations **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** US YD **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 233 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 181): 36.9 years; TPM 200 mg (n = 45): 38.6 years; TPM 400 mg (n = 45): 38.9 years; TPM 600 mg (n = 46): 33.8 years; placebo (n = 45): 36.2 years (SDs are not stated); total (n = 181): 19–68 years; TPM 200 mg (n = 45): 19–67 years; TPM 400 mg (n = 45): 19–61 years; TPM 600 mg (n = 46): 20–58 years; placebo (n = 45): 19–68 years **Gender** Total (n = 181): men = 143, women = 38; TPM 200 mg (n = 45): men = 29, women = 19; TPM 400 mg (n = 45): men = 39, women = 6; TPM 600 mg (n = 46): men = 39, women = 7; placebo (n = 45): men = 36, women = 9 **Age at onset of seizures** Not stated **Pretrial medication** Total (n = 181): CBZ (75%), PHT (38%); TPM 200 mg (n = 45): CBZ (73%), PHT (36%); TPM 400 mg (n = 45): CBZ (67%), PHT (38%); TPM 600 mg (n = 46): CBZ (78%),	**Intervention 1** TPM; 200 mg/day; 16 weeks No. randomised: 45 No. completed: NS **Intervention 2** TPM; 400 mg/day; 16 weeks No. randomised: 45 No. completed: NS **Intervention 3** TPM; 600 mg/day; 16 weeks No. randomised: 46 No. completed: NS **Comparator** Placebo; NA; 16 weeks No. randomised: 45 No. completed: NS	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** TPM 200 mg/day: discontinuation due to limiting AE (4%); TPM 400 mg/day: discontinuation due to limiting AE (9%); TPM 600 mg/day: discontinuation due to limiting AE (13%); placebo: discontinuation due to limiting AE (7%) **Adverse events** **Intervention 1** Treatment-emergent AEs during double-blind treatment (includes AEs reported by ≥ 20% of patients in one or more treatment groups): dizziness (36%), fatigue (11%), thinking abnormally (20%), headache (29%), ataxia (20%), somnolence (29%), nystagmus (18%), paraesthesia (18%), diplopia (7%) **Intervention 2** Dizziness (33%), fatigue (7%), thinking abnormally (13%), headache (31%), ataxia (29%), somnolence (27%), nystagmus (20%), paraesthesia (20%), diplopia (24%) **Intervention 3** Dizziness (35%), fatigue (20%), thinking abnormally (30%), headache (28%), ataxia (26%),	**Authors' conclusions** Results of this initial well-controlled study indicate that TPM is an effective drug for partial onset epilepsies, given the safety and efficacy profile **Comments** The 16-week follow-up period included a 4-week titration period. This may have influenced the study findings as patients may not have been receiving a therapeutic dose of TPM in these 4 weeks. In addition, even though the double-blind phase was 16 weeks, the length of time individuals were maintained on the target dose was not strictly 16 weeks. Depending on the target dose to which individuals were randomised (200, 400, 600 mg/day), some individuals were maintained on the target dosage longer than other individuals, as each different group reached its target dose at a different time during the titration period The number of patients who completed the trial for each treatment group is not stated. Only the total number of participants who completed the trial is stated, namely 160 of 181 patients (88%). The stated number of completers is unclear, since after subtraction for discontinuation due to AEs, the

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 12-week baseline phase, followed by a 16-week double-blind study phase, which consisted of a 4-week titration segment and a 12-week stabilisation period. Patients were continued on their AED(s) at stable dosages throughout both periods. During the titration period, patients were started on one 100-mg TPM tablet or one placebo tablet every morning for 1 week, and during the second week received a 100-mg TPM or one placebo tablet twice daily. Subsequently, the dosage increment for each 1-week titration interval was TPM 100 mg twice daily or one placebo tablet twice daily until the assigned target dose or the maximum tolerated dose, if less, was achieved. Patients were then continued at that dose throughout the stabilisation period. Patients were required to have experienced at least 12 partial seizures during the 12-week baseline period while maintained at therapeutic AED plasma concentrations in order to be randomised to the double-blind treatment. Each patient received no more than 6 tablets per day. Patients in the 200 and 400 mg/day TPM groups received combinations of TPM and placebo tablets to preserve the blinding **ITT analysis performed/method** Authors state yes; data for patients who discontinued prematurely were averaged for that portion of the double-blind phase **Sample size calculation** Not stated **Analysis methods** To assess efficacy of the three TPM dosages,	PHT (41%); placebo (n = 45): CBZ (80%), PHT 36%) **Ongoing concurrent medication** See baseline information **Co-morbidities** Not stated **Baseline seizure frequency** Mean monthly (28 days) seizure rate: total (n = 181): 26.0; TPM 200 mg (n = 45): 31.3; TPM 400 mg (n = 45): 33.0; TPM 600 mg (n = 46): 23.6; placebo (n = 45): 16.0 Median monthly (28 days) seizure rate: total (n = 181): 10.8; TPM 200 mg (n = 45): 11.5; TPM 400 mg (n = 45): 11.0; TPM 600 mg (n = 46): 11.2; placebo (n = 45): 10.0 **Other characteristics** Seizure history (individual patients may have had a history of more than one seizure type): Simple partial: total (n = 181): 47%; TPM 200 mg (n = 45): 40%; TPM 400 mg (n = 45): 47%; TPM 600 mg (n = 46): 57%; placebo (n = 45): 44% Complex partial: total (n = 181): 92%; TPM 200 mg (n = 45): 93%; TPM 400 mg (n = 45): 96%; TPM 600 mg (n = 46): 94%; placebo (n = 45): 87% Secondarily generalised: total (n = 181): 64%; TPM 200 mg (n = 45): 60%; TPM 400 mg		somnolence (30%), nystagmus (15%), paraesthesia (9%), diplopia (7%) **Comparator** Dizziness (29%), fatigue (11%), thinking abnormally (2%), headache (29%), ataxia (9%), somnolence (9%), nystagmus (18%), paraesthesia (2%), diplopia (4%)	number is 148 patients remaining (67%) For the double-blind stabilisation period, actual mean daily TPM dosages were 200 mg/day for the 200 mg/day group, 391 mg/day for the 400 mg/day group and 556 mg/day for the 600 mg/day group Treatment × centre interactions were detected for both the TPM 200 mg/day (p = 0.051) and TPM 400 mg/day (p = 0.07) versus placebo comparisons in this efficacy parameter. Further analysis conducted to investigate the consistency of results across centres in the comparison of each TPM group and placebo revealed that results favoured TPM 200 mg/day over placebo in 56% of centres and TPM 400 mg/day in 73% of centres. There was no significant treatment × centre interaction for TPM 600 mg/day, and its use was favoured over placebo in 88% of centres Results of the dose–response analysis showed a progressive reduction in the average monthly seizure rate with increasing dosage of TPM. The dose–response relationship was statistically significant whether data from the placebo group were included (p = 0.001) or excluded (p = 0.023). The dose–response

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
pairwise comparisons with placebo were made using three separate two-factor ANOVA on ranks. Treatment groups were compared with respect to percentage of responders, using the Cochran–Mantel–Haenszel method. For the statistical assessment of generalised seizures, all TPM groups were combined and compared with the placebo group, using ANOVA on rank of percentage generalised seizure reduction from the baseline to double-blind phase. A dose–response analysis for percentage reduction in the average monthly seizure rate was performed using the Jonckheere–Terpstra test. A similar analysis comparing treatment groups with respect to percent responders used the Cochran–Armitage test. Investigators' global evaluation of improvement and subjects' overall assessment of medication were analysed using Wilcoxon rank-sum tests stratified by centre **Length of trial/frequency of follow-up** 16 weeks; at the initiation of double-blind treatment and at each visit thereafter, neurological examination, measurement of vital signs, and laboratory tests were repeated	(n = 45): 58%; TPM 600 mg (n = 46): 70%; placebo (n = 45): 76% **Inclusion/exclusion criteria** Inclusion: patients in good health aged 18–65 years; with an unequivocal history of POSs with or without secondarily generalised seizures; stabilised on one or two appropriate AEDs at therapeutic plasma concentrations. An EEG taken during the preceding 5 years and documenting the presence of a lateralised or localised epileptiform pattern consistent with a diagnosis of partial epilepsy was required. A CT or MRI scan during the past two years was required to exclude progressive neurological disease. Women were required to be postmenopausal or otherwise incapable of becoming pregnant Exclusion: progressive neurological disease; history of status epilepticus during appropriate treatment; significant acute or chronic confounding disease; history of serious psychiatric disorder; alcohol or drug abuse; nephrolithiasis; non-compliance with prior therapy; recent treatment with experimental drug or device; and clinically significant abnormal baseline laboratory parameters			analysis conducted on treatment responders was significant both with (p = 0.001) or without (p = 0.033) inclusion of the placebo group Mean changes in plasma concentrations of concomitant AEDs from the baseline to double-blind phases were small and not statistically significant. Also, no interactions between TPM and any of the concomitant AEDs were detected. There were no remarkable abnormal clinical laboratory findings among TPM-treated patients and no clinically significant treatment-emergent changes were observed in vital signs, ECGs, neurological and physical examinations, audiometric tests or ophthalmological evaluations The authors do not provide figures for the total number of withdrawals for each treatment group separately – they only provide the total number of withdrawals for all groups combined and the figures for withdrawals due to limiting AEs for each treatment group separately One patient aged 67 and one aged 68 were also allowed to participate

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; reported as the percentage reduction in the average monthly seizure rate in the double-blind phase relative to the baseline phase **Intervention 1** TPM 200 mg/day: (n = 45): 29.6%; TPM vs placebo p = 0.051 Median percentage reduction in secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: TPM 200 mg/day (n = 14): 62%; p-value not stated **Intervention 2** TPM 400 mg/day: (n = 45): 47.8%; TPM vs placebo p = 0.007 Median percentage reduction in secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: TPM 400 mg/day (n = 15): 100%; p-value not stated **Intervention 3** TPM 600 mg/day: (n = 46): 44.7%; TPM vs placebo $p < 0.001$ Median percentage reduction in secondarily generalised seizures during double-blind treatment for patients demonstrating	**Outcome** Proportion of responders (at least 50% or other specified criteria); responders were defined as having the specified reductions in seizure rate from the baseline to the double-blind phase **Intervention 1** At least a 50% reduction: n = 12/45 (27%); p = 0.620 75–100% reduction: n = 4/45 (9%); p-value not stated Changes in the occurrence of secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: At least a 50% reduction: n = 10/14 (71%); p-value not stated **Intervention 2** At least a 50% reduction: n = 21/45 (47%); p = 0.013 75–100% reduction: n = 10/45 (22%); p-value not stated Changes in the occurrence of secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: At least a 50% reduction: n = 13/15 (87%); p-value not stated **Intervention 3** At least a 50% reduction: n = 21/46 (46%); p = 0.027	**Outcome** Proportion of seizure-free patients; number of participants with secondarily generalised seizures who experienced a 100% reduction in seizure frequency **Intervention 1** n = 3/14 (21%); p-value not stated **Intervention 2** n = 8/15 (53%); p-value not stated **Intervention 3** n = 4/13 (31%); p-value not stated All TPM doses: n = 15/42 (36%) **Comparator** n = 0/42 (0%)	**Outcome** Patients' global evaluation of improvement/efficacy/tolerability; patients' subjective rating of the medication. Ratings were as follows: 1 = poor; 2 = fair; 3 = good; 4 = excellent. Mean scores were presented **Intervention 1** TPM vs placebo (n = 44): mean score = 2.6; p = 0.030 Percentage of patients rating their medication as good to excellent: TPM 200 mg/day: 64%; TPM vs placebo $p \leq 0.03$ Percentage showing improvement over baseline during double-blind therapy: TPM 200 mg/day: 80%; TPM vs placebo $p \leq 0.004$ **Intervention 2** TPM vs placebo (n = 43): mean score = 2.8; p = 0.007 Percentage of patients rating their medication as good to excellent: TPM 400 mg/day: 65%; TPM vs placebo $p \leq 0.03$ Percentage showing improvement over baseline during double-blind therapy: TPM 400 mg/day: 80%; TPM vs placebo $p \leq 0.004$ **Intervention 3** TPM vs placebo (n = 45): mean score = 2.6; p = 0.053

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
generalised seizures during the baseline study phase: TPM 600 mg/day (n = 13): 89%; p-value not stated **Comparator** Placebo: (n = 45): 13.1% Median percentage reduction in secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: Baseline data: NA Follow-up data: placebo (n = 14): 1%	75–100% reduction: n = 10/46 (22%); p-value not stated Changes in the occurrence of secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: At least a 50% reduction: n = 10/13 (77%); p-value not stated All TPM doses: n = 33/42 (79%); p = 0.003 **Comparator** At least a 50% reduction: n = 8/45: (18%) 75–100% reduction: n = 4/45 (9%) Changes in the occurrence of secondarily generalised seizures during double-blind treatment for patients demonstrating generalised seizures during the baseline study phase: At least a 50% reduction: n = 3/14 (21%); p-value not stated		Percentage of patients rating their medication as good to excellent (TPM vs placebo): TPM 600 mg/day: 54%; p = 0.053 Percentage showing improvement over baseline during double-blind therapy: TPM 600 mg/day: 82%; TPM vs placebo $p \leq 0.004$ **Comparator** Placebo (n = 45): mean score = 2.2 Percentage of patients rating their medication as good to excellent: placebo: 38% Percentage showing improvement over baseline during double-blind therapy: placebo: 42%

Outcome 5

Outcome
Physician's global evaluation of improvement/efficacy/tolerability
Physician's subjective rating of patient's condition. Ratings were as follows: 1 = worse; 2 = none; 3 = minimal; 4 = moderate; 5 = marked. Mean scores were presented

Intervention 1
TPM 200 mg/day: (n = 45): mean score = 3.3; p = 0.004
Intervention 2
TPM 400 mg/day (n = 44): mean score = 3.8; $p < 0.001$
Intervention 3
TPM 600 mg/day (n = 46): mean score = 3.6; $p < 0.001$

Comparator
Comparator (n = 45): mean score = 2.7

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Guberman, 2002[150] **Related publications** Abstracts[413,414] **Country** Multinational **Source** Industry submission **Aim** To evaluate, in a double-blind, placebo-controlled study, 200 mg/day TPM in adults with treatment-resistant POSs receiving a concurrent enzyme-inducing AED **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** EPAJ-119 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Computerised; after pretrial period **Details of pretrial period** There was a 4-week baseline phase followed by a 12-week double-blind	**Number of participants** 263 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** TPM (n = 171): 37 years (SD not stated); placebo (n = 92): 36 years (SD not stated); TPM (n = 171): 18–64 years; placebo (n = 92): 18–67 years **Gender** TPM (n = 171): men = 46%, women = 54%; placebo (n = 92): men = 50%, women = 50% **Age at onset of seizures** Median years since diagnosis: TPM (n = 171): 19 years (range 0.2–54 years); placebo (n = 92): 18 years (range 0.4–42 years) **Pretrial medication** CBZ, VPA, VGB, LTG Baseline AEDs: 1 AED: TPM (n = 171): 45%; placebo (n = 92): 42%. 2 AEDs: TPM (n = 171): 55%; placebo (n = 92): 58% **Ongoing concurrent medication** CBZ, VPA, VGB, LTG **Co-morbidities** Not stated	**Intervention 1** TPM; 200 mg/day; 12 weeks No. randomised: 171 No. completed: 148 **Comparator** Placebo; NA; 12 weeks No. randomised: 92 No. completed: 89	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** TPM 25/25: AEs (n = 7), patient choice (n = 3); TPM 50/50: AEs (n = 6), patient choice (n = 6), lost-to follow-up (n = 1); placebo: AEs (n = 2), lost to follow-up (n = 1) **Adverse events** **Intervention 1** Most common AEs [AEs more frequent in TPM-treated patients (combined) vs placebo and incidence ≥ 5% in any treatment group]: TPM 25/25 (n = 85): somnolence (15%), fatigue (9%), paraesthesia (7%), nervousness (11%), anorexia (8%), weight loss (7%), dizziness (8%), abdominal pain (2%), concentration/attention difficulty (4%) TPM 50/50 (n = 86): somnolence (14%), fatigue (8%), paraesthesia (10%), nervousness (7%), anorexia (10%), weight loss (8%), dizziness (6%), abdominal pain (7%), concentration/attention difficulty (6%) All TPM (n = 171): somnolence (15%), fatigue (9%), paraesthesia (9%), nervousness (9%), anorexia (9%), weight loss (8%), dizziness (7%), abdominal pain (5%),	**Authors' conclusions** TPM 200 mg/day is an appropriate target dose as adjunctive therapy in adults with treatment-resistant POSs, even when receiving an enzyme-inducing agent; 100 mg/day also appears to be effective. A significant therapeutic effect may be seen in the second week of treatment **Comments** All extracted data come from industry submission marked commercial-in-confidence 171 patients were randomised to TPM treatment: TPM 25/25, n = 85; TPM 50/50, n = 86 The 12-week follow-up period included an 8-week titration period for the TPM group incremented by 25 mg/day and a 4-week titration period for the TPM incremented by 50 mg/day. This means that the TPM groups may not have been on the therapeutic dose of TPM for the full 12-week follow-up period and this may affect the results In addition to TPM, some patients were taking other newer AEDs including VGB and LTG. The authors do not state the number/percentage of patients in each group taking these additional

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
treatment phase. After the baseline phase, patients were randomised to placebo or one of two TPM treatment regimens: TPM 25/25 group where TPM was started on 25 mg/day and increased weekly in 25 mg/day increments (8-week escalation); or TPM 50/50 group where TPM was started on 50 mg/day and increased weekly in 50 mg/day increments (4-week escalation). The target dose was reached, therapy was maintained for the duration of the double-blind phase. The number of placebo tablets was titrated accordingly to maintain the blinding. Patients were required to experience at least 3 POSs, with or without secondary generalisation, within the 4-week baseline in order to proceed.These seizures could not be clustered **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** Statistical analyses used data from the ITT population (all patients who had at least one postrandomisation assessment). All statistical analyses were two-sided with $\alpha = 0.05$. To assess treatment effects on median percentage seizure frequency reduction, a two-way ANOVA on ranks was used. To analyse treatment response and reduction of secondarily generalised seizures, the Cochran–Mantel–Haenszel test was used. Kaplan–Meier estimates of cumulative occurrence rates were evaluated	**Baseline seizure frequency** Median monthly seizure frequency: POS: TPM ($n = 171$): 7 (range 2–184); placebo ($n = 92$): 7 (range 2–462). Secondarily generalised: TPM ($n = 171$): 1 (range 0–34); placebo ($n = 92$): 1 (range 0–27) **Other characteristics** Median CBZ dose: TPM ($n = 171$): 1000 mg/day (range 100–2400); placebo ($n = 92$): 1200 mg/day (range 200–1800) Baseline seizure type: SPS: TPM ($n = 171$): 27%; placebo ($n = 92$): 29%. CPS: TPM ($n = 171$): 77%; placebo ($n = 92$): 74%. Secondarily generalised: TPM ($n = 171$): 32%; placebo ($n = 92$): 39% **Inclusion/exclusion criteria** Inclusion: male and female participants aged 18–65 years, weighing at least 45 kg and receiving CBZ with or without another AED in stable dosages. Women had to be postmenopausal or incapable of childbearing; women of childbearing potential had to be practising a medically acceptable method of birth control Exclusion: a treatable cause of seizures; progressive neurological disorder or primary generalised epilepsy; a documented history of status epilepticus during the past 3 months were also excluded		concentration/attention difficulty (5%) **Comparator** Placebo ($n = 92$): somnolence (9%), fatigue (4%), paraesthesia (2%), nervousness (2%), anorexia (7%), weight loss (4%), dizziness (4%), abdominal pain (3%), concentration/attention difficulty (0%)	newer AEDs. This may affect the findings of the study 93% of the TPM 25/25 group and 94% of the TPM 50/50 group achieved the target dosage of 200 mg/day TPM At the end of double-blind treatment, mean body weight was reduced by 1.9 kg (2.6% of baseline body weight) in TPM-treated patients, and 0.1 kg (0.1%) in placebo-treated patients. Weight was reduced at the first on-treatment visit (week 2) and continued during double-blind treatment Authors claim to have used ITT analysis, but this does not seem to be the case according to the number of patients used in the analyses in each treatment group

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
for the comparison of tolerability vs titration rate **Length of trial/frequency of follow-up** 12 weeks; days 1, 15, 29, 43, 57 and 85 (final visit)				
Results				
Outcome 1		**Outcome 2**		**Outcome 3**
Outcome Change in seizure frequency; the median percentage reduction from baseline in monthly POS frequency **Intervention 1** Double-blind treatment (1–12 weeks): TPM (n = 168): 44%; $p < 0.001$ (TPM vs placebo) Maintenance period (9–12 weeks): TPM (n = 150): 53%; $p < 0.001$ Early titration period (1–2 weeks): TPM 50 mg/day (n = 85): 25%; $p = 0.521$ Early titration period (1–2 weeks): TPM 100 mg/day (n = 84): 60%; $p < 0.001$ Early titration period (1–2 weeks): all TPM (n = 169): 33%; $p = 0.013$ Median percentage reduction from baseline in monthly secondarily generalised seizure frequency for patients with secondarily generalised seizures during the baseline phase: Double-blind treatment (1–12 weeks): TPM (n = 55): 50%; $p = 0.003$ (TPM vs placebo) **Comparator** Double-blind treatment (1–12 weeks): placebo (n = 91): 20% Maintenance period (9–12 weeks): placebo (n = 88): 13% Early titration period (1–2 weeks): placebo (n = 91): 17% Median percentage reduction from baseline in monthly secondarily generalised seizure frequency for patients with secondarily generalised seizures during the baseline phase: Double-blind treatment (1–12 weeks): placebo (n = 36): 1%		**Outcome** Proportion of responders; percentage of patients whose seizures were reduced by at least 50% **Intervention 1** Double-blind treatment (1–12 weeks): TPM (n = 168): 45%; $p = 0.001$ (TPM vs placebo): Maintenance period (9–12 weeks): TPM (n = 150): 58%; $p = 0.001$ Early titration period (1–2 weeks): TPM 50 mg/day (n = 85): 35%; $p = 0.458$ Early titration period (1–2 weeks): TPM 100 mg/day (n = 84): 48%; $p = 0.01$ Early titration period (1–2 weeks): all TPM (n = 169): 41%; $p = 0.056$ Percentage of patients whose secondarily generalised seizures were reduced ≥50% for patients with secondarily generalised seizures during the baseline phase: Double-blind treatment (1–12 weeks): TPM (n = 55): 50%; $p = 0.05$ **Comparator** Double-blind treatment (1–12 weeks): placebo (n = 91): 24% Maintenance period (9–12 weeks): placebo (n = 88): 33% Early titration period (1–2 weeks): placebo (n = 91): 30% Percentage of patients whose secondarily generalised seizures were reduced ≥50% for patients with secondarily generalised seizures during the baseline phase: Double-blind treatment (1–12 weeks): placebo (n = 36): 34%		**Outcome** Proportion of seizure-free patients; percentage of patients having no seizures **Intervention 1** Double-blind treatment (1–12 weeks): TPM (n = 168): 6%; p-value not stated Maintenance period (9–12 weeks): TPM (n = 150): 20%; p-value not stated **Comparator** Double-blind treatment (1–12 weeks): placebo (n = 91): 2% Maintenance period (9–12 weeks): placebo (n = 88): 9%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Korean Topiramate Study Group, 1999[149] **Related publications** None **Country** Korea **Source** Literature search **Aim** To evaluate the efficacy and safety of TPM as add-on therapy in medically intractable partial epilepsies **Type of publication** Full paper (final analysis) **Funding** Janssen Korea **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** In a ratio of 1:1 in blocks of 4 per study centre; after pretrial period **Details of pretrial period** There was a 12-week baseline phase after which randomisation occurred, followed by	**Number of participants** 235 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** TPM (n = 91): 29.58 years (SD 7.80 years); placebo (n = 86): 29.77 years (SD 8.71 years); p = 0.88; not stated **Gender** TPM (n = 91): men = 47, women = 44; placebo (n = 86): men = 48, women = 38; p = 0.58 **Age at onset of seizures** Duration of illness: TPM (n = 91): 15.0 years (SD 8.8); placebo (n = 86): 17.5 years (SD 8.2); p = 0.06 **Pretrial medication** TPM (n = 91): 1 AED n = 22 (24.2%) p = 0.37, 2 AEDs n = 69 (75.8%) p-value not stated; placebo (n = 86): 1 AED n = 16 (18.6%), 2 AEDs n = 70 (81.4%) **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated	**Intervention 1** TPM; 600 mg/day; 18 weeks No. randomised: 91 No. completed: 76 **Comparator** Placebo; 18 weeks No. randomised: 86 No. completed: 77	**Withdrawals prerandomisation** Total: screening failure (n = 58): non-permitted medication (n = 18), fewer than 2 seizures (n = 16), patient's non-cooperation and lost to follow-up (n = 15), change of AED dose (n = 3), other non-drug-related reasons (n = 5) **Withdrawals postrandomisation** TPM: withdrawal during titration phase due to AE (n = 6), withdrawal during titration phase due to non-drug-related cause (n = 7); withdrawal during stabilisation phase due to AE (n = 1), withdrawal during stabilisation phase due to non-drug-related cause (n = 1) Placebo: withdrawal during titration phase due to AE (n = 3), withdrawal during titration phase due to non-drug-related cause (n = 3); withdrawal during stabilisation phase due to non-drug-related cause (n = 3) **Adverse events** **Intervention 1** Treatment-emergent AEs reported in >5% of the study patients: (TPM vs placebo): TPM (n = 91): anorexia (n = 19, 20.9%, p = 0.003), abdominal discomfort/pain (n = 19, 20.9%, p = 0.001), dizziness (n = 18,	**Authors' conclusions** TPM was highly effective and safe as add-on therapy in medically intractable partial epilepsies. Slower titration of TPM might be responsible for the lower drop-out rate than previous trials, but the incidence of AEs was still high. The AE profile of TPM in Koreans was different from that in whites **Comments** The follow-up period of 18 weeks included a 10-week titration phase, which may influence the study findings as patients may not have been receiving a therapeutic dose of TPM during these 10 weeks 49 patients in the TPM group and 70 patients in the placebo group reached the target dose at the end of the titration phase. This was significantly different (p = 0.0001), which may affect the study findings. The mean doses of study drugs were 448.9 mg (SD 170.7 mg) in the TPM group and 544.1 mg (SD 119.4 mg), based on the same size and appearance of TPM tablets, in the placebo group (p = 0.0003), which may affect the study findings. In the TPM group, 17 patients took ≤200 mg/day, 21 patients took ≤400 mg/day and 51 patients took >400 mg/day. (It is not clear whether ≤400 mg/day is actually meant to state between

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
a 10-week titration phase and an 8-week stabilisation phase. The starting dose of drugs was 50 mg/day. This was increased by 50 mg every week until 400 mg/day was reached. Thereafter the dose was increased by 100 mg every week over the next 2 weeks to reach the target dose of 600 mg/day or the maximally tolerable dose. If intolerable AEs occurred, the dose was decreased to that of the previous week. Patients were required to have two or more episodes of clinical seizures every four weeks during three consecutive 4-week periods during the baseline phase in order to enter into the titration phase. Patients who were able to take 200 mg/day or more at the end of the titration phase were entered into the stabilisation phase **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Sample size was calculated by using an established formula. SDs of the TPM and placebo groups, using calculations from the related YE study, were 98.7 and 74.3, respectively. Difference of efficacy between the TPM and the placebo groups was 58.6, which yielded $n = 47$. Considering a drop-out rate of 12%, the adequate number of patients for each group was 54 **Analysis methods** ITT analysis was performed for efficacy and safety measurements. The primary data set for the efficacy analysis consisted of all randomised patients for whom at least one seizure evaluation was available in the double-blind period. Seizure frequency	**Baseline seizure frequency** Mean seizure frequency (episodes/4 weeks): TPM ($n = 91$): 9.4 (SD 14.8); placebo ($n = 86$): 11.5 (SD 2.4); $p = 0.47$ Median seizure frequency (episodes/4 weeks): TPM ($n = 91$): 5.6; placebo ($n = 86$): 5.6; $p = 0.94$ <4/4 weeks: TPM ($n = 91$): 34 (37.4%); placebo ($n = 86$): 30 (34.9%); $p = 0.73$ **Other characteristics** Body weight: TPM ($n = 91$): 63.7 kg (SD 10.9); placebo ($n = 86$): 63 kg (SD 10.5); $p = 0.81$ Seizure types: Simple partial motor seizures (SPMSs): TPM ($n = 91$): 11 (12.1%); placebo ($n = 86$): 5 (5.8%); $p = 0.15$ CPSs: TPM ($n = 91$): 70 (76.9%); placebo ($n = 86$): 72 (83.7%); $p = 0.26$. GTC seizures: TPM ($n = 91$): 31 (34.1%); placebo ($n = 86$): 39 (45.4%); $p = 0.13$ **Inclusion/exclusion criteria** Inclusion: aged 16–65 years; with well-established partial epilepsies refractory to the maximally tolerable doses of one to two AEDs; were required to have been treated with one or two marketed AEDs at clinically maximally tolerable doses, which required a clear documentation of toxic symptoms at current or higher doses of AEDs on their medical charts. The seizure types for counting were clinically identifiable seizures: SPMSs, CPSs		19.8%, $p = 0.85$), somnolence ($n = 18$, 19.8%, $p = 0.85$), nausea/vomiting ($n = 15$, 16.5%, $p = 0.09$), headache ($n = 10$, 11.0%, $p = 0.52$), amblyopia ($n = 10$, 11.0%, $p = 0.12$), speech disturbance ($n = 9$, 9.9%, $p = 0.01$), psychomotor slowing ($n = 8$, 8.8%, $p = 0.02$), weight loss ($n = 8$, 8.8%, $p = 0.005$), ataxia ($n = 7$, 7.7%, $p = 0.10$), memory impairment ($n = 6$, 6.6%, $p = 0.06$), general weakness ($n = 5$, 5.5%, $p = 0.28$) % of TPM ($n = 91$) patients with treatment-emergent AEs: 81.3% ($n = 74$), TPM vs placebo $p = 0.001$ **Comparator** Placebo ($n = 86$): anorexia ($n = 5$, 5.8%), abdominal discomfort/pain ($n = 2$, 2.3%), dizziness ($n = 18$, 21%), somnolence ($n = 8$, 9.3%), nausea/vomiting ($n = 7$, 8.1%), headache ($n = 6$, 7.0%), amblyopia ($n = 4$, 4.7%), speech disturbance ($n = 1$, 1.1%), psychomotor slowing ($n = 1$, 1.2%), weight loss ($n = 0$, 0.00%); ataxia ($n = 2$, 2.3%), memory impairment ($n = 1$, 1.2%), general weakness ($n = 2$, 2.3%) Proportion of placebo ($n = 86$) patients with treatment-emergent adverse events: 48.8% ($n = 42$)	200 and 400 mg/day, in which case $n = 89$. As stated above, ≤ 400 mg/day implies that $n = 72$. Also, it is stated earlier that patients who were able to take ≥ 200 mg/day at the end of the titration phase were entered into the stabilisation period) When efficacy in different types of seizure was analysed, only CPS reached a significant level of improvement in the TPM group. The improvement of SPMS and GTC seizures did not reach significance No serious systemic or haematological AEs were found and none developed nephrolithiasis during the trial. The results of laboratory tests performed before and after the study drugs did not show any appreciable differences Mean weight loss (TPM vs placebo): TPM: 4.43 kg (SD 4.85); placebo: –0.88 kg (SD 4.54); $p < 0.0001$ No. of patients with loss of ≥ 5% of baseline bodyweight (TPM vs placebo): TPM: 36; placebo: 3; $p = 0.001$

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
reduction rates were compared using the Wilcoxon rank-sum test and *t*-test. The χ^2 test was used to compare responder rates between the two groups. The Cochran–Mantel–Haenszel test with study centres as the strata was performed. The multifactorial analysis to control for other characteristics of patients was performed by using logistic regression for responder rate **Length of trial/frequency of follow-up** 18 weeks; baseline phase: clinic visits every 4 weeks; titration phase: clinic visits every 2 weeks and telephone contact in between; stabilisation phase: clinic visits every 4 weeks	and GTC seizures. All patients or their guardians were required to give signed informed consent at the time of screening Exclusion: auras or subjective sensory seizures that were not clinically apparent; female patients of childbearing potential who were not using an approved method of birth control; a history of pseudoseizures; any active systemic or neurological diseases; a history of drug or alcohol abuse; a history of non-compliance; use of drugs known to cause nephrolithiasis (i.e. triamterene, AZM, ZNS, vitamin C) within the past 6 months			

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; reported as the median seizure frequency reduction rate (MSFRR) **Intervention 1** All seizures ($n = 89$): 51.3%, $p = 0.0001$ CPS ($n = 70$): 49.4%, $p = 0.0001$ SPMS ($n = 9$): 87.5%, $p = 0.94$ GTC seizures ($n = 28$): 100%, $p = 0.25$ No significant differences in MSFRR were found between the following three groups: patients taking ≤200 mg TPM, patients taking >200 mg but ≤400 mg TPM, patients taking >400 but ≤600 mg TPM	**Outcome** Proportion of responders; defined as achieving at least a 50% reduction in seizure frequency **Intervention 1** $n = 45/89$ (50.6%), $p = 0.001$ Cochran–Mantel–Haenszel relative responder rate of TPM to placebo = 4.38 (95% CI: 2.21 to 8.69) No significant differences in responder rate or seizure free rate were found between the following three groups: patients taking ≤200 mg TPM, patients taking >200 mg but ≤400 mg TPM, patients taking >400 but ≤600 mg TPM	**Outcome** Proportion of seizure-free patients **Intervention 1** $n = 7/89$ (7.9%), $p = 0.04$ No significant differences in seizure-free rate were found between the following three groups: patients taking ≤200 mg TPM, patients taking >200 but ≤400 mg TPM, patients taking >400 but ≤600 mg TPM **Comparator** $n = 1/85$ (1.2%)	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; subjective rating by patients as to how they have improved **Intervention 1** TPM ($n = 76$): excellent = 27 (35.5%); good = 23 (30.3%); fair = 21 (27.6%); no effect = 5 (6.6%); TPM vs placebo $p = 0.001$ **Comparator** Placebo ($n = 77$): excellent = 5 (6.5%); good = 14 (18.2%); fair = 23 (29.9%); no effect = 35 (45.5%)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Comparator All seizures (n = 85): 9.1% CPS (n = 72): –14.3% SPMS (n = 4): 72.9% GTC seizures (n = 35): 40.26%	**Comparator** n = 11/85 (12.9%)		

Outcome 5	Outcome 6
Outcome Physician's global evaluation of improvement/efficacy/tolerability; assessment by physician as to how patients have improved **Intervention 1** TPM (n = 76): excellent = 26 (34.2%); good = 20 (26.3%); fair = 12 (15.8%); no effect = 18 (23.9%); TPM vs placebo p = 0.001 **Comparator** Placebo (n = 77): excellent = 6 (7.8%); good = 13 (16.9%); fair = 20 (25.8%); no effect = 38 (49.4%)	**Outcome** Median seizure frequency (episodes/ 4 weeks) **Intervention 1** Follow-up data: TPM (n = 89): 2.4, TPM vs placebo p = 0.0001 **Comparator** Follow-up data: placebo (n = 85): 5.1

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Meador, 2001[44] **Related publications** None **Country** USA **Source** Literature search **Aim** To evaluate effects on cognitive function of TPM and VPA as add-on therapy to CBZ in adults with POSs **Type of publication** Abstract (final analysis) **Funding** Ortho-McNeill Pharmaceutical **Trial ID** Not stated **Study design** Add-on therapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** Patients with ≥3 seizures during a 4-week baseline period were randomised; the titration period ended at 8 weeks; the study ended at 20 weeks	**Number of participants** 76 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated (SD not stated); total (n = 76): 17–66 years **Gender** Total: men = 33, women = 43 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** CBZ 1020–1200 mg/day **Co-morbidities** Not stated **Baseline seizure frequency** Not stated. However, randomised patients had ≥3 seizures during the 4-week baseline period **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: adults with POSs with ≥3 seizures during the 4-week baseline period	**Intervention 1** TPM; 400 mg/day; 20 weeks No. randomised: not stated No. completed: 34 **Intervention 2** VPA; 2250 mg/day; 20 weeks No. randomised: not stated No. completed: 29 **Comparator** Placebo; 20 weeks No. randomised: not stated No. completed: 13	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Intervention 2** Not stated **Comparator** Not stated	**Authors' conclusions** A subset of patients were more sensitive to drug effects from both TPM and VPA (based on a *post hoc* analysis) **Comments** Randomisation is reported to have occurred after the baseline period. Withdrawal, drop-out and loss to follow-up are not mentioned Explicit denominators are not reported. The mean dose of TPM was 395, VPA 1928 and CBZ 1020–1200 mg/day Of the 30 tests, six (7%) showed significantly greater negative baseline-to-titration changes for TPM versus VPA. Results for the neuropsychometric and mood measures are reported in summary only, not per test. Placebo results are not reported Cognitive complaints with TPM and VPA were similar. The outcomes listed represent selective reporting by the authors of tests where slightly more TPM patients had cognitive complaints compared with VPA patients. At the end of the study (20 weeks), only SDM and COWA test results were significantly different for TPM versus VPA. This 'sensitivity' was used to distinguish the subsets used in the *post hoc* analysis of Z-score changes for

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
ITT analysis performed/method Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** In the *post hoc* analysis, mean *Z*-scores were calculated for the remaining 28 tests in TPM- and VPA-treated patients with >1 SD on the symbol digit modalities (SDM) test or controlled oral word association (COWA) test (SDM/COWA sensitive) and <1 SD change (SDM/COWA insensitive) **Length of trial/frequency of follow-up** 24 weeks; at baseline, end of titration (8 weeks) and study end (20 weeks)				the other 28 tests on which the authors' conclusion is based. With TPM the mean *Z*-score change was –0.01 in the sensitive subset and 0.10 in the insensitive subset. With VPA the mean *Z*-score change was –0.34 in the sensitive subset and 0.19 in the insensitive subset

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Psychomotor slowing; not defined **Intervention 1** 3/34 **Intervention 2** 1/29 **Comparator** Not reported	**Outcome** Mood problems; not defined **Intervention 1** 3/34 **Intervention 2** 0/29 **Comparator** Not reported	**Outcome** Speech difficulty; this included, for example, difficulty in word finding **Intervention 1** 4/34 **Intervention 2** 2/29 **Comparator** Not reported	**Outcome** Confusion; not defined **Intervention 1** 2/34 **Intervention 2** 1/29 **Comparator** Not reported

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Privitera, 1996[68] **Related publications** Abstract[417] **Country** USA **Source** Literature search **Aim** To evaluate the safety and efficacy of three doses of TPM (600, 800 and 1000 mg/day) as adjunctive therapy for patients with refractory partial epilepsy **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** US YE **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a 12-week baseline phase followed by an 18-week double-blind	**Number of participants** 240 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 190): 35.5 years (SD not stated); TPM 600 mg/day (n = 48): 35.6 years; TPM 800 mg/day (n = 48): 34.3 years; TPM 1000 mg/day (n = 47): 36.3 years; placebo (n = 47): 35.0 years; total (n = 190): 18–68 years; TPM 600 mg/day (n = 48): 18–57 years; TPM 800 mg/day (n = 48): 18–67 years; TPM 1000 mg/day (n = 47): 18–64 years; placebo (n = 47): 18–68 years **Gender** Total (n = 190): men = 152, women = 38; TPM 600 mg/day (n = 48): men = 38, women = 10; TPM 800 mg/day (n = 48): men = 41, women = 7; TPM 1000 mg/day (n = 47): men = 40, women = 7; placebo (n = 47): men = 33, women = 14 **Age at onset of seizures** Not stated **Pretrial medication** Total: CBZ (70%), PHT (35%); TPM 600 mg/day: CBZ (75%), PHT (31%); TPM 800 mg/day: CBZ (69%), PHT (27%); TPM 1000 mg/day: CBZ (74%), PHT (45%); placebo: CBZ (64%), PHT (36%)	**Intervention 1** TPM; 600 mg/day; 18 weeks No. randomised: 48 No. completed: 38 **Intervention 2** TPM; 800 mg/day; 18 weeks No. randomised: 48 No. completed: 43 **Intervention 3** TPM; 1000 mg/day; 18 weeks No. randomised: 47 No. completed: 39 Comparator Placebo; 18 weeks No. randomised: 47 No. completed: 46	**Withdrawals prerandomisation** Total: lost owing to not meeting the qualification criteria (n = 50) **Withdrawals postrandomisation** TPM 600 mg/day: discontinued owing to limiting AE (n = 10); TPM 800 mg/day: discontinued owing to limiting AE (n = 5); TPM 1000 mg/day: discontinued owing to limiting AE (n = 8); placebo: discontinued owing to limiting AE (n = 1) **Adverse events** **Intervention 1** Treatment-emergent AEs and discontinuations for limiting AEs (includes AEs reported by ≥ 20% of patients in any treatment group): TPM 600 mg/day (n = 48): dizziness (n = 33), fatigue (n = 38), diplopia (n = 15), nystagmus (n = 8), confusion (n = 21), somnolence (n = 13), thinking abnormal (n = 33), ataxia (n = 15), concentration impaired (n = 17), anorexia (n = 10), headache (n = 33), paraesthesia (n = 23) **Intervention 2** TPM 800 mg/day (n = 48): dizziness (n = 35), fatigue (n = 23), diplopia (n = 21), nystagmus (n = 23), confusion (n = 23), somnolence (n = 31), thinking abnormal (n = 44), ataxia	**Authors' conclusions** Results of this study indicate that TPM is a highly efficacious and generally well-tolerated AED when used as adjunctive therapy in patients with refractory partial seizures. When groups of patients are compared, dosages of TPM >600 mg/day do not appear to produce significant incremental efficacy and may result in a higher incidence and greater severity of AEs. However, higher dosages may prove beneficial to individuals who can tolerate them **Comments** The 18-week follow-up period included a 6-week titration period. This may have influenced the study findings as patients may not have been receiving a therapeutic dose of TPM in these 6 weeks. In addition, even though the double-blind phase was 18 weeks, the length of time individuals were maintained on the target dose was not strictly 18 weeks. Depending on the target dose to which individuals were randomised (600, 800, 1000 mg/day), some individuals were maintained on the target dosage longer than other individuals, as each different group reached its target dose at a different time during the titration period. Those in the TPM 600 mg/day group were maintained on this target dose for

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
phase. Patients were randomised after the 12-week baseline phase. For admission to the double-blind phase, patients were required to have experienced at least 12 partial seizures during the baseline phase while being maintained on one or two AEDs at therapeutic plasma concentrations. During that phase the longest allowable seizure-free interval was 3 weeks and only one such interval was permitted. The 18-week double-blind phase consisted of a 6-week titration period and a 12-week stabilisation period. All patients were scheduled to eventually receive 5 tablets b.d. of TPM or placebo in a combination that matched their dose assignment. Patients received either 100 mg of TPM or one placebo tablet once daily during the 1st week of the titration period and 100 mg of TPM or one placebo tablet b.d. during the 2nd week. The subsequent dosage increment for each remaining titration week was 100 mg of TPM b.d. or one placebo tablet b.d. until the lesser of the assigned dosage or the maximum tolerated dosage was reached. Patients were then followed on this regimen throughout the stabilisation period **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** ITT analyses of efficacy measures included all patients entering the double-	**Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Mean baseline average seizure rate/28 days: Total (n = 190): 26.6; TPM 600 mg/day (n = 48): 23.5; TPM 800 mg/day (n = 48): 39.8; TPM 1000 mg/day (n = 47): 24.7; placebo (n = 47): 18.2 Median baseline average seizure rate/28 days: Total (n = 190): 11.0; TPM 600 mg/day (n = 48): 10.0; TPM 800 mg/day (n = 48): 16.2; TPM 1000 mg/day (n = 47): 11.7; placebo (n = 47): 9.3 **Other characteristics** No. of patients with seizure history (patients may have had a seizure history of more than 1 seizure type): Simple partial: total (n = 190): 90; TPM 600 mg/day (n = 48): 22; TPM 800 mg/day (n = 48): 22; TPM 1000 mg/day (n = 47): 27; placebo (n = 47): 19 Complex partial: total (n = 190): 177; TPM 600 mg/day (n = 48): 46; TPM 800 mg/day (n = 48): 42; TPM 1000 mg/day (n = 47): 45; placebo (n = 47): 44 Secondarily generalised: total (n = 190): 119; TPM 600 mg/day (n = 48): 29; TPM 800 mg/day (n = 48): 33; TPM 1000 mg/day (n = 47): 21; placebo (n = 47): 36		(n = 19), concentration impaired (n = 8), anorexia (n = 6), headache (n = 27), paraesthesia (n = 19) **Intervention 3** TPM 1000 mg/day (n = 47): dizziness (n = 38), fatigue (n = 23), diplopia (n = 28), nystagmus (n = 28), confusion (n = 28), somnolence (n = 34), thinking abnormal (n = 26), ataxia (n = 19), concentration impaired (n = 21), anorexia (n = 21), headache (n = 19), paraesthesia (n = 13) Other AEs: abdominal pain (n = 1); shortness of breath (n = 1); death (n = 0) **Comparator** Placebo (n = 47): dizziness (n = 15), fatigue (n = 9), diplopia (n = 13), nystagmus (n = 17), confusion (n = 9), somnolence (n = 13), thinking abnormal (n = 6), ataxia (n = 9), anorexia (n = 4), headache (n = 32), paresthesia (n = 6)	15 weeks, those in the 800 mg/day group were maintained for 14 weeks and those in the 1000 mg/day group were maintained for 13 weeks Target study medication dosages were not reached by all patients; this may influence the study findings. For the double-blind stabilisation period, actual mean daily TPM dosages were as follows: TPM 600 mg/day: 544 mg/day TPM 800 mg/day: 739 mg/day TPM 1000 mg/day: 799 mg/day Proportion of patients reaching target dose: TPM 600 mg/day: 73% TPM 800 mg/day: 69% TPM 1000 mg/day: 55% The highest dose of TPM (1000 mg/day) is outwith the recommended dosage Despite the inclusion/exclusion criteria, one 68- and one 67-year-old patient were also admitted to the trial With regard to the field 'number of patients who completed the trial who were originally assigned to intervention group', it is possible that the figures given could be lower since the number of drop-outs is unclear. The authors state the number of persons discontinuing treatment

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
blind study phase and all seizure data from both the titration and stabilisation periods. For the principal efficacy variable, percentage reductions in seizure rate from baseline to double-blind phase were computed, and pairwise comparisons of the 3 TPM dosages with placebo were performed using 3 separate 2-factor ANOVA on ranks. Percentage responders in the treatment groups were also compared using the Cochran–Mantel–Haenszel test, whereas investigator and subject overall assessments were analysed by Wilcoxon rank-sum tests. Because there were few patients with generalised seizures, all TPM groups were combined and compared with the placebo group using ANOVA on rank of percentage generalised seizure reduction **Length of trial/frequency of follow-up** 18 weeks; not specifically stated. All that is stated is that safety measures were taken at baseline and repeated during and at the conclusion of the study, and that patients were evaluated for AEs at each visit	GTC: total (n = 190): 1; TPM 600 mg/day (n = 48): 0; TPM 800 mg/day (n = 48): 0; TPM 1000 mg/day (n = 47): 1; placebo (n = 47): 0 **Inclusion/exclusion criteria** Inclusion: 18–65 years of age; with a history of refractory partial epilepsy with or without secondary generalisation; have good physical health. Women were required to be postmenopausal or otherwise incapable of becoming pregnant. Required pre-entry confirmatory studies included an EEG within the last 5 years demonstrating an epileptiform pattern consistent with a diagnosis of partial epilepsy and a CT or MRI scan within the last 2 years to exclude the possibility of progressive neurological disease Exclusion: patients with a treatable cause of seizures; progressive neurological condition; a history of status epilepticus; serious psychiatric disorder; nephrolithiasis; substance abuse; or significant confounding acute or chronic disease; treated with another experimental drug within 60 days before the study; those with clinically significant laboratory abnormalities at baseline and patients considered unable to maintain a seizure diary or having a history of poor compliance with AED therapy were also excluded			owing to a limiting AE for each group. However, it is unclear whether there were others that dropped out for reasons other than a limiting AE With regard to the field number of patients discontinuing treatment: 1. The number of those discontinuing owing to limiting AEs (according to the figures given in the table) is fairly high, particularly in the TPM 600 and 1000 mg/day groups, which may affect the results of the study. 2. Most of the patients who discontinued dropped out during the titration period, and most limiting events were CNS-related symptoms There were no clinically significant mean changes from baseline in any of the clinical laboratory tests, and no individual abnormality was considered to represent a clinically relevant drug-related change

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; the median percentage reduction in the average seizure rate from the baseline phase to the double-blind phase (negative numbers denote an increase in seizure rate) **Intervention 1** TPM 600 mg/day (n = 48): 40.7%; TPM vs placebo $p < 0.001$ Changes in secondarily generalised seizure rate for patients reporting generalised seizures during the baseline study phase: TPM 600 mg/day (n = 12): 65.5%; p-value not stated **Intervention 2** TPM 800 mg/day (n = 48): 41.0%; TPM vs placebo $p < 0.001$ Changes in secondarily generalised seizure rate for patients reporting generalised seizures during the baseline study phase: TPM 800 mg/day (n = 17): 44.4%; p-value not stated **Intervention 3** TPM 1000 mg/day: (n = 47): 37.5%; TPM vs placebo $p < 0.001$ Changes in secondarily generalised seizure rate for patients reporting generalised seizures during the baseline study phase: TPM 1000 mg/day (n = 11): 78.0%; p-value not stated All TPM (n = 40): 55.3%; p-value not stated **Comparator** Placebo: (n = 47): 1.2%	**Outcome** Proportion of responders (at least 50% or other specified criteria); numbers of responders were reported according to specified criteria **Intervention 1** At least 50% reduction: n = 21/48 (43.8%); $p < 0.001$ 75–100% reduction: n = 11/48 (23%); p-value not stated Analyses of seizure rate reductions and treatment responders were also conducted using only stabilisation period data and including only patients who completed the trial at their assigned dosage. In both cases, the results were congruent with the ITT analysis Changes in secondarily generalised seizures for patients reporting generalised seizures during the baseline study phase: At least 50% reduction: n = 8/12 (67%); p-value not stated **Intervention 2** At least 50% reduction: n = 19/48 (39.6%); $p < 0.001$ 75–100% reduction: n = 12/95 (13%); p-value not stated Analyses of seizure rate reductions and treatment responders were also conducted using only stabilisation period data and including only patients who completed the trial at their assigned dosage. In both cases, the results were congruent with the ITT analysis	**Outcome** Physicians' global evaluation of improvement/efficacy/tolerability; investigators' subjective rating of the global improvement in patients. Reported as mean scores. Ratings were as follows: 1 = worse; 2 = none; 3 = minimal; 4 = moderate; 5 = marked **Intervention 1** TPM 600 mg/day: (n = 47): mean score = 3.5; TPM vs placebo $p < 0.001$ Proportion showing improvement over baseline during double-blind therapy: TPM 600 mg/day: 72%; $p \leq 0.001$ **Intervention 2** TPM 800 mg/day: (n = 48): mean score = 3.5; TPM vs placebo $p < 0.001$ Proportion showing improvement over baseline during double-blind therapy: TPM 800 mg/day: 85%; $p \leq 0.001$ **Intervention 3** TPM 1000 mg/day: (n = 47): mean score = 3.5; TPM vs placebo $p < 0.001$ Proportion showing improvement over baseline during double-blind therapy: TPM 1000 mg/day: 72%; $p \leq 0.001$ **Comparator** Placebo: (n = 47): mean score = 2.4 Proportion showing improvement over baseline during double-blind therapy: placebo: 28%	**Outcome** Patients' global evaluation of improvement/efficacy/tolerability; patients' overall subjective rating of the study medication. Reported as mean scores. Ratings were as follows: 1 = poor; 2 = fair; 3 = good; 4 = excellent **Intervention 1** TPM 600 mg/day: (n = 48): mean score = 2.6; TPM vs placebo $p < 0.001$ Proportion of patients rating their medication as good to excellent: TPM 600 mg/day: 62%; $p \leq 0.015$ **Intervention 2** TPM 800 mg/day: (n = 48): mean score = 2.6; TPM vs placebo $p < 0.001$ Proportion of patients rating their medication as good to excellent: TPM 800 mg/day: 57%; $p \leq 0.015$ **Intervention 3** TPM 100 mg/day: (n = 47): mean score = 2.4; TPM vs placebo $p < 0.015$ Proportion of patients rating their medication as good to excellent: TPM 1000 mg/day: 47%; $p \leq 0.015$ **Comparator** Placebo (n = 47): mean score = 1.9 Proportion of patients rating their medication as good to excellent: placebo: 26%

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Changes in secondarily generalised seizure rate for patients reporting generalised seizures during the baseline study phase: Baseline data: NA Follow-up data: placebo (n = 17): 40.3%; p-value not stated	Changes in secondarily generalised seizures for patients reporting generalised seizures during the baseline study phase: At least 50% reduction: n = 8/17 (47%); p-value not stated **Intervention 3** At least 50% reduction: n = 18/47 (38.3%); $p < 0.001$ 75–100% reduction in seizure frequency: n = 95 (13%); p-value not stated Analyses of seizure rate reductions and treatment responders were also conducted using only stabilisation period data and including only patients who completed the trial at their assigned dosage. In both cases, the results were congruent with the ITT analysis Changes in secondarily generalised seizures for patients reporting generalised seizures during the baseline study phase: At least 50% reduction: n = 6/11 (55%); p-value not stated All TPM doses: n = 22/40 (55%); p-value not stated **Comparator** At least 50% reduction: n = 4/48 (8.5%) 75–100% reduction in seizure frequency: n = 0/48 (0%); p-value not stated Analyses of seizure rate reductions and treatment responders were also conducted using only stabilisation period data and including only patients who completed the trial at their assigned dosage. In both cases, the results were congruent with the ITT analysis Changes in secondarily generalised seizures for patients reporting generalised seizures during the baseline study phase: At least 50% reduction: n = 6/17 (35%); p-value not stated		

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Privitera, 2002[94] Originally submitted as commercial-in-confidence, but subsequently published **Related publications** Industry trial report,[462] abstracts[415,416] **Country** Multinational **Source** Industry submission **Aim** To compare TPM with investigator's choice of CBZ or VPA for initial treatment in patients with newly diagnosed epilepsy **Type of publication** Industry trial report **Funding** Janssen-Cilag **Trial ID** EPMN105 **Study design** Monotherapy; new vs old; parallel trial; non-inferiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after enrolment **Details of pretrial period** On enrolment, investigators selected CBZ (600 mg/day) or VPA (1250 mg/day) as	**Number of participants** 621 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** Median age TPM 100/200 mg/day (n = 409): 29 years; CBZ (n = 126): 34 years; VPA (n = 78): 25 years (SD not stated) Age ranges: TPM 100/200 mg/day: 6–16 years = 19%, 17–64 years = 72%, ≥ 65 years = 9%; CBZ 600: 6–16 years = 18%, 17–64 years = 74%, ≥ 65 years = 8%; VPA 1250 g/d: 6–16 years = 24%, 17–64 years = 67%, ≥ 65 years = 9%; not stated **Gender** TPM 100/200 mg/day (n = 409): men = 55%, women = 45%; CBZ (n = 126): men = 52%, women = 48%; VPA (n = 78): men = 44%, women = 56% **Age at onset of seizures** Median duration of epilepsy: TPM 100/200 mg/day (n = 409): 4.0 months (range 0–732); CBZ (n = 126): 5.5 months (range 0–456); VPA (n = 78): 5.5 months (range 0–408) **Pretrial medication** None stated	**Intervention 1** TPM; 100 mg/day; 6 months No. randomised: 210 No. completed: 105 **Intervention 2** TPM; 200 mg/day; 6 months No. randomised: 199 No. completed: 87 **Intervention 3** CBZ; 600 mg/day; 6 months No. randomised: 126 No. completed: 63 **Comparator** VPA; 1250 mg/day; 6 months No. randomised: 78 No. completed: 30	**Withdrawals prerandomisation** Total: no on-treatment medication, seizure or safety data available (n = 8) **Withdrawals postrandomisation** TPM 100 mg (n = 210): AE (n = 40), ineffective treatment (n = 23), subject choice (n = 18), lost to follow-up (n = 8), protocol violation (n = 14), other (n = 2) TPM 200 mg (n = 199): AE (n = 55), ineffective treatment (n = 18), subject choice (n = 16), lost to follow-up (n = 5), protocol violation (n = 17), other (n = 1) CBZ (n = 126): AE (n = 32), ineffective treatment (n = 10), subject choice (n = 7), lost to follow-up (n = 7), protocol violation (n = 7), other (n = 0) VPA (n = 78): AE (n = 18), ineffective treatment (n = 9), subject choice (n = 9), lost to follow-up (n = 6), protocol violation (n = 5), other (n = 1) **Adverse events** **Intervention 1** Data not reported separately for each treatment arm against CBZ and VPA. Combined totals are not separable into appropriate treatment arms TPM 100 mg (n = 210): paraesthesia (n = 53),	**Authors' conclusions** In patients with newly diagnosed epilepsy, TPM is at least as effective as CBZ and VPA. TPM 100 mg/day is an appropriate initial target dose in patients with newly diagnosed epilepsy **Comments** The authors state that 8 patients were lost to follow-up at the beginning of the study and were not included in the analysis. Hence the initial randomisation of 621 patients is reduced to 613 for the ITT analysis If TPM 200 mg/day was significantly superior to TPM 100 mg/day, then TPM 200mg was to be compared with CBZ and VPA for the ITT population. If TPM 200 mg/day was not significantly superior to TPM 100 mg/day, the protocol required TPM dosage groups to be pooled within each branch and compared with CBZ and VPA groups for the ITT population Baseline seizure data were collected retrospectively on enrolment, which could lead to recall bias The trial randomised part of the TPM 100 mg/day group and part of the TPM 200 mg/day group to comparison against either CBZ or VPA. The results are reported combining all TPM groups

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
preferred therapy, based on the patient's clinical presentation. Patients were then randomised to double-blind treatment with investigators' treatment choice, TPM 100 or 200 mg/day. There was a 35-day titration period and a stabilisation period in which the dosage of study medication remained constant. The starting dose was 25 mg/day increased weekly in 25-mg increments for the 100 mg/day TPM group; for the 200 mg/day TPM group, 25 mg/day was increased weekly to 50, 100, 150 and 200 mg/day. The starting dose for CBZ was 250 mg/day increased 200 mg every 2 weeks. For VPA the starting dose was 250 mg/day increased weekly in 250-mg increments. The background AED, if any, was tapered during the titration period **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The sample size of 600 patients was calculated based on the method of Lachin and Foulkes[473] to achieve 85% power to detect, at the 5% (two-sided) significance level, a difference in time to exit for the combined TPM groups (400 patients) versus CBZ and VPA (200 patients) **Analysis methods** All analyses were stratified by treatment branch, with treatment groups compared using the two-sided log-rank test at the 0.05 significance level CIs were calculated for comparisons of TPM and traditional AEDs with regard to	**Ongoing concurrent medication** CBZ and VPA **Co-morbidities** Not stated **Baseline seizure frequency** Baseline seizure frequency was collected retrospectively on enrolment **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged ≥ 6 years; weighing >30 kg; diagnosed and an EEG performed within the 3 months before study entry; during the 3-month retrospective baseline, patients had to have at least one seizure to confirm active epilepsy; never have been treated for epilepsy or treated less than 6 weeks with not more than one AED if temporary or urgent AED use was necessary; females had to be incapable of bearing children or be practising adequate birth control and have a negative pregnancy test within 1-week of entering the study; absence of a progressive cerebral lesion confirmed by CT or MRI imaging prior to study entry Exclusion: non-epileptic seizures or a treatable cause of seizures; progressive or degenerative disorder; significant history of unstable medical disease within previous 2 years or		upper respiratory tract infection (n = 38), anorexia (n = 23), weight loss (n = 21), insomnia (n = 21), depression (n = 17), nervousness (n = 15), fatigue (n = 42), headache (n = 53), nausea (n = 15), dizziness (n = 27), rash (n = 13), abdominal pain (n = 6), menstrual disorder (n = 4), pharyngitis (n = 11), constipation (n = 4), tremor (n = 6), alopecia (n = 8), weight increase (n = 4), urinary tract infection (n = 2) **Intervention 2** TPM 200 mg (n = 199): paraesthesia (n = 66), upper respiratory tract infection (n = 34), anorexia (n = 28), weight loss (n = 24), insomnia (n = 14), depression (n = 22), nervousness (n = 18), fatigue (n = 46), headache (n = 36), nausea (n = 28), dizziness (n = 24), rash (n = 8), abdominal pain (n = 14), menstrual disorder (n = 2), pharyngitis (n = 12), constipation (n = 6), tremor (n = 2), alopecia (n = 4), weight increase (n = 4), urinary tract infection (n = 4) **Intervention 3** CBZ (n = 122): paraesthesia (n = 5), upper respiratory tract infection (n = 19), anorexia (n = 6), weight loss (n = 10), insomnia (n = 4), depression (n = 5), nervousness (n = 3),	regardless of original randomisation. The results presented cannot be used in further analysis in this review

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
time to exit, time to first seizure and seizure-free rate. The differences in the Kaplan–Meier curves between treatment groups at 3-month intervals (90, 180, 270 and 365 days) were estimated by 95% CIs using the method proposed by Laird and Mosteller.[480] Cochran's homogeneity test was used to compare the two treatment branches and thereby ensure that the TPM and CBZ/VPA groups could be pooled across branches in arriving at an overall estimate of the difference between TPM and these traditional AEDs **Length of trial/frequency of follow-up** 6 months; days 1, 22, 36, 64 and 92 and every 3 months thereafter	malignancy within previous 5 years; psychiatric or mood disorder requiring electroconvulsive or drug therapy within previous 6 months, suicide attempt, or mental retardation or impairment; alcohol or drug abuse; history of nephrolithiasis; clinically significant laboratory or ECG abnormalities; inability to take medication either independently or with assistance; treatment with an experimental drug or device within previous 30 days; treatment with benzodiazepines or barbiturates on more than an occasional basis. Patients using AZM, ZNS or triamterence within 1 month of study entry were excluded because of an increased possibility of renal stone formation		fatigue (n = 37), headache (n = 37), nausea (n = 25), dizziness (n = 20), rash (n = 13), abdominal pain (n = 13), menstrual disorder (n = 13), pharyngitis (n = 8), constipation (n = 9), tremor (n = 3), alopecia (n = 3), weight increase (n = 3), urinary tract infection (n = 5) **Comparator** For the TPM 100 mg total patients (n = 210): VPA (n = 78): paraesthesia (n = 2), upper respiratory tract infection (n = 9), anorexia (n = 3), weight loss (n = 1), insomnia (n = 1), depression (n = 2), nervousness (n = 0), fatigue (n = 14), headache (n = 14), nausea (n = 11), dizziness (n = 8), rash (n = 4), abdominal pain (n = 3), menstrual disorder (n = 2), pharyngitis (n = 1), constipation (n = 0), tremor (n = 13), alopecia (n = 11), weight increase (n = 9), urinary tract infection (n = 5)	

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Time to exit/withdrawal; time to exit for any reason (including AE, ineffective treatment, lost to follow-up, patient choice) **Intervention 1** Kaplan–Meier curves presented. HR not presented TPM 100/200 mg/day versus CBZ: median time = 610 vs 434 days TPM 100/200 mg/day versus VPA: median time = 378 vs 308 days **Comparator** Kaplan–Meier curve presented	**Outcome** Time to first seizure **Intervention 1** Kaplan–Meier curve presented. No HR presented. No statistically significant differences detected between the treatment groups (p = 0.34) **Comparator** Kaplan–Meier curve presented	**Outcome** Proportion of seizure-free patients; defined as the number of seizure-free patients during the last 6 months of double-blind treatment **Intervention 1** TPM (100 and 200 mg/day combined): 191/409 (49%) **Intervention 3** CBZ: 55/126 (44%) **Comparator** VPA: 34/78 (44%)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Rosenfeld, 1996[41] **Related publications** None **Country** USA **Source** Literature search **Aim** To carry out a placebo-controlled trial which extended the evaluated range of TPM up to 1000 mg/day as adjunctive therapy in adults with partial epilepsy **Type of publication** Abstract (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** US YF-YG **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was an 8-week baseline period followed by a double-blind phase, which	**Number of participants** 209 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** PHT, CBZ **Ongoing concurrent medication** PHT, CBZ **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: adult participants receiving PHT or CBZ, with at least 6 POSs during baseline	**Intervention 1** TPM; 1000 mg/day; 19 weeks No. randomised: 167 No. completed: not stated **Comparator** Placebo; NA; 19 weeks No. randomised: 42 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** TPM: withdrawal due to AEs, generally related to the CNS (23%); placebo: withdrawal due to AEs, generally related to the CNS (7%) **Adverse events** **Intervention 1** Most common AEs: dizziness (30%); somnolence (30%); fatigue (29%); headache (28%); paraesthesia (25%) **Comparator** Most common AEs: dizziness (19%); somnolence (7%); fatigue (10%); headache (33%); paraesthesia (10%)	**Authors' conclusions** TPM is effective as adjunctive therapy for partial epilepsy. In this trial, the target dose and titration rate were probably too high for some patients; appropriate titration of TPM should be guided by clinical outcomes **Comments** This trial is in an abstract form only and very few details are given. With regard to withdrawals, the authors only give the percentage of withdrawals due to AEs for each group. However, it is possible that there were other withdrawals for reasons other than AEs The 19-week follow-up period included an 11-week titration period, therefore participants may not have been receiving the therapeutic dose of TPM for these 11 weeks, which may affect the results 53% of TPM patients attained a daily dosage of 1000 mg. This may affect the study findings. The mean/median target dose achieved by the TPM group is not stated. The drug does not appear to be used according to its licensed use. The target was 1000 mg/day. According to its licensed use, the maximum dose is 800 mg/day

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
included an 11-week titration period followed by an 8-week stabilisation period. TPM was initiated at 100 mg/day for 1 week, then 100 mg b.d. for 2 weeks, then 200 mg/day increments every 2 weeks to 1000 mg/day or maximum tolerated dose. Patients were required to have at least six POSs during the 8-week baseline period in order to proceed to the double-blind phase **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 19 weeks; not stated				Additional information for results data taken from industry submission from Janssen-Cilag

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; the median percentage reduction in seizure frequency **Intervention 1** TPM (*n* not stated): 51%; $p < 0.001$ **Comparator** Placebo (*n* not stated): 1%	**Outcome** Proportion of responders (at least 50% or other specified criteria); responders were defined as patients showing at least a 50% reduction in total seizure frequency. The percentage of patients fulfilling this criterion was reported **Intervention 1** TPM: 87/167 (52%); *p*-value not stated **Comparator** Placebo: 8/42 (19%)	**Outcome** Proportion of seizure-free patients; reported as the percentage of participants who were free of seizures **Intervention 1** TPM: 10/167 (6%); *p*-value not stated **Comparator** Placebo: 0/42 (0%)	**Outcome** Change in seizure frequency; reported as the median percentage reduction in frequency of GTC seizures **Intervention 1** TPM (*n* not stated): 65%; $p = 0.04$ **Comparator** Placebo (*n* not stated): 9%

continued

Outcome 5	
	Outcome Proportion of responders; defined as patients showing at least a 75% reduction in total seizure frequency. The percentage of patients fulfilling this criterion was reported **Intervention 1** TPM (*n* not stated): 25%; *p*-value not stated **Comparator** Placebo (*n* not stated): 5%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Sharief, 1996[148] **Related publications** Abstract[418] **Country** European **Source** Literature search **Aim** To assess the safety and efficacy of TPM as adjunctive therapy to traditional AEDs for subjects with refractory POSs with or without secondarily generalised seizures in a double-blind, parallel-group, placebo-controlled trial **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Research Institute **Trial ID** Europe Y1 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 47 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 47): 34.0 years (SD 12.6 years); TPM (n = 23): 35.4 years (SD 14.0 years); placebo (n = 24): 32.6 years (SD 11.1 years); not stated **Gender** Total (n = 47): men = 40, women = 7; TPM (n = 23): men = 21, women = 2; placebo (n = 24): men = 19, women = 5 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** PHT (n = 18), CBZ (n = 32), VPA (n = 7), PB (n = 11) and PRM (n = 5). CLB and CZP (n = 2) were also allowed but only if used in combination with PHT, CBZ, VPA, PB or PRM **Co-morbidities** Not stated	**Intervention 1** TPM; 400 mg/day; 11 weeks No. randomised: 23 No. completed: 17 **Comparator** Placebo; 11 weeks No. randomised: 24 No. completed: 22	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: withdrawals (n = 8) (7 of these were due to limiting AEs); TPM: withdrawals (n = 6) (all 6 of these were due to limiting AEs: 1 due to dyspepsia and abdominal pain, 5 CNS related); placebo: withdrawals (n = 2) (1 of these was due to limiting AEs, CNS related) **Adverse events** **Intervention 1** Incidence of the most common treatment-emergent AEs during the double-blind phase (reported by ≥ 10% of the patients in either treatment group) (n = 23): General and peripheral nervous system disorders: headache (n = 3), speech disorder (n = 3), aphasia (n = 3). Vision disorders: vision abnormal (n = 6). Psychiatric disorders: somnolence (n = 8), confusion (n = 3), anxiety (n = 5), concentration impaired (n = 4), depression (n = 2), nervousness (n = 2), amnesia (n = 3), emotional lability (n = 3). Metabolic and nutritional disorders: weight decrease (n = 6). Respiratory disorders: upper respiratory tract infection (n = 4), pharyngitis (n = 3). Body as a whole, general disorders:	**Authors' conclusions** Results of this trial strongly suggest that TPM 400 mg/day is effective and well tolerated in the treatment of refractory partial epilepsy with or without secondarily generalised seizures **Comments** The total number of patients initially recruited is not stated; only the number of patients who were randomised (n = 47) is given The follow-up period of 11 weeks includes a 3-week titration period, therefore patients were not receiving the therapeutic dose of TPM for these full 3 weeks; this may influence the study findings Protocol variations included the enrolment of two patients aged <18 years: one (aged 15 years) in the placebo group and one (aged 17 years) in the TPM group Changes from baseline in the plasma concentrations of CBZ, PHT, VPA, PB, CZP and PRM and its active metabolite were similar for the TPM and placebo groups Titration to the target or maximum-tolerated dosage resulted in a mean dosage of 387 mg/day for the TPM group during the stabilisation period

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was an 8-week baseline followed by randomisation into the double-blind treatment phase, which consisted of a 3-week titration phase and an 8-week stabilisation period. During the titration period the following doses were taken in 3 consecutive 1-week intervals: TPM 100 mg/day or one placebo tablet every morning; TPM 100 mg b.d. or one placebo tablet b.d., and the target dose of TPM 200 mg b.d. or two placebo tablets b.d., or the maximum tolerated dosage, if less. Upon completion of the TPM therapy, all patients had their doses of TPM tapered in decrements of 100 or 200 mg/day at intervals of 1 week or more. Patients who had at least 8 partial seizures during an 8-week baseline period in which they were maintained at therapeutic plasma AED concentrations were qualified to enter the double-blind treatment phase. Patients with a seizure-free interval that exceeded 3 weeks or with more than one seizure-free interval of 3 weeks during the baseline period were excluded **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The sample size was based on practical considerations and was smaller than most AED trials. Retrospective power calculations showed that 25 patients per group would provide 68% power to detect a between-group difference in monthly seizure rate change of about 6 seizures per month assuming a standard deviation of	**Baseline seizure frequency** Mean baseline average monthly (28-day) seizure rate: total (n = 47): 28.4 (SD 44.1); TPM (n = 23): 33.4 (SD 52.6); placebo (n = 24): 23.6 (SD 34.5) Median baseline average monthly (28-day) seizure rate: total (n = 47): 12.5; TPM (n = 23): 18; placebo (n = 24): 10 **Other characteristics** Mean weight: total (n = 47): 74 kg (SD 12.2 kg); TPM (n = 23): 74.9 kg (SD 12.4 kg); placebo (n = 24): 73.1 kg (SD 12.3 kg) History of seizures by type (individual patients may have had a history of more than one seizure type): Simple partial: total (n = 47): 16; TPM (n = 23): 9; placebo (n = 24): 7 Complex partial: total (n = 47): 43; TPM (n = 23): 20; placebo (n = 24): 23 Secondarily generalised: total (n = 47): 35; TPM (n = 23): 19; placebo (n = 24): 16 Other types: total (n = 47): 8; TPM (n = 23): 5; placebo (n = 24): 3 **Inclusion/exclusion criteria** Inclusion: aged 18–65 years; with an unequivocal history of partial seizures with or without secondarily generalised seizures; in good mental and physical health. A CT or MRI within the preceding 2 years that excluded potentially progressive neurological diseases and an EEG		fatigue (n = 6), asthenia (n = 4), injury (n = 1) **Comparator** Placebo (n = 24): General and peripheral nervous system disorders: headache (n = 5), speech disorder (n = 2). Vision disorders: vision abnormal (n = 0). Psychiatric disorders: somnolence (n = 4), confusion (n = 4), anxiety (n = 1), concentration impaired (n = 1), depression (n = 3), nervousness (n = 3). Metabolic and nutritional disorders: weight decrease (n = 2). Respiratory disorders: upper respiratory tract infection (n = 2). Body as a whole, general disorders: fatigue (n = 4), asthenia (n = 1), injury (n = 3)	Among TPM-treated patients there were no noteworthy abnormal laboratory findings in the results of liver function, renal function, haematological function and other tests. There were no clinically noteworthy mean changes from baseline to the final visit in any laboratory values. There were no clinically noteworthy treatment-emergent changes in vital signs, electrocardiograms, neurological examinations, and physical examinations. Body weight tended to decrease in the TPM group: mean decrease during the double-blind phase was 3 kg. In contrast, no consistent body weight changes were observed among placebo-treated patients

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
10 seizures per month in the seizure rate change in each treatment group **Analysis methods** The ITT efficacy analyses included all seizure data from the entire double-blind phase of the trial. Average monthly (28-day) seizure rates were computed for both the baseline phase and the double-blind phase. A 2-factor ANOVA on ranks was performed on the percentage reduction in average seizure rate from baseline to the double-blind phase. Percentage responders was analysed using the Cochran–Mantel–Haenszel method with data stratification by centre. Investigators' global evaluation of improvement and patients' overall assessment of medication (stratified by centre) were analysed by Wilcoxon rank-sum tests. All statistical tests were 2-sided. For patients with secondarily generalised seizures during the baseline or double-blind phases, comparison between the TPM- and placebo-treated groups was by ANOVA based on rank of percentage reduction in secondarily generalised seizures **Length of trial/frequency of follow-up** 11 weeks; titration phase: day 1 and then at weekly intervals (clinical laboratory tests were performed biweekly); stabilisation phase: every 2 weeks	within the preceding 5 years that documented the presence of a lateralised epileptiform pattern consistent with the diagnosis of partial epilepsy were also required. Eligible patients had to be receiving one or two of the following AEDs: PHT, CBZ, VPA, PB or PRM. CLB or CZP were also permitted, but only in combination with one of the previous AEDs. The enrolment of women of childbearing potential who were not pregnant or nursing and were using birth-control measures was permitted Exclusion: a history of nephrolithiasis or known allergy or hypersensitivity to carbonic anhydrase inhibitors or sulphonamide. During the trial, no anti-anxiety agents, antidepressants, neuroleptics or sedatives (other than chloral hydrate), and no other centrally acting drugs, including antihistamines, were permitted			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; median percentage reduction from baseline in average monthly (28-day) seizure rate during the double-blind phase **Intervention 1** TPM (n = 23): 40.7%; p = 0.065 Median percentage reduction from baseline in secondarily generalised seizure rate during the double-blind phase among patients who reported generalised seizures during the baseline phase: TPM (n = 14): 83.9%; p = 0.002 **Comparator** Placebo (n = 24): 1.1% Median percentage reduction from baseline in secondarily generalised seizure rate during the double-blind phase among patients who reported generalised seizures during the baseline phase: Placebo (n = 8): 8.7%	**Outcome** Proportion of responders; defined as having at least a 50% reduction in seizure frequency from baseline during the double-blind phase **Intervention 1** TPM (n = 23): 35%; p = 0.033 ≥ 75% reduction from baseline in seizure rate during the double-blind phase: TPM (n = 23): 22%; p-value not stated Changes in secondarily generalised seizure rates during the double-blind phase of the trial compared with baseline among patients who reported generalised seizures during the baseline phase (percentage responders): TPM 10/14 (71%); p-value not stated Changes in secondarily generalised seizure rates during the double-blind phase of the trial compared with baseline among patients who reported generalised seizures during the baseline phase (secondarily generalised seizure free): TPM 6/14 (43%); p-value not stated **Comparator** Placebo (n = 23): 8% ≥ 75% reduction from baseline in seizure rate during the double-blind phase: Placebo (n = 24): 4% Changes in secondarily generalised seizure rates during the double-blind phase of the trial compared with baseline among patients	**Outcome** Physician/patient global evaluation of improvement/efficacy; investigators' global evaluation of improvement at the end of the double-blind phase compared with baseline. Ratings are as follows: 1 = worse; 2 = none; 3 = minimal; 4 = moderate; 5 = marked **Intervention 1** TPM (n = 23): mean score = 3.5; p = 0.002 Proportion showing either moderate or marked improvement: TPM: 57%; p-value not stated **Comparator** Placebo (n = 24): mean score = 2.2 Proportion showing either moderate or marked improvement: placebo: 8%	**Outcome** Physician/patient global evaluation of improvement/efficacy/tolerability; patients' overall assessment of study medication at the end of the double-blind phase compared with baseline. Ratings are as follows: 1 = poor; 2 = fair; 3 = good; 4 = excellent **Intervention 1** TPM (n = 23): mean score = 2.3; p = 0.021 Proportion rating medication as good or excellent: TPM: 43%; p-value not stated **Comparator** Placebo (n = 24): mean score = 1.6 Proportion rating medication as good or excellent: placebo: 8%

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	who reported generalised seizures during the baseline phase (percentage responders): Placebo 3/8 (38%) Changes in secondarily generalised seizure rates during the double-blind phase of the trial compared with baseline among patients who reported generalised seizures during the baseline phase (secondarily generalised seizure free): TPM vs placebo: placebo 2/8 (25%)		
Outcome 5			
Outcome Seizure free **Intervention 1** TPM 2/23; *p*-value not stated Changes in secondarily generalised seizure rates during the double-blind phase of the trial compared with baseline among patients who reported no secondarily generalised seizures during the baseline phase (secondarily generalised seizure free): TPM 9/9 (100%); *p*-value not stated **Comparator** Placebo 0/24 Changes in secondarily generalised seizure rates during the double-blind phase of the trial compared with baseline among patients who reported no secondarily generalised seizures during the baseline phase (secondarily generalised seizure free): placebo 11/16 (69%)			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Tassinari, 1996[42] **Related publications** Abstract[419] **Country** European **Source** Literature search **Aim** To evaluate adjunctive therapy for POSs with TPM for efficacy and safety in a double-blind, placebo-controlled, randomised, parallel-group study **Type of publication** Full paper (final analysis) **Funding** R. W. Johnson Pharmaceutical Research Institute **Trial ID** Europe Y2 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was an 8-week baseline phase followed by a 12-week double-blind phase, which	**Number of participants** 60 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 60): 32.9 years (SD not stated); TPM: not stated; Placebo: not stated; not stated **Gender** Total (n = 60): men = 47 (68%), women = 13 (22%); TPM: not stated; placebo: not stated **Age at onset of seizures** Not stated **Pretrial medication** CBZ, PBI, PHT, PRM, VPA **Ongoing concurrent medication** CBZ, PBI, PHT, PRM, VPA **Co-morbidities** Not stated **Baseline seizure frequency** Median seizure rate: TPM: 16.8 (range 4–230); placebo: 15.0 (range 4–925) **Other characteristics** Mean weight: total: 69.4 kg; TPM: not stated; placebo: not stated	**Intervention 1** TPM; 600 mg/day; 12 weeks No. randomised: 30 No. completed: 25 **Comparator** Placebo; 12 weeks No. randomised: 30 No. completed: 28	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** TPM: withdrawals (n = 5) (4 of these were due to limiting AEs) Placebo: withdrawals (n = 2) (1 of these was due to limiting AEs) **Adverse events** **Intervention 1** Incidence of the most common treatment-emergent AEs during the double-blind phase (reported by ≥ 10% of the patients in either treatment group): (n = 30): headache (n = 8, 27%), somnolence (n = 7, 23%), dizziness (n = 7, 23%), fatigue (n = 7, 23%), thinking abnormal (n = 6, 20%), depression (n = 5, 17%), weight decrease (n = 5, 17%), nausea (n = 4, 13%), emotional lability (n = 4, 13%), confusion (n = 4, 13%), anxiety (n = 3, 10%), convulsions aggravated (n = 3, 10%), concentration impaired (n = 3, 10%), diarrhoea (n = 3, 10%), upper respiratory tract infection (n = 3, 10%), amnesia (n = 2, 7%) **Comparator** Placebo (n = 30): headache (n = 3, 10%), somnolence (n = 4, 13%), dizziness (n = 3, 10%), fatigue (n = 3, 10%),	**Authors' conclusions** The results indicate that TPM 600 mg/day is effective in the treatment of refractory POSs with or without secondary generalised seizures **Comments** The follow-up time of 12 weeks includes a 4-week titration period, which may influence the study findings as patients may not have been receiving a therapeutic dose of TPM during these 4 weeks The total number of patients initially recruited prior to randomisation is not stated The authors do not provide baseline characteristics for the TPM and placebo groups separately. Therefore, it is not possible to determine if the two groups are comparable, even though the authors do state that 'the demographic and baseline characteristics were comparable for the two treatment groups' 57% of patients in the TPM group reached the target dose of 600 mg/day and the overall mean dosage during the stabilisation period was 519.3 mg/day. This may have affected the study findings There were no clinically significant changes in laboratory findings

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
consisted of a 4-week titration period followed by an 8-week stabilisation period. The titration period consisted of four 1-week intervals: during the 1st interval patients received TPM 100 mg or one placebo tablet every morning; during the second, the dosage was increased to TPM 100 mg b.d. or one placebo tablet b.d.; and during each of the next two intervals, the dosage was increased by one tablet b.d. until each patient achieved a dosage of six tablets (TPM 600 mg) or the maximum tolerated dosage if less. Patients were required to have at least 8 partial seizures while being maintained at therapeutic plasma AED concentrations during the baseline phase **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Sample size for the study was based on practical considerations; however, power calculations for a sample size of 30 patients per treatment group indicated a 75% power to detect (at the 0.05 level) a between-group difference in mean seizure rate change of about six seizures a month, assuming an SD of 10 seizures a month for seizure rate change in each treatment group (at an α-level of 0.05) **Analysis methods** ITT efficacy analyses used all double-blind phase data (both titration and stabilisation periods). Average monthly (28-day) seizure rates were computed for both the baseline phase and the double-blind phase. Percentage reduction in average seizure rate from baseline to the double-blind phase was analysed by a two-factor ANOVA on ranks. Percentage responders were analysed using the	**Inclusion/exclusion criteria** Inclusion: aged 18–65 years; with good mental and physical health; and a documented history of partial seizures with or without secondarily generalised seizures. An EEG in the preceding 5 years to verify the presence of a lateralised epileptiform pattern consistent with a diagnosis of partial epilepsy and CT or MRI scan in the preceding 2 years to exclude potentially progressive neurological diseases were required. Eligible patients were receiving a fixed regimen of one or two of the following AEDs: PHT, CBZ, VPA, PB or PRM. CLB or CBZ were also permitted, but only in combination with PHT, CBZ, PB or PRM. Women of childbearing potential were permitted only if they were not pregnant or nursing and were using birth control measures Exclusion: patients were excluded if they were known to be allergic to or hypersensitive to carbonic anhydrase inhibitors or sulphonamides (or to have any contraindications to treatment with carbonic anhydrase inhibitors) or if they had a history of nephrolithiasis. No antianxiety, antidepressant, or neuroleptic agents or sedatives (other than chloral hydrate) and no other centrally acting drugs (including antihistamines) were permitted		thinking abnormal (n = 0, 0%), depression (n = 2, 7%), weight decrease (n = 2, 7%), nausea (n = 2, 7%), emotional lability (n = 1, 3%), anxiety (n = 3, 10%), convulsions aggravated (n = 2, 7%), concentration impaired (n = 1, 3%), diarrhoea (n = 1, 3%), upper respiratory tract infection (n = 1, 3%), amnesia (n = 3, 10%)	(including results of liver function, renal function and haematological tests) or in vital signs, ECGs, neurological examinations and physical examinations during the double-blind phase. Mean decreases in body weight, ranging from 0.2 kg (at week 1) to 2.4 kg (at week 12) were noted during periodic, double-blind phase visits in patients treated with TPM

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Cochran–Mantel–Haenszel method, and the percentage of patients with at least 75% reduction in seizure rate were analysed similarly. Investigators' global evaluation of improvement and patients' overall assessment of medication were analysed by Wilcoxon rank-sum tests. All statistical tests were 2-sided **Length of trial/frequency of follow-up** 12 weeks; titration period: at the end of each week. Stabilisation period: at the end of each 2-week interval				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; median percentage reduction in average seizure rate during the double-blind phase as compared with baseline **Intervention 1** TPM (n = 30): 46.4%; p = 0.004 **Comparator** Placebo (n = 30): –12.2%	**Outcome** Proportion of responders; defined as having at least a 50% reduction in seizure frequency from baseline during the double-blind phase **Intervention 1** TPM: 14/30 (47%); p = 0.001 Patients with ≥75% reduction from baseline in seizure rate during the double-blind phase: TPM: 7/30 (23%); p = 0.028 **Comparator** Placebo: 3/30 (10%) Patients with ≥75% reduction from baseline in seizure rate during the double-blind phase: Placebo: 1/30 (3%)	Outcome Physician/patient global evaluation of improvement/efficacy; investigators' global evaluation of improvement at the end of the double-blind phase compared with baseline. Ratings are as follows: 1 = worse; 2 = none; 3 = minimal; 4 = moderate; 5 = marked **Intervention 1** Proportion showing either moderate or marked improvement: TPM: 50%; p-value not stated **Comparator** Proportion showing either moderate or marked improvement: Placebo: 13%	**Outcome** Patients' global evaluation of improvement/efficacy; patients' overall assessment of study medication at the end of the double-blind phase compared with baseline. Ratings are as follows: 1 = poor; 2 = fair; 3 = good; 4 = excellent **Intervention 1** Proportion rating their medication as good or excellent: TPM: 47%; p-value not stated **Comparator** Proportion rating their medication as good or excellent: Placebo: 13%

Outcome 5

Outcome
Seizure free

Intervention 1
TPM (n = 30): 0

Comparator
Placebo (n = 30): 0

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Yen, 2000[165] **Related publications** Abstract[420] **Country** China **Source** Literature search **Aim** To evaluate the efficacy and safety of TPM as adjunctive therapy in the treatment of adult Chinese patients with refactory partial epilepsy in a randomised, double-blind, placebo-controlled study **Type of publication** Full paper (final analysis) **Funding** Taipei Veterans General Hospital and the Yen Tjing Ling Medical Foundation **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was a baseline phase of 8 weeks,	**Number of participants** 46 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** TPM: 31.4 years (SD 10.9 years); placebo: 32.0 years (SD 8.7 years); total: 18–54 years; TPM: 18–54 years; placebo: 22–48 years **Gender** Total: men = 19, women = 27; TPM: men = 6, women = 17; placebo: men = 13; women = 10 **Age at onset of seizures** Mean seizure history: TPM: 14.9 years (SD 10.9 years, range 5–45 years); placebo: 18.9 years (SD 11.1 years, range 2–39 years) **Pretrial medication** CBZ (n = 36), VPA (n = 21), LTG (n = 13), PHT (n = 7), PB (n = 7), CZP (n = 4), VGB (n = 3), PRM (n = 3), AZM (n = 1) **Ongoing concurrent medication** On average, the patients were taking 2.48 (SD 0.90) concomitant AEDs in the TPM group and 2.78 (SD 0.80) AEDs in the placebo group **Co-morbidities** Not stated	**Intervention 1** TPM; 300 mg/day; 14 weeks No. randomised: 23 No. completed: 20 **Comparator** Placebo; 14 weeks No. randomised: 23 No. completed: 21	**Withdrawals prerandomisation** NA **Withdrawals postrandomisation** TPM: intolerable somnolence (n = 1), severe secondary generalised seizures (n = 1), protocol violation by refusing to have blood sampling (n = 1) Placebo: intolerable headache (n = 1), skin rashes (n = 1) **Adverse events** **Intervention 1** TPM: 39.1% (9 patients) reported AEs; p = 0.536 Dizziness/somnolence (n = 4), nausea (n = 1), headache (n = 1), eye pain (n = 1), skin rashes/skin itching (n = 1), weight loss (n = 2), paraesthesia (n = 1); severe attacks (n = 1) **Comparator** Placebo: 30.4% (7 patients) reported AEs Dizziness/somnolence (n = 2), headache (n = 3), eye pain (n = 1), skin rashes/skin itching (n = 2), tinnitus (n = 1)	**Authors' conclusions** TPM adjunctive therapy at 300 mg/day is effective and well tolerated as treatment for refractory partial epilepsy in adult Chinese patients **Comments** The authors decided to use 300 instead of 400 mg/day dosage, based on the assumption that their Chinese patients would have a smaller body mass than non-Asians

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
followed by randomisation into the double-blind phase. Patients had to have four or more complex partial seizures, with or without secondary generalisation, in the baseline phase to be admitted to the double-blind phase. Dosing started with 50 mg/day once a night in the 1st week, increased by 50 mg at weekly intervals to a target dosage of TPM 300 mg/day in two divided doses during the 6th week. The target dose was maintained during a stabilisation phase of 8 weeks. For individual cases of mild AEs in the titration phase, the dosage could be decreased by 50 mg/day for 1 week and then increased **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** The χ^2 test or Wilcoxon rank-sum test was used. $p < 0.05$ was considered significant **Length of trial/frequency of follow-up** 14 weeks; after trial completion (specific time points not stated)	**Baseline seizure frequency** Seizure rate per 4 weeks: TPM: <5 = 16, 5–10 = 3, >10 = 4; placebo: <5 = 11, 5–10 = 7, >10 = 5 **Other characteristics** Mean body weight: TPM: 58.2 kg (SD 12.7 kg, range = 39.5–85 kg); placebo: 60.4 kg (SD 12.6 kg, range = 34–83 kg) **Inclusion/exclusion criteria** Inclusion: Chinese adults aged 18–65 years with a history of partial seizures that had not responded to adequate doses of AED treatment for ≥ 2 years. Auras or simple partial seizures were not included for analysis Exclusion: patients with intracranial tumours, female patients who were pregnant or breastfeeding and patients who had severe renal or hepatic dysfunction regardless of cause or nephrolithiasis. Patients who did not benefit from previous temporal lobotomy were not excluded			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of responders; seizure reduction during the stabilisation phase relative to the baseline phase was divided into the following categories: ≥ 50% seizure reduction (responders); 25–50% reduction; change within ≥ 25% of baseline; 25% seizure increase **Intervention 1** ≥ 50% reduction (responders): TPM: 47.8% (n = 11); p = 0.01 25–50% reduction: TPM: n = 5; p-value not stated Change within ≥ 25% of baseline: TPM: n = 3; p-value not stated 25% seizure increase: TPM: n = 1; p-value not stated **Comparator** ≥ 50% reduction (responders): placebo: 13.0% (n = 3) 25–50% reduction: placebo: n = 6; p-value not stated Change within ≥ 25% of baseline: placebo: n = 8; p-value not stated 25% seizure increase: placebo: n = 4; p-value not stated	**Outcome** Change in seizure frequency; mean reduction in CPSs during the stabilisation phase **Intervention 1** TPM: 43.5% (95% CI: 22.0 to 65.0%) **Comparator** Placebo: 7.4% (95% CI: –13.0 to 27.9%)	**Outcome** Physician global evaluation of improvement/efficacy/tolerability; the investigators' global evaluation of improvement graded on a 5-point scale: 5 = marked, 4 = moderate, 3 = minimal, 2 = none, 1 = worse **Intervention 1** TPM: mean = 3.55 (SD 1.19); p = 0.014 **Comparator** Placebo: mean = 2.48 (SD 1.36)	**Outcome** Patient global evaluation of improvement/efficacy/tolerability; Patients' overall assessment of medication scored on a 4-point scale: 4 = excellent, 3 = good, 2 = fair, 1 = poor **Intervention 1** TPM: mean = 3.00 (SD 1.12); p = 0.0005 **Comparator** TPM: mean = 1.62 (SD 0.97); p = 0.0005 Placebo: mean = 1.62 (SD 0.97); p = 0.0005

Vigabatrin (licensed use)

Crossover studies (*n* = 7)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Beran, 1996[87] **Related publications** None **Country** Australia **Source** Literature search **Aim** The efficacy and tolerability of VGB as add-on therapy was assessed in patients with uncontrolled partial seizures **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** AUS01 **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after pretrial period	**Number of participants** 97 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: mean = 33.2 years (SD is not stated; mean is for the 80 patients who were included in the analysis and not for the 97 originally recruited into the study); total: 17–64 years **Gender** Total: men = 45, women = 52 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Up to three other AEDs **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated	**Intervention 1** VGB/placebo; 3 g/day; 8 weeks No. randomised: 20 No. completed: not stated **Comparator 1** Placebo/VGB; NA; 8 weeks No. randomised: 18 No. completed: not stated **Intervention 2** VGB/placebo; 2 g/day; 8 weeks No. randomised: 20 No. completed: not stated **Comparator 2** Placebo/VGB; NA; 8 weeks No. randomised: 22 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** AEs (*n* = 2); non-compliance (*n* = 6), withdrew consent (*n* = 4), other (*n* = 5) **Adverse events** **Intervention 1** VGB (3 g/day) (*n* = 49): drowsiness (20.9%), fatigue (11.6%), weight increase (9.3%), convulsions (2.3%), headache (4.7%), depression (9%), agitation (2.3%), diplopia (11.6%), dizziness (9.3), ataxia (7%), visual abnormality (7%) **Comparator 1** Placebo (for 3 g/day treatment group) (*n* = 41): drowsiness (12.2%), fatigue (4.9%), weight increase (7.3%), headache (4.9%), agitation (2.4%), tremor (2.4%), diplopia (4.9%), dizziness (7.3%), ataxia (2.4%), visual abnormality (4.9%) **Intervention 2** VGB (2 g/day) (*n* = 43): drowsiness (14.3%), fatigue (14.3%), weight increase (12.2%), convulsions (12.2%),	**Authors' conclusions** The results of this study indicate that VGB, given in a daily dose of either 2 or 3 g, is significantly more effective than placebo in reducing seizure frequency among patients with partial seizures **Comments** Number of participants who completed the trial who were originally assigned to the following sequence groups: VGB (3 g) (*n* = 20); VGB (2 g) (*n* = 18) The number of participants in each sequence group are reported only for those participants included in the efficacy analysis (which excluded withdrawals), therefore it is not clear how many were originally randomised to each group There was no significant difference in reduction in seizure frequency between the two dose groups. The reduction in mean back transformed seizure rate was –34% for placebo vs VGB (*n* = 80)

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There were five phases to the study. There was an initial 8-week screening phase (Phase I) with patients who met the study entry criteria continuing to Phase II when they were randomised to receive 2 g/day of VGB, 3 g/day of VGB or placebo. This treatment phase lasted 8 weeks. This was followed by a 4-week washout period (Phase III) where patients receiving VGB had their dose reduced by 1 g/week. All patients were then crossed over for the second 8-week treatment period (Phase IV). Patients previously receiving VGB received placebo and those receiving placebo received 2 or 3 g VGB. Patients then entered a final 4-week dose reduction phase (Phase V), which was similar in design to Phase III. All patients were maintained on their established AED treatment throughout the study **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** The primary efficacy variable was total seizure rate. Baseline seizure rates were analysed by the Kruskal–Wallis test. A square root transformation was conducted on seizure rates. Statistical analyses were performed using ANOVA accounting for variations due to patient, dose group, treatment and treatment period. Means for the square root transformed data and for the back transformed data were presented. The carry-over effect of VGB into the	**Inclusion/exclusion criteria** Inclusion: aged 16–65 years; at least 9 documented complex partial seizures during the previous 2 months despite a stable regimen of treatment (AEDs confirmed by steady-state plasma drug levels) with currently available AEDs recorded in a patient diary; seizure activity must have seriously affected the patient's way of life; must have been treated with stable regimens of up to three other AEDs during the 2 months before the study; women of childbearing potential were required to use an acceptable form of contraception Exclusion: a treatable seizure aetiology (e.g. metabolic or neoplastic cause); more than one episode of status epilepticus during the previous 6 months; a history of alcoholism or drug addiction; unable to comply with completing the seizure frequency calendars; evidence of other systemic disease that would subject them to undue risk or would compromise the objective of the study		headache (10.2%), depression (8.2%), agitation (8.2%), tremor (8.2%), diplopia (6.1%), dizziness (6.1%), ataxia (4.1%), visual abnormality (2.0%) **Comparator 2** Placebo (for 2 g/day treatment group) ($n = 49$): drowsiness (8.2%), fatigue (10.2%), weight increase (2.0%), convulsions (2.0%), headache (8.2%), depression (2.0%), agitation (6.1%), tremor (2.0%), dizziness (2.0%), visual abnormality (2.0%)	

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
washout phase was assessed using square root transformed seizure rates for the run in and washout periods. The number of seizure-free days and longest seizure-free interval between treatments were analysed by the sign-rank test. Global evaluations of well-being made by the investigator and the patient were analysed by the Cochran–Mantel–Haenszel test. The incidence of AEs was compared using the χ^2 test. Changes in pretreatment baseline were assessed using the sign-rank matched pair test **Length of trial/frequency of follow-up** 32 weeks; after 4 and 8 weeks of treatment				

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Change in seizure frequency; mean monthly seizure rate during double-blind therapy **Intervention 1** VGB (3 g) (n = 38) Follow-up data: mean back transformed seizure rate = 13.83 Reduction in mean back transformed seizure rate (VGB 3 g vs placebo) = –31% **Comparator 1** Placebo (n = 38) (for 3 g/day treatment group) Follow-up data: mean back transformed seizure rate = 20.1 **Intervention 2** VGB (2 g) (n = 42)	**Outcome** Proportion of responders; responders were defined as having at least a 50% reduction in seizure frequency **Intervention 1** 34/80 (42%) (VGB 2 and 3 g results combined by trial authors) **Intervention 2** See above **Comparators 1 and 2** Not stated	**Outcome** Change in seizure-free interval; reported as number of seizure-free days and longest seizure-free period **Intervention 1** VGB (n = 80) Median number of seizure-free days = 22 ($p < 0.01$) Longest seizure-free period = 10.5 days ($p < 0.01$) **Intervention 2** See above **Comparators 1 and 2** Placebo (n = 80)	**Outcome** Change in seizure severity; reported as patient rating of change in seizure severity and duration **Intervention 1** VGB (n = 80) 42% reported a reduction is seizure severity 36% reported a decrease in the duration of length of individual seizures 32% reported a trend towards less severe shorter seizures (p = 0.06) **Intervention 2** See above **Comparators 1 and 2** Placebo (n = 80)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Follow-up data: mean back transformed seizure rate = 14.1 Reduction in mean back transformed seizure rate (VGB 3 g vs placebo) = –31% **Comparator 2** Placebo (n = 42) (for 2 g/day treatment group) Follow-up data: mean back transformed seizure rate = 21.9		Median number of seizure-free days = 19 Longest seizure-free period = 6 days	20% reported a reduction in seizure severity 20% reported a decrease in the duration of length of individual seizures 16% reported a trend towards less severe shorter seizures
Outcome 5			
Outcome Global evaluation of well-being; made by the investigator and the patient after 8 weeks of treatment) **Intervention 1** Investigator assessment VGB: 23% (n = 18) patients were assessed as 'very good' or good'. Patient assessment VGB: 30% (n = 24) patients were assessed as 'very good' or good' **Intervention 2** See above **Comparators 1 and 2** Placebo: 9% (n = 7) were assessed as 'very good' or 'good' (p = 0.001) Placebo: 13% (n = 10) were assessed as 'very good' or 'good' (p = 0.01)			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Gillham, 1993[51] **Related publications** Paper[54] **Country** UK **Source** Literature search **Aim** Patients with refractory epilepsy on one or more AEDs were given additional VGB and matched placebo in a double-blind, randomised crossover study. A battery of neuropsychological tests was administered at baseline and at weeks 2, 6 and 12 of both treatment periods **Type of publication** Full paper (final analysis) **Funding** Marion Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated	**Number of participants** 24 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total: 32.9 years (SD not stated); total: 17–53 years **Gender** Total: men = 8, women = 16 **Age at onset of seizures** Duration of epilepsy: total: 19.8 years **Pretrial medication** Monotherapy (n = 11) CBZ (n = 9); PHT (n = 1); VPA (n = 1) Two AEDs (n = 13): CBZ (n = 10); PRM (n = 6); VPA (n = 4); PHT (n = 4); PB (n = 2) **Ongoing concurrent medication** See pretrial medication **Co-morbidities** Not stated **Baseline seizure frequency** Not stated; however, patients averaged at least one seizure per week during the 3 months before recruitment	**Intervention 1** VGB/placebo; 2–3 g/day; 12 weeks No. randomised: not stated No. completed: 11 **Comparator** Placebo/VGB; NA; 12 weeks No. randomised: not stated No. completed: 10	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: pregnancy (n = 1), withdrew consent owing to lack of efficacy (n = 1), psychotic episode (n = 1) **Adverse events** **Intervention 1** Not stated (see Ref. 474) **Comparator** Not stated (see Ref. 474)	**Authors' conclusions** VGB did not cause cognitive impairment either acutely or in the long term. Phased introduction, however, seems a prudent policy to allow tolerance to early subjective sedation **Comments** VGB as add-on therapy is not licensed for primary generalised seizures. This study contains 2 participants with primary generalised seizures, which needs to be addressed in the analysis Apart from type of epilepsy, no inclusion or exclusion criteria are reported. Therefore, it is possible that participants may have had concomitant conditions which may have had a confounding effect on neuropsychological performance It is unclear how many were originally randomised to each treatment sequence The findings for change in seizure frequency are very limited and not clear enough for data extraction. See #1061 for full data on seizure outcome Data are not reported for the neuropsychological assessment; however, the authors report that from the within-patient analysis there were no significant

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Following a 4-week run-in there were 2 treatment periods of 12 weeks separated by a 4-week washout period. Each treatment period consisted of 6 weeks of 2 g of VGB/matched placebo followed by 6 weeks of 3 g of VGB/matched placebo. Group 1 took VGB first and Group 2 took the placebo first **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** ANOVA was used to investigate practice effects for all tests. Student's *t*-test for paired values was used to compare placebo and VGB on the psychomotor and memory tests. The Wilcoxon matched pairs test was used for self-report scales. Spearman correlations were used to test the hypothesis that sedation influenced test performances. Seizure frequencies for VGB and placebo were compared using the Wilcoxon rank test for matched pairs. Seizure frequency during follow-up was compared using Friedman's test. The composite scores used in the long-term part of the study are *Z*-scores examined by repeated measures ANOVA followed by paired *t*-tests to identify where significant changes had occurred. Significance levels were 1% **Length of trial/frequency of follow-up** 30 weeks; after run-in and 2, 6 and 12 weeks in each phase	**Other-characteristics** CPSs with secondary generalisation ($n = 14$), CPSs ($n = 8$), GTC seizures ($n = 2$) **Inclusion/exclusion criteria** Inclusion: refractory epilepsy; currently receiving one or more AEDs; at least two generalised or one partial seizure/week during the 3 months before recruitment (obtained from #1061, McKee 1993) Exclusion: criteria not stated			differences between VGB and placebo except for self-rating of sedation level with patients rating their sedation level significantly higher ($p < 0.01$) when they had been taking VGB for 2 and 6 weeks compared with placebo Twelve patients whose seizure frequency improved by >25% were continued on VGB and followed up for a mean of 14.75 months in an open phase of the trial; however, these data have not been extracted for this review

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Neuropsychological assessment; between-patient analysis **Intervention 1** There was an improvement in performance on the tracking task over the first three testings regardless of treatment ($p < 0.005$). This test was excluded from further analysis. No other test revealed a significant practice effect **Comparator** Not stated	**Outcome** Change in functional capacity; sedation rate **Intervention 1** Patients rated their sedation level significantly higher ($p < 0.01$) when they had been taking VGB for 2 and 6 weeks compared with placebo. This effect was not sustained at 12 weeks. There were no significant differences between the treatments for any other test in the battery **Comparator** Not stated	**Outcome** Sedation scores **Intervention 1** Sedation scores correlated significantly with side-effect scoring during the 6th and 12th weeks and with backward digit span during the 12th week (all $p < 0.05$). Sedation scoring correlated significantly during the placebo phase with the side-effect score during the 2nd, 6th and 12th weeks, with decision time and general health questionnaire in the 2nd week, and with backward digit span in the 12th week (all $p < 0.05$) **Comparator** Not stated

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Loiseau, 1986[83] **Related publications** None **Country** France **Source** Literature search **Aim** To compare oral VGB (3 g/day) and placebo as add-on to standard therapy in severe therapy-resistant epileptic patients using a double-blind crossover design with randomised treatment allocation (The authors abbreviate vigabatrin to GVG) **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** The study consisted of three treatment	**Number of participants** 23 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Based on those participants completing the trial: total (n = 19): 28.5 years; VGB/placebo (n = 12): 28.9 years; placebo/VGB (n = 7): 27.7 years. Based on those participants completing the trial: total (n = 19): 12–58 years; VGB/placebo (n = 12): 13–58 years; placebo/VGB (n = 7): 12–50 years **Gender** Based on those participants completing the trial: total (n = 19): men = 7, women = 12; VGB/placebo (n = 12): men = 5, women = 7; placebo/VGB (n = 7): men = 2, women = 5 **Age at onset of seizures** Mean duration of seizures: based on those participants completing the trial: total (n = 19): 13.4 years (range 2–40 years, SD 8.34); VGB/placebo (n = 12): 14.5 years (range 8–40 years); placebo/VGB (n = 7): 11.4 years (range 2–20 years) **Pretrial medication** See concurrent medications	**Intervention 1** VGB/placebo; 3 g/day; 10 weeks No. randomised: not stated No. completed: 12 **Comparator** Placebo/VGB; NA; 10 weeks No. randomised: not stated No. completed: 7	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: increased seizure frequency following cross-over from VGB to placebo (n = 1); intolerance to VGB therapy after 12 days of treatment (n = 1); intolerance to VGB therapy after 45 days of treatment (n = 1); non-quantifiable seizure occurrence (n = 1) **Adverse events** **Intervention 1** Subjective and AEs during the VGB period: joint pain (n = 1), drowsiness (n = 4), irritability (n = 1), gastrointestinal cramps (n = 1), subjectively felt slow (n = 1), nausea (n = 2), nervousness (n = 1), fatigue (n = 1), mental confusion (n = 1), constipation (n = 1), mood elevation (n = 1) **Comparator** Subjective and AEs during the double-blind placebo period: vomiting (n = 1), joint pain (n = 1), drowsiness (n = 2), impaired attention (n = 1), irritability (n = 2), deterioration of condition following cross-over (n = 1), GI complaints (n = 1), malaise (n = 1), slowing (n = 1)	**Authors' conclusions** These results confirm the antiepileptic efficacy of oral VGB in refractory epileptics **Comments** VGB as add-on therapy is not licensed for primary generalised seizures. This study contains 2 participants with primary generalised seizures, which needs to be addressed in the analysis. VGB was supplied in individual sachets containing 1.5 g. Identical placebo sachets contained 1.5 g of lactose and 1 mg of quinine sulphate for taste masking Only one patient did not adhere to the study schedule. This patient received only half the dose (1.5 g/day) owing to the appearance of intolerance (gastrointestinal upset) at the beginning of P1 Length of follow-up includes P1, P2, P3 and the 1-week transition period between P2 and P3. The 10-week length of treatment with intervention 1 drug (VGB) and comparator drug (placebo) does not include the 1-week transition period between P2 and P3, in which patients were receiving half the target dose of the VGB dose and half of the placebo dose; however, it does include a 1-week titration period in which patients were receiving half the target

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
periods preceded by an initial 5-week observation phase (P0), in which only constant doses of pre-existing AEDs were used: two periods of 10 weeks each (P1, P2), in which VGB and placebo were added to pre-existing AED in double-blind manner; and a final 5-week single period (P3), in which placebo was administered as add-on therapy. This final placebo period was incorporated into the design to evaluate any potential carry-over or withdrawal effects in patients receiving VGB during the second double-blind period. Following random allocation of treatment and completion of period P0, patients received half the dose (1.5 g, i.e. one sachet) of the P1 treatment for 1 week, followed by 9 weeks of P1 treatment administered twice a day. The initial week of P2 constituted the cross-over period, at which time administration of half of the dose of the P1 treatment plus half the dose of the P2 treatment was administered in an attempt to prevent any adverse reactions that may have been precipitated by abrupt discontinuation of the study drug used in P1. A similar 1 week transition period was used between the completion of the 9 weeks of therapy with the full dose per day of the P2 study drug and the commencement of the final 5-week placebo period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated	**Ongoing concurrent medication** CBZ, CLB, CZP, PB, PHT, VPA, progabide, sultiame **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Number of patients taking concurrent AEDs: based on those participants completing the trial: total (n = 19): 1 AED (n = 2), 2 AEDs (n = 11), 3 AEDs (n = 6) Number of patients with seizure types: based on those participants completing the trial: total (n = 19): CPSs without secondary generalised (n = 9), CPSs with secondary generalised (n = 8), generalised tonic or tonic–clonic seizures (n = 2); VGB/placebo (n = 12): CPSs without secondary generalised (n = 5), CPSs with secondary generalised (n = 5), generalised tonic or tonic–clonic seizures (n = 2); placebo/VGB (n = 7): CPSs without secondary generalised (n = 4), CPSs with secondary generalised (n = 3), generalised tonic or tonic–clonic seizures (n = 0) **Inclusion/exclusion criteria** Inclusion: CPSs or primary generalised epilepsy; a total seizure frequency of at least one per week, despite treatment with no more than		Subjective and AEs during P3 (placebo): joint pain (n = 1), constipation (n = 1), urticaria (n = 1), irritable (n = 1)	dose of the VGB dose and half of the placebo dose The authors state that no period effect or treatment × period interaction was observed, indicating the lack of statistically significant carry-over or withdrawal effects The authors state that no clinically significant alterations in laboratory test results were observed and that no treatment-related changes in plasma concentrations of concomitant AEDs were noted The authors state that with the exception of 1 patient, no clinically significant treatment-related alterations of laboratory test results were noted during administration of VGB. Statistical analysis showed no significant difference between the VGB and placebo periods. Additionally, no trends within patients were noted

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods Mean weekly seizure frequencies from the VGB, placebo and P3 (placebo) periods were compared using the method for cross-over trials outlined by Hills and Armitage (1979).[475] Only the final 9 weeks of the two double-blind periods and the final week of the single-blind placebo period (P3) were included, thus eliminating the 1-week cross-over periods, during which only half the dose was used. Treatment effects, period effects and the treatment × period interaction were subjected to analysis. The global efficacy ratings performed at the end of each treatment were analysed by means of the sign test, comparing the efficacy scores of the VGB period with those of the placebo period **Length of trial/frequency of follow-up** 26 weeks; each patient was evaluated at 5-week intervals	3 standard AEDs; age 10–60 years; constant doses of AED during the 5 weeks prior to study entry; and informed consent Exclusion: history or evidence of a progressive neurological disorder, based on either the type of epileptic syndrome, duration of epilepsy or a recent CT scan; serious medical disorders other than epilepsy (e.g., liver disease, renal dysfunction, cardiac disease, abnormal haematology results or allergic disease); and pregnancy or risk of pregnancy			

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Seizure frequency; mean weekly seizure frequency during the placebo, VGB, and P3 (placebo) periods **Intervention 1** Follow-up data for double-blind phase (VGB vs placebo): VGB (n = 19): 6.33 (SE 1.82, range 0–29.1), t = –2.92, p < 0.01 Follow-up data for P3 (placebo) vs VGB period: VGB (n = 19): 6.33 (SE 1.82, range 0–29.1), t = –2.22, p < 0.05 **Comparator** Follow-up data for double-blind phase (VGB vs placebo): placebo (n = 19): 10.7 (SE 2.81, range 0.11–46) Follow-up data for P3 (placebo) vs VGB period: P3 (n = 19): 9.72 (SE 2.67, range 0–38.25)	**Outcome** Proportion of responders; reported as the number of patients with the specified reductions in seizure frequency during the VGB period compared with placebo **Intervention 1** VGB vs placebo (n = 19): >50% reduction = 11/19 25–50% reduction = 2/19 No change = 4/19 Overall increase in seizure frequency = 2/19 There was no differentiation of efficacy on the basis of seizure type with the 2 patients diagnosed as having tonic or tonic–clonic seizures, experiencing 64 and 100% reduction in seizure frequency, respectively **Comparator** Not stated	**Outcome** Physicians' global evaluation of improvement/efficacy/tolerability; global efficacy rating at the end of each study period made by the attending neurologist (double-blind rating based on seizure frequency, seizure severity (qualitative assessment) and adverse reactions **Intervention 1** Follow-up data [VGB vs placebo (n = 18)]: efficacy was greater during the VGB period for 15 patients compared with the placebo period. Results were identical for 1 patient **Comparator** Results were better for 2 patients in the placebo group	**Outcome** Physician/patient preference; evaluation of patients' preference among the three study periods based on perception of efficacy and comfort **Intervention 1** VGB vs placebo (n = 19): Preferred the VGB period n = 14 Did not indicate a preference n = 2 **Comparator** Preferred 10-week placebo period n = 2 Preferred final 5-week placebo period n = 1

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
McKee, 1993[54] **Related publications** Paper[51] **Country** UK **Source** Literature search **Aim** A double-blind randomised, crossover study of additional VGB (1.0 g twice daily for 6 weeks followed by 1.5 g twice daily for 6 weeks) and matched placebo was undertaken in 24 patients with refractory epilepsy **Type of publication** Full paper (final analysis) **Funding** Marion Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated	**Number of participants** 24 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total: 32.9 years; total: 17–53 years **Gender** Total: men = 8, women = 16 **Age at onset of seizures** Duration of epilepsy: total: 19.8 years **Pretrial medication** Monotherapy (n = 11) CBZ (n = 9); PHT (n = 1); VPA (n = 1) Two AEDs (n = 13): CBZ (n = 10); PRM (n = 6); VPA (n = 4); PHT (n = 4); PB (n = 2) **Ongoing concurrent medication** See medications used before enrolment **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** CPS (n = 8); CPS with secondary generalisation (n = 14); GTC seizures (n = 2)	**Intervention 1** VGB/placebo; 2–3 g/day; 12 weeks No. randomised: not stated No. completed: 11 **Comparator** Placebo/VGB; NA; 12 weeks No. randomised: not stated No. completed: 10	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: pregnancy (n = 1), withdrew consent owing to lack of efficacy (n = 1), psychotic episode while on VGB (n = 1) **Adverse events** **Intervention 1** VGB (2 g): tiredness (n = 7), dizziness (n = 3), headache (n = 2), blurred vision (n = 2), weight gain (n = 2), ankle swelling (n = 1), pruritus (n = 1), vertigo (n = 1), nightmares (n = 1), ataxia (n = 1), painful legs (n = 1), rash (n = 1) VGB (3 g): tiredness (n = 3), weight gain (n = 1), ankle swelling (n = 2) **Comparator** Placebo (for 2 g VGB): dizziness (n = 1), headache (n = 1), blurred vision (n = 2), weight gain (n = 1), ankle swelling (n = 1) Placebo (for 3 g VGB): tiredness (n = 1), dizziness (n = 1), headache (n = 1)	**Authors' 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 **Comments** VGB as add-on therapy is not licensed for primary generalised seizures. This study contains 2 participants with primary generalised seizures, which needs to be addressed in the analysis The inclusion/exclusion criteria are very limited, therefore it is possible that participants may have had concomitant conditions which may have had a confounding effect It is reported that there was no evidence of a treatment period interaction for either partial or generalised seizures Withdrawals are not reported by treatment group. Another two individuals were also excluded from the analysis because they failed to record their seizure numbers adequately

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period After an initial 4-week run-in period there were 2 treatment periods of 12 weeks separated by a 4-week washout period. The treatment period consisted of 6 weeks of 2 g of VGB/matched placebo followed by 6 weeks of 3 g of VGB/matched placebo **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Calculations suggested a power of 0.92 to detect a 50% decrease in total seizures, of 0.95 for a similar reduction in partial seizures and of 0.78 for generalised seizures. Power to detect a 25% decrease was 0.95, 0.97 and 0.91, respectively **Analysis methods** Comparison of seizure frequencies and AED concentrations between VGB and placebo treatment phases were made by Wilcoxon rank test for matched pairs and 95% CIs were calculated around median values. The comparison of partial and generalised seizure control with 2 and 3 g VGB daily was made by subtracting the number of seizures reported after treatment with the active drug from those documented during the matched placebo phase. Correlations were obtained with Pearson's moment correlation. The method outlined by Hills and Armitage (1979)[475] was used to test for treatment × period interaction effects **Length of trial/frequency of follow-up** 30 weeks; after 2, 6 and 12 weeks of treatment in each phase	**Inclusion/exclusion criteria** Inclusion: refractory epilepsy; at least two generalised or one partial seizure/week during the 3 months before recruitment; currently receiving one or more AEDs Exclusion: criteria not stated			

continued

Results		
Outcome 1	**Outcome 2**	**Outcome 3**
Outcome Seizure days; median number of seizure days over specified periods **Intervention 1** VGB (n = 19) Phase 1 (weeks 1–6): median = 10 (95% CI: –0.5 to –6.5), $p < 0.05$ Phase 2 (weeks 7–12): median = 20 (95% CI: –4.5 to 0.5) Overall (weeks 1–12): median = 23 (95% CI: –1.5 to –14), $p < 0.05$ **Comparator** Placebo (n = 19) Phase 1 (weeks 1–6): median = 16 Phase 2 (weeks 7–12): median = 24 Overall (weeks 1–12): median = 41	**Outcome** Change in seizure frequency; median seizure frequency over specified periods **Intervention 1** Total seizures (n = 19) Week 2: median = 7 (95% CI: –8 to 0.5) Week 6: median = 16 (95% CI: –17 to 0.5) Week 12: median = 20 (95% CI: –21.5 to 11) Weeks 1–12: median = 32 (95% CI: –17.5 to 23.5) Partial seizures (n = 17) Week 2: median = 7 (95% CI: –17 to 0) Week 6: median = 13 (95% CI: –16.5 to –0.5) Week 12: median = 22 (95% CI: –18 to 11) Weeks 1–12: median = 32 (95% CI: –16.5 to 22.5) GTC seizures (n = 12) Week 2: median = 2 (95% CI: –1 to 2) Week 6: median = 7 (95% CI: –6.5 to 6.5) Week 12: median = 6.5 (95% CI: –7 to 5) Weeks 1–12: median = 15 (95% CI: –13.5 to 9) **Comparator** Total seizures (n = 19) Week 2: median = 1 Week 6: median = 26 Week 12: median = 29 Weeks 1–12: median = 52 Partial seizures (n = 17) Week 2: median = 12 Week 6: median = 22 Week 12: median = 28 Weeks 1–12: median = 52 GTC seizures (n = 12) Week 2: median = 1.5 Week 6: median = 8.5 Week 12: median = 5.5 Weeks 1–12: median = 15.5	**Outcome** Proportion of responders; reported as number of patients achieving specified ranges of reduction in seizure frequency with VGB compared with placebo **Intervention 1** Total seizures (n = 19) Weeks 1–6: >50% reduction: n = 9; 25–50% reduction: n = 2; no change: n = 5; worse: n = 3 Weeks 7–12: >50% reduction: n = 6; 25–50% reduction: n = 1; no change: n = 6; worse: n = 6 Weeks 1–12: >50% reduction: n = 8; 25–50% reduction: n = 3; no change: n = 6; worse: n = 2 Partial seizures (n = 17) Weeks 1–6: >50% reduction: n = 7; 25–50% reduction: n = 4; no change: n = 3; worse: n = 3 Weeks 7–12: >50% reduction: n = 6; 25–50% reduction: n = 2; no change: n = 5; worse: n = 4 Weeks 1–12: >50% reduction: n = 8; 25–50% reduction: n = 4; no change: n = 2; worse: n = 3 GTC seizures (n = 12) Weeks 1–6: >50% reduction: n = 3; 25–50% reduction: n = 2; no change: n = 3; worse: n = 4 Weeks 7–12: >50% reduction: n = 3; 25–50% reduction: n = 0; no change: n = 3; worse: n = 6 Weeks 1–12: >50% reduction: n = 3; 25–50% reduction: n = 1; no change: n = 1; worse: n = 7 **Comparator** Not stated

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Rimmer, 1984[49] **Related publications** Paper[430] **Country** UK **Source** Literature search **Aim** 24 patients with frequent drug-resistant seizures were recruited into a randomised double-blind placebo-controlled crossover trial of the GABA transaminase inhibitor γ-vinyl-GABA (VGB). It was added to their usual drug treatment in a dose of 3 g/day **Type of publication** Full paper (final analysis) **Funding** Wellcome Foundation; drugs supplied by Merrell International, Strasbourg **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated	**Number of participants** 24 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 32.9 years (SD not stated); Total: 16–61 years **Gender** Total: men = 9, women = 15 **Age at onset of seizures** Duration of epilepsy: total: mean = 20.8 years (range 6–45 years) **Pretrial medication** Not stated **Ongoing concurrent medication** One concurrent AED: *n* = 8 Two concurrent AEDs: *n* = 13 Three concurrent AEDs: *n* = 4 PHT (*n* = 10) CBZ (*n* = 18) PB (*n* = 5) (from Ref. 430) **Co-morbidities** Mental disability: *n* = 8 (one of whom had associated psychiatric problems) **Baseline seizure frequency** Total: mean = 5.85 per week	**Intervention 1** VGB/placebo; 3 g/day; 9 weeks No. randomised: 12 No. completed: not stated **Comparator** Placebo/VGB; NA; 9 weeks No. randomised: 12 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: acute confusional state during first week of VGB (*n* = 1), non-compliance (*n* = 2) **Adverse events** **Intervention 1** Confusion (*n* = 1), drowsiness (*n* = 7), mood changes (*n* = 8), speech difficulty (*n* = 1), scanty periods (*n* = 1), constipation (*n* = 1), no complaints (*n* = 8) **Comparator** Drowsiness (*n* = 2), mood changes (*n* = 2), visual hallucinations (*n* = 1), nightmares (*n* = 1), constipation (*n* = 1), no complaints (*n* = 17)	**Authors' conclusions** These results suggest that VGB is an effective antiepileptic compound in human epilepsy particularly against CPSs **Comments** 21/24 participants completed the trial; however, it is not clear how many completed in each sequence group The inclusion/exclusion criteria are very limited, therefore it is possible that participants may have had concomitant conditions which may have had a confounding effect on the findings It is not clear whether the authors carried out a within-subject analysis, which is the appropriate form of analysis for a crossover trial. The paper reports that some of the patients had an increased fit frequency in the first week after stopping VGB, but when all the patients were considered together the increase in fit frequency compared with baseline was not statistically significant. However, they did not carry out a formal analysis to investigate the possibility of a period effect

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was an initial baseline assessment period of 4 weeks during which fit frequency was recorded to ensure adequate seizure rates and to assess the ability of patients and their relatives to record fits reliably in the diaries provided. Each treatment period lasted 9 weeks and consisted of either a 3-g dose of VGB or identically matched placebo capsules. Treatment order was randomised and double-blind with half the patients receiving the active drug first. There was an abrupt crossover between treatments. The patient's usual antiepileptic medication was continued unchanged throughout the trial **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Two-way ANOVA was used to compare the active drug period with placebo and baseline **Length of trial/frequency of follow-up** 18 weeks; at end of each treatment period	**Other characteristics** All patients had normal renal and hepatic function **Inclusion/exclusion criteria** Inclusion: poorly controlled epilepsy resistant to conventional drug therapy Exclusion: criteria not stated			

continued

Results	
Outcome 1	**Outcome 2**
Outcome Seizure frequency; mean weekly seizure frequency **Intervention 1** Total seizures (n = 21): baseline data: mean = 6.14; follow-up data: mean = 3.54 ($p < 0.001$) CPSs (n = 21): baseline data: mean = 5.77; follow-up data: mean = 3.30 ($p < 0.001$) Tonic–clonic seizures (n = 11): baseline data: mean = 0.68; follow-up data: mean = 0.46 ($p < 0.05$) **Comparator** Total seizures (n = 21): follow-up data: mean = 6.23 CPSs (n = 21): follow-up data: mean = 5.71 Tonic–clonic seizures (n = 11): follow-up data: mean = 1.02	**Outcome** Proportion of responders; responders were defined as having at least a 50% reduction in seizures **Intervention 1** n = 14/21 **Comparator** Not stated

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Tartara, 1986[86] **Related publications** None **Country** European **Source** Literature search **Aim** To assess the efficacy and tolerability of VGB, given as an add-on therapy to 23 adult outpatients with severe drug-resistant epilepsy (17 with partial seizures), using a double-blind, placebo-controlled crossover design **Type of publication** Full paper (final analysis) **Funding** Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after enrolment	**Number of participants** 23 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total: 30.5 years; total: 17–50 years **Gender** Total: men = 13, women = 10 **Age at onset of seizures** Duration of epilepsy: total: mean = 17.9 years (range 2–42 years) **Pretrial medication** See concurrent medications **Ongoing concurrent medication** One concurrent AED (n = 3) Two concurrent AEDs (n = 20) CBZ (n = 18); PB (n = 18); VPA (n = 4); PHT (n = 2); ethosuximide (n = 1) **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated	**Intervention 1** VGB/placebo; 2 or 3 g/day; 7 weeks No. randomised: not stated No. completed: not stated **Comparator** Placebo/VGB; NA; 7 weeks No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Total: non-compliance while taking VGB (n = 1); AEs while on VGB, poor recording of seizures (n = 1) **Adverse events** **Intervention 1** Drowsiness (n = 7), dizziness or vertigo (n = 2), nausea or vomiting (n = 2), abdominal pain (n = 1), headache (n = 2), anxiety (n = 1), insomnia (n = 1), irritability (n = 1), apathy or poor motivation (n = 1), dry mouth (n = 1), hypersalivation (n = 1), ataxia (n = 1), anorexia (n = 1), flu-like symptoms (n = 1), facial flushing (n = 1), sweating hands (n = 1), leg cramps (n = 1) **Comparator** Drowsiness (n = 1), dizziness or vertigo (n = 1), headache (n = 1), insomnia (n = 1), apathy or poor motivation (n = 1), depression (n = 2), fatigue (n = 2)	**Authors' conclusions** Add-on treatment with VGB is effective and well tolerated in adult patients with drug-resistant epilepsy **Comments** Of the original 23 participants, 20 completed the study; however, a breakdown is not provided for the number who were allocated to or withdrew from each sequence group Baseline data are presented for the total group only. There was no baseline period in the study, therefore a measure of baseline seizure frequency was obtained by history. This may not provide a reliable measure VGB dose: 2 g/day was received by 15 patients (≤ 65 kg); 5 patients (>65 kg) received 3 g/day It is reported that no treatment-related changes were observed on physical or neurological examination It is reported that no statistically significant period or carryover effects were identified

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Patients were randomised to receive either VGB or placebo first. VGB and placebo were supplied as identical sachets. Dosage of VGB was stratified according to body weight: patients weighting ≤ 65 kg took 2 g/day and patients weighing >65 kg took 3 g/day. Each dose group was individually randomised for sequence of drug/placebo administration depending on order of entrance into the study. Each treatment period was 7 weeks and crossover was performed abruptly at the end of the first treatment period. The dosage of concurrent medications was maintained unchanged throughout the study **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Analysis of seizure frequency was performed by applying the two-tailed Wilcoxon signed ranks test to the within-patient differences in the average number of seizures/week during each 7-week treatment period. The method outlined by Hills and Armitage (1979)[475] was used to test for the occurrence of period or carryover effects. Plasma concentrations of concomitant medications and evoked potentials data were analysed using an analysis of variance for repeated measurements **Length of trial/frequency of follow-up** 7 weeks; at the end of weeks 2, 4 and 7 of each treatment period	**Inclusion/exclusion criteria** Inclusion: aged 16–65 years; epilepsy uncontrolled by conventional treatment irrespective of seizure type; minimum seizure frequency of one seizure per week with a stable seizure frequency during the previous 6 months; treatment with no more than two AEDs without major changes in drug therapy during the 2 months prior to entry; routine haematology, blood chemistry and urinalysis values within the expected ranges; absence of psychiatric, cardiac, renal, hepatic, metabolic or progressive neurological diseases; no pregnancy or risk of pregnancy; no history of poor compliance Exclusion: no criteria stated			

continued

Results	
Outcome 1	**Outcome 2**
Outcome Seizure frequency; mean weekly seizure frequency for all seizures and partial seizures	**Outcome** Proportion of responders; reported as number of patients achieving specified reductions in seizure frequency during the VGB period compared with the placebo period
Intervention 1 All seizures (n = 20): Baseline: mean = 4.8 (SD 4.4) Follow-up: mean = 2.22 (SD 2.6) (p < 0.01 VGB follow-up versus both baseline and placebo) Partial seizures (n = 17): Follow-up: mean = 2.0 (SD 2.4) (p < 0.01)	**Intervention 1** (n = 20) >50% decrease in seizure frequency (n = 12) 25–50% decrease (n = 3) 0–25% decrease (n = 1) Increase in seizure frequency (n = 4)
Comparator All seizures (n = 20): Follow-up: mean = 3.80 (SD 3.7) Partial seizures (n = 17): Follow-up: mean = 3.7 (SD 3.8)	**Comparator** Not stated

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Tassinari, 1987[85] **Related publications** None **Country** Italy **Source** Literature search **Aim** To assess the efficacy and tolerance of oral VGB as add-on therapy in the treatment of patients with drug-resistant epilepsy **Type of publication** Full paper (final analysis) **Funding** Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated **Details of pretrial period** There was a 2-month run-in period during which only constant doses of pre-existing antiepileptic medications were administered. Following this, patients	**Number of participants** 31 **Type of epilepsy** Refractory **Type of seizures** Combination of partial/generalised **Mean age/age range** Total: mean = 28.9 years (SD 11.5); total: 10–58 years **Gender** Total: men = 16, women = 15 **Age at onset of seizures** Not stated **Pretrial medication** See concurrent medications **Ongoing concurrent medication** 1 concurrent AED: *n* = 2; 2 concurrent AEDs: *n* = 9; 3 concurrent AEDs: *n* = 18; 4 concurrent AEDs: *n* = 2; PB: *n* = 26; benzodiazepines: *n* = 20; PHT: *n* = 19; CBZ: *n* = 12; VPA: *n* = 2; PRM: *n* = 1; trimethadione: *n* = 1 **Co-morbidities** Mental disability: *n* = 10 (2 of whom had associated psychiatric problems) **Baseline seizure frequency** Seizure frequency is provided separately for two subgroups of patients. Group 1 was defined as	**Intervention 1** VGB/placebo; 2 or 3 g/day; 3 months No. randomised: not stated No. completed: not stated **Comparator** Placebo/VGB; NA; 3 months No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** One patient developed leucopenia thought to be due to concomitant treatment with trimethadione **Adverse events** **Intervention 1** VGB (*n* = 31): drowsiness (*n* = 18), irritability (*n* = 4), headache (*n* = 3), dizziness (*n* = 3), abdominal discomfort (*n* = 3), ataxia (*n* = 2), confusion (*n* = 2), menorrhagia (*n* = 2), muscle weakness (*n* = 1), difficulty concentrating (*n* = 10), constipation (*n* = 1), leucopenia (*n* = 1), anorexia (*n* = 1), nausea (*n* = 1) **Comparator** Double-blind placebo (*n* = 30): drowsiness (*n* = 10), irritability (*n* = 3), headache (*n* = 1), abdominal discomfort (*n* = 1), menorrhagia (*n* = 1), fatigue (*n* = 1), constipation (*n* = 1)	**Authors' conclusions** The results demonstrate the efficacy and good tolerability of VGB therapy in patients with severe complex partial epilepsy **Comments** 30/31 patients completed the study. The numbers of participants randomised to each treatment sequence group are not specified Intervention 1 dose: 2 g/day for body weight 40–60 kg and 3 g/day for body weight >60 kg Data on change in seizure frequency are also provided for individual patients in graph format

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
received either VGB or placebo for 3 months. VGB and placebo were supplied in identical packets containing 1.0 or 1.5 g to be dissolved in water. VGB was administered twice daily with the dose stratified according to body weight. This was followed by an abrupt crossover to the alternative treatment for 3 months. At the conclusion of the double-blind period all patients received placebo for 1 month under single-blind conditions **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Statistical analyses of seizure frequency and plasma concentrations of concomitant medications were performed using the method outlined by Hills and Armitage (1979)[475] that allows examination of treatment effects, order effects and the treatment × period interaction **Length of trial/frequency of follow-up** 9 months; at the end of the 2 month run-in period, every 6 weeks during the two double-blind periods and at the end of the 4-week single-blind period	those patients with CPSs only and temporal EEG abnormalities. Group 2 was defined as the remaining patients who presented with various seizure types (atonic, elementary partial, absences, secondarily generalised) and multifocal EEG abnormalities or diffuse slow discharges combined with focal abnormalities. Group 1: mean weekly seizure frequency '<5' Group 2: '≥ 10 seizures per week' **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: any form of epilepsy; no more than 4 concomitant AEDs; at least 4 seizures/month while receiving optimal doses of current AEDs Exclusion: criteria not stated			

continued

Results	
Outcome 1	**Outcome 2**
Outcome Proportion of responders; reported as the number of participants experiencing the specified decreases in seizure frequency during VGB vs placebo treatment	**Outcome** Physician/patient preference; at the end of the trial each patient and the investigator were formally questioned as to which treatment course was preferred
Intervention 1 Total: (n = 30) 50–100% decrease: n = 10 25–49% decrease: n = 6 0–24% decrease: n = 5 0–25% increase: n = 4 >25% increase: n = 5 Group 1 (n = 15) ($p < 0.02$) 50–100% decrease: n = 6 25–49% decrease: n = 5 0–24% decrease: n = 1 0–25% increase: n = 1 >25% increase: n = 2 Group 2 (n = 15) 50-100% decrease: n = 4 25-49% decrease: n = 1 0-24% decrease: n = 4 0-25% increase: n = 3 >25% increase: n = 3	**Intervention 1** Investigator preferred treatment with VGB: n = 20/30 Patient preferred treatment with VGB: n = 13/30
Comparator See above	**Comparator** Investigator preferred treatment with placebo: n = 3/30 Investigator had no preference: n = 7/30 Patient preferred treatment with placebo: n = 6/30 Patient had no preference: n = 11/30

Parallel studies (*n* = 10)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Brodie, 1999[66] **Related publications** None **Country** Multinational **Source** Literature search **Aim** To evaluate treatment with additional VGB (2–4 g daily) or VPA (1–2 g daily) using a double-blind, double dummy design, for patients taking optimal doses of CBZ **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy and monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; not stated	**Number of participants** 215 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** VGB (*n* = 108): median = 37 years; VPA (*n* = 107): median = 36 years; VGB (*n* = 108): 12–78 years; VPA (*n* = 107): 16–66 years **Gender** VGB (*n* = 108): men = 52, women = 56; VPA (*n* = 107): men = 54, women = 53 **Age at onset of seizures** Not stated **Pretrial medication** VGB: mean CBZ dose = 1089 mg; VPA: mean CBZ dose = 1021 mg **Ongoing concurrent medication** See details of pretrial period **Co-morbidities** Learning disabilities (the number is not stated) **Baseline seizure frequency** VGB: mean (per month) = 6.8 seizures	**Intervention 1** VGB; 1–4 g/day; 12 weeks maintenance phase for mono- and duotherapy No. randomised: 108 No. completed: 72 **Comparator** VPA; 1–3 g/day; 12 weeks No. randomised: 107 No. completed: 59	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Note: more than one reason for withdrawal may be reported for individual participants VGB: total withdrawn (*n* = 36); VPA: total withdrawn (*n* = 48) Lack of drug effect: Phase II: VGB (*n* = 2), VPA (*n* = 2); Phase III: VGB (*n* = 9), VPA (*n* = 17); Phase IV: VGB (*n* = 5), VPA (*n* = 8); Phase V: (*n* = 3), VPA (*n* = 4) AEs: Phase II: VGB (*n* = 7), VPA (*n* = 7); Phase III: VGB (*n* = 5), VPA (*n* = 5); Phase IV: VGB (*n* = 1), VPA (*n* = 1); Phase V: (*n* = 0), VPA (*n* = 0) Other: Phase II: VGB (*n* = 1), VPA (*n* = 0); Phase III: VGB (*n* = 0), VPA (*n* = 0); Phase IV: VGB (*n* = 0), VPA (*n* = 0); Phase V: (*n* = 3), VPA (*n* = 1) Exclusion criteria: Phase II: VGB (*n* = 1), VPA (*n* = 1); Phase III: VGB (*n* = 1), VPA (*n* = 0); Phase IV: VGB (*n* = 0), VPA (*n* = 2); Phase V: (*n* = 0), VPA (*n* = 1) Worsening seizures: Phase II: VGB (*n* = 0), VPA (*n* = 2); Phase III: VGB (*n* = 2), VPA (*n* = 4); Phase IV: VGB (*n* = 2), VPA (*n* = 1); Phase V: (*n* = 3), VPA (*n* = 3) Lost to follow-up: Phase II: VGB (*n* = 0), VPA (*n* = 1); Phase III:	**Authors' conclusions** VGB and VPA, which increase neuronal inhibition mediated by GABA, can be added to or substituted for CBZ when this sodium channel blocker fails to control partial seizures. This lends credence to the hypothesis in support of a mechanistic approach to the management of epilepsy **Comments** Although the definition of treatment response used baseline seizure levels from the 1-month prospective baseline, the ANCOVA used the composite baseline, which was presumably the 6-month retrospective baseline in addition to the 1-month prospective baseline. The authors do not specify how seizure frequency data were gathered for the 6-month retrospective phase. If the authors were relying on retrospective records or patient recall (although they do not state this), then this could be an unreliable baseline estimate of seizure frequency It is not clear from the paper how many patients were initially recruited into the trial and randomised to each group. The authors state that 215 patients met the criteria for the ITT analysis, which was defined as

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a 6-month retrospective baseline during which the CBZ dose remained unchanged. Patients were then recruited into the study. There was a 4-week prospective baseline of CBZ monotherapy (Phase I). This was followed by an 8-week titration phase during which VGB or VPA was administered with CBZ at an unchanged dosage (Phase II). Double dummy dosing was employed. VGB was titrated from 1 to 3 g/day by 1-g increments at fortnightly intervals. The dose of VPA was titrated from 0.5 to 1.5 g/day by 0.5-g increments at fortnightly intervals. Participants who remained seizure free with additional therapy or demonstrated a reduction in seizure rate ≥ 50% of baseline without evidence of toxicity were maintained on this dose. If optimal seizure control was not obtained despite acceptable tolerability, further dosing adjustment could be undertaken to a maximum of 4 g of VGB and 2 g of VPA. If participants experienced side-effects, the dose was reduced by decrements of 1 g for VGB and 0.5 g for VPA, provided that this was not accompanied by deterioration in seizure control. Participants who did not achieve a sufficient degree of seizure control despite taking the maximally permitted dose of either drug were withdrawn from the study. Titration was followed by a 12-week assessment phase on duotherapy (Phase III) and an 8-week CBZ withdrawal phase in responders (participants who had a ≥ 50% reduction in seizures compared with baseline) (Phase IV). If seizure control deteriorated, participants were returned to combination therapy with the original dose	All seizures: median = 5 (n = 108/108); SPS: median = 4 (n = 33/108); CPS: median = 4 (n = 74/108); secondary generalised: median = 1 (n = 17/108); not known median = 2 (n = 2/108) VPA: mean (per month) = 6.9 seizures All seizures: median = 5 (n = 107/107); SPS: median = 5 (n = 35/107); CPS: median = 4 (n = 71/107); secondary generalised: median = 2 (n = 19/107); not known median = 0 (n = 0/107) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 12–75 years; with SPSs or CPSs with or without secondary generalisation inadequately controlled on CBZ monotherapy; a minimum of 1 seizure per month for the previous 6 months and at least 6 seizures during the last 3 months; prestudy treatment with CBZ must have been at the highest tolerated dose within an effective concentration range (4–10 mg/l) measured at least twice in the preceding 6 months Exclusion: criteria not stated		VGB (n = 0), VPA (n = 1); Phase IV: VGB (n = 1), VPA (n = 0); Phase V: (n = 0), VPA (n = 0) Non-compliance: Phase II: VGB (n = 1), VPA (n = 4); Phase III: VGB (n = 1), VPA (n = 1); Phase IV: VGB (n = 0), VPA (n = 0); Phase V: (n = 1), VPA (n = 0) **Adverse events** **Intervention 1** (n = 108) Serious AEs: 10% (n = 11) Most common AEs reported during the study: drowsiness (n = 30), fatigue (n = 15), headache (n = 13), dizziness (n = 13), weight gain (n = 10), vomiting (n = 7), nausea (n = 6), diplopia (n = 7) **Comparator** (n = 107) Serious AEs: 9% (n = 10) Most common AEs reported during the study: drowsiness (n = 21), fatigue (n = 14), headache (n = 15), dizziness (n = 9), weight gain (n = 13), vomiting (n = 10), nausea (n = 10), diplopia (n = 6)	exposure to treatment with at least one postbaseline seizure diary record. It is not clear whether this included all the patients initially recruited or whether some of the patients recruited did not meet the ITT criteria, therefore the figure entered above for number of patients initially recruited into the trial and number randomised to each group may not be accurate Although an inclusion criterion was patients aged 12–75 years, the age range for the VGB group extends to 78 years. The exclusion criteria are very limited compared with other similar studies Some participants were taking 4 g/day of VGB, which is higher than the maximum of 3 g/day stated in current manufacturers' information provided for health professionals There were no statistically significant differences in seizure reduction between the two treatment groups. There was no statistically significant difference between the groups with respect to the incidence of serious AEs. The authors report that there were no consistent clinically relevant changes in clinical or laboratory safety variables, although no data are reported on these aspects

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
of CBZ for the remainder of the study. There was a 12-week maintenance phase of VGB or VPA as monotherapy or in combination with CBZ (Phase V) **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Treatment response was defined as a reduction in seizure rate of ≥50% relative to baseline. Response rates at the end of Phase III of 65% in the VGB group and 45% in the VPA group were assumed. It was estimated that 96 patients per treatment group would be required to demonstrate a difference between the two groups of 20%, at 80% power and a 5% significance level. With some allowance for drop-outs, it was estimated that 100 patients per treatment group were required **Analysis methods** Efficacy was assessed by ANCOVA on the percentage change in monthly seizure rates from the composite baseline to each time point (Phases III, IV and V). The primary efficacy analysis was the ANCOVA comparing monthly seizure rates at baseline with those during Phases IV and V of the study. Safety was assessed by comparison of the incidence of AEs using Fisher's exact test **Length of trial/frequency of follow-up** 12 weeks for duotherapy and 12 weeks for monotherapy; monthly seizure frequency for each study phase				

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Change in seizure frequency; mean reduction in seizures (%) from baseline with combined Phase IV and V data **Intervention 1** 45% reduction **Comparator** 38% reduction	**Outcome** Withdrawal due to inefficacy **Intervention 1** 16% **Comparator** 27%	**Outcome** Proportion of responders; responders were defined as having achieved at least a 50% decrease in seizure frequency. Percentage values were reported **Intervention 1** (n = 108): 53% **Comparator** (n = 107): 51%	**Outcome** Proportion of seizure-free patients; the number of participants who remained seizure free for the final 3 months of the trial **Intervention 1** (*n* = 108): 17% (7% monotherapy, 10% duotherapy) **Comparator** (*n* = 107): 19% (8% monotherapy, 11% duotherapy)
Outcome 5			
Outcome Maintained monotherapy; number of patients who maintained on therapy throughout the trial, completing Phases IV and V **Intervention 1** *n* = 29/108 (27%) **Comparator** *n* = 33/107 (31%)			

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Bruni, 2000[153] **Related publications** None **Country** Canada **Source** Literature search **Aim** To extend further the clinical experience with VGB as adjunctive therapy in the treatment of adult patients with difficult to control CPSs and/or partial seizures secondarily generalised. In addition to the assessments of efficacy and tolerability to VGB, neuropsychological evaluations were also carried out **Type of publication** Full paper (final analysis) **Funding** Hoeschst Marion Roussel **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 111 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 34 years (SD 7.39); VGB: 34 years (SD 7.54); placebo: 34 years (SD 7.93); total: 18–50 years; VGB: 18–50 years; placebo: 18–49 years **Gender** Total: men = 61, women = 50; VGB: men = 32, women = 26; placebo: men = 29, women = 24 **Age at onset of seizures** Mean duration of epilepsy Total: 20 years (SE 0.9); VGB: 21 years (SE 1.2); placebo: 19 years (SE 1.4) Mean age of onset Total: 13 years (SE 0.9); VGB: 13 years (SE 1.2); placebo: 14 years (SE 1.5) **Pretrial medication** See concurrent medications **Ongoing concurrent medication** 1 concurrent AED: total: 30% (33/110); VGB: 29% (17/58); placebo: 31% (16/52) 2 concurrent AEDs: total: 70% (77/110); VGB: 71% (41/58); placebo: 69% (36/52)	**Intervention 1** VGB; max. 4 g/day; 4 weeks No. randomised: 58 No. completed: 46 **Comparator** Placebo; NA; 36 weeks No. randomised: 53 No. completed: 44	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** VGB (total = 12): AEs (n = 6, only 4 were thought to be related to study medication), major protocol violation (n = 6) Placebo (total = 9): AEs (n = 4, only 2 were thought to be related to study medication), major protocol violation (n = 5) [protocol violations not broken down by group: insufficient number of seizures during baseline period (n = 5), seizure-free interval >28 days (n = 3), increase in dosage of concomitant AEDs (n = 1), missing data (n = 1), voluntary withdrawal (n = 1)] **Adverse events** **Intervention 1** Headache (n = 19), fatigue (n = 15), dizziness (n = 13), drowsiness (n = 10), insomnia (n = 6), abnormal vision (n = 8), diplopia (n = 6), amnesia (n = 9), confusion (n = 5), ataxia (n = 4), vertigo (n = 4), speech disorder (n = 5), agitation (n = 7), aggressive reaction (n = 5), dyspepsia (n = 5), weight gain (n = 7)	**Authors' conclusions** VGB is a highly effective and well-tolerated AED when used as adjunctive therapy in patients with difficult to control CPSs and partial seizures secondarily generalised **Comments** The usual recommended maximum dose of VGB is 3 g, so most of the participants will be receiving doses above this. The number of participants receiving the various doses were as follows: VGB (2 g) n = 4; VGB (3 g) n = 9; VGB (4 g): n = 45) The postrandomisation phase consists of a 36-week period. However, the first 32 weeks comprise the titration phase and the participants are only maintained on a fixed maintenance dose for the final 4 weeks of the 36-week period The authors define their ITT population as all randomised patients who consumed double-blind study medication The authors also investigated the relationship between the change in seizure frequency and gender, use of any of concurrent AEDs, body weight and age at onset of epilepsy. Only age at onset of seizures showed a significant interaction (p = 0.018), but no

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Prior to randomisation there was a 12-week baseline period used for monitoring seizure frequency and blood levels of concomitant AEDs. This was followed by a 32-week titration period (starting dose 500 mg/day). During this titration period at 8-week intervals, the daily dose was increased by 1-g increments to maximum of 4-g. Patients with no seizures during last 6 weeks of the 8-week period had their dose increased by 1 g. If complete seizure control was maintained, that dose was continued throughout the remainder of segment. Dose escalation occurred if additional seizures occurred further to this. The titration period was followed by a maintenance phase of 4 weeks **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** Between-group baseline characteristics were compared using Fisher's exact test, likelihood ratio χ^2 test and the Wilcoxon test. The change in seizure frequency from baseline to end of study was analysed using an ANCOVA model, adjusting for baseline and investigation site. Between-group comparisons of the number of patients achieving therapeutic success and physician assessments were analysed using the Cochran–Mantel–Haenszel method, stratified by investigation site. Finally, changes from baseline to end of study in terms of evoked potentials,	**Co-morbidities** Not stated **Baseline seizure frequency** See Outcome 1 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 16–50 years; definite diagnosis of CPSs or partial with secondary generalisation by focal EEG abnormalities; minimum of 6 CPSs or partial secondarily generalised seizures over 8 weeks preceding entry; stable regimen of 1 or 2 AEDs; IQ $\geq$65 Exclusion; treatable causes of seizures; >1 event of status epilepticus in previous 6 months; progressive neurological disorders; epilepsy surgery in previous 6 months; surgery for brain tumour in previous 12 months; history of radiation therapy to brain; alcoholism; drug addiction; serious psychiatric illness; significant systemic disease; used investigational drug in previous 60 days; discontinued any AED in previous 60 days; displaying a seizure-free interval >28 days; pregnancy		**Comparator** Headache (n = 12), fatigue (n = 9), dizziness (n = 7), drowsiness (n = 8), insomnia (n = 5), abnormal vision (n = 2), diplopia (n = 2), amnesia (n = 4), confusion (n = 2), ataxia (n = 0), vertigo (n = 0), speech disorder (n = 1), agitation (n = 4), aggressive reaction (n = 0), dyspepsia (n = 6), weight gain (n = 1)	clear pattern emerged in the data and the authors do not discuss this finding further. In addition, no statistically significant differences were observed between the study groups in terms of plasma levels of concurrent AEDs and VGB

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
neuropsychological tests and change in the plasma levels of concomitant AEDs were analysed using the Wilcoxon test **Length of trial/frequency of follow-up** 4 weeks; neurological evaluations and clinical laboratory tests were carried out every 2–4 weeks. All other assessments were carried out at the end of the maintenance period				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Seizure frequency; the number of seizures in a 28-day period **Intervention 1** CPSs Baseline data (n = 56): median = 6.5 (95% CI: 5.5 to 11.0) Follow-up data (n = 56): median = 3.0 (95% CI: 1.5 to 4.0) VGB vs placebo p = 0.0004 CPSs plus partial seizures secondarily generalised Baseline data (n = 58): median = 7.3 (95% CI: 6.0 to 11.0) Follow-up data (n = 58): median = 3.5 (95% CI: 2.5 to 4.5) VGB vs placebo p = 0.001 **Comparator** CPSs Baseline data (n = 53): median = 7.0 (95% CI: 5.5 to 10.5)	**Outcome** Seizure-free days; the number of seizure-free days in a 28-day period **Intervention 1** Baseline data (n = 58): median = 21.3 (95% CI: 17.5 to 22.5) Follow-up data (n = 58): median = 24.0 (95% CI: 22.0 to 25.0) **Comparator** Baseline data (n = 53): median = 21.0 (95% CI: 19.5 to 23) Follow-up data (n = 53): median = 22.0 (95% CI: 20.0 to 24.0)	**Outcome** Proportion of responders; defined as the number of patients achieving at least a 50% reduction in mean monthly seizure rate from baseline to end of study **Intervention 1** n = 28/58 (48%) VGB vs placebo p = 0.022 **Comparator** n = 14/53 (26%)	**Outcome** Physicians' global evaluation of improvement/efficacy/tolerability; the percentage of participants classified according to specific categories **Intervention 1** Improved: 67%; unchanged/minimally changed: 24%; worse: 9%; seizure-free: 9% VGB vs placebo p = 0.004 Physicians' evaluation of tolerability (% participants): Extremely well tolerated 36% (21/58) Well tolerated 36% (21/58) Fairly well tolerated 16% (9/58) Poorly tolerated 9% (5/58) Very poorly tolerated 4% (2/58) Global evaluations: % patients categorised as: Improved: 54% Deteriorated: 10% VGB vs placebo p = 0.047	

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Outcome 5	Outcome 6	Outcome 7	Outcome 8
Follow-up data (n = 53): median = 6.0 (95% CI: 4.5 to 8.7) CPSs plus partial seizures secondarily generalised Baseline data (n = 53): median = 8.6 (95% CI: 6.0 to 10.5) Follow-up data (n = 53): median = 6.0 (95% CI: 5.0 to 11.5)			**Comparator** Improved: 38%; unchanged/minimally changed: 55%; worse: 8%; seizure-free: 4% Physicians' evaluation of tolerability (% participants): Extremely well tolerated 36% (19/53) Well tolerated 55% (29/53) Fairly well tolerated 2% (1/53) Poorly tolerated 4% (2/53) Very poorly tolerated 4% (2/53) Global evaluations: % patients categorised as: Improved: 36% Deteriorated: 10%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Dean, 1999[154] **Related publications** Abstracts,[164, 326] cognitive and QoL outcomes[168] **Country** USA **Source** Literature search **Aim** To compare the efficacy and safety of a range of dosages (1, 3 and 6 g/day) of VGB as add-on therapy for patients with CPSs, with or without secondary generalisation, who are poorly controlled by an optimal regimen of conventional AEDs **Type of publication** Full paper (final analysis) **Funding** Hoechst Marion Roussel **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period	**Number of participants** 203 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total 35 years (SD 10); placebo 35 years (SD 11); VGB (1 g) 34 years (SD 9); VGB (3 g) 34 years (SD 9); VGB (6 g) 35 years (SD 11); not stated **Gender** Total: men = 83, women = 91; placebo: men = 17, women = 28; VGB (1 g): men = 19, women = 26; VGB (3 g): men = 24, women = 19; VGB (6 g): men = 23, women = 18 **Age at onset of seizures** **Age at onset** Total: mean = 13 years (SD 10); placebo: mean = 13 years (SD 10); VGB (1 g): mean = 10 years (SD 8); VGB (3 g): mean = 14 years (SD 10); VGB (6 g): mean = 15 years (SD 10) Duration of epilepsy Total: mean = 22 years (SD 10); placebo: mean = 22 years (SD 11); VGB (1 g): mean = 24 years (SD 8); VGB (3 g): mean = 20 years (SD 9); VGB (6 g): mean = 21 years (SD 11) **Pretrial medication** See concurrent medication	**Intervention 1** VGB; 1 g/day; 12 weeks No. randomised: 45 No. completed: 36 **Intervention 2** VGB; 3 g/day; 12 weeks No. randomised: 43 No. completed: 38 **Intervention 3** VGB; 6 g/day; 12 weeks No. randomised: 41 No. completed: 32 **Comparator** Placebo; NA; 12 weeks No. randomised: 45 No. completed: 40	**Withdrawals prerandomisation** 29/203 participants withdrew. The most common reasons given were failure to meet entry IQ requirements or inadequate number of seizures (no further information given) **Withdrawals postrandomisation** 25/174 participants withdrew. Reasons given were AEs (n = 17), not stated (n = 8) **Adverse events** **Intervention 1** AEs reported by at least 5% of the participants in any one treatment group VGB 1 g (n = 46): fatigue (n = 11), drowsiness (n = 10), dizziness (n = 4), nystagmus (n = 8), agitation (n = 5), headache (n = 5), tremor (n = 5), amnesia (n = 4), abnormal vision (n = 1), ataxia (n = 0) weight increase (n = 3), confusion (n = 1), depression (n = 2), abnormal coordination (n = 4), diarrhoea (n = 1), paraesthesia (n = 2), hyporeflexia (n = 2), nausea (n = 5), asthenia (n = 2), diplopia (n = 1), abnormal gait (n = 1), abnormal thinking (n = 0), chest pain (n = 0), impaired concentration (n = 0), menstrual disorder (n = 3), rash (n = 1), vertigo (n = 1), vomiting (n = 1)	**Authors' conclusions** 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, AEs may limit the use of the 6 g/day dose in some patients **Comments** Overall 149/172 completed the study; however, the authors do not state the number of participants who completed the trial according to the four study groups. Completer numbers taken from data in an associated paper by Dodrill[168] Cognitive and psychosocial evaluations Including 42 subtests within the following 11 neurophysiological tests: POMS, WPSI, Lafayette Grooved Pegboard, Stroop Test, BVRT, COWA, Mood Rating Scale, Symbol Digit Modalities, Rey Auditory–Verbal Learning Test, Wonderlic Personnel Test and Digit Cancellation Test Of the 42 tests performed, significant trends were only seen in the results of the Digit Cancellation Test. As the dose increased, the average number correct decreased (ANOVA, p = 0.0004; ANCOVA, p = 0.0011) and the average

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period A pretreatment period of 12 weeks was used to train patients in the use of the seizure calendar (weeks 1–4). This was followed by an initial evaluation period (week 1) and a baseline period to assess the frequency of seizures (weeks 5–12). Participants were then randomised to the different study groups and then entered a 6-week titration period for their assigned therapy **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** An ANCOVA model was used to assess the primary efficacy measure (seizure frequency) and the secondary analysis according to the individual seizure types. This analysis adjusted for baseline seizure frequency, study site and investigative site by treatment interaction. The frequency of therapeutic successes was evaluated using logistic regression and treatment by physician assessments using the Mantel–Haenszel method. The effect of increasing VGB dose on the change in seizure frequency from baseline to follow-up was assessed using both ANCOVA and ANOVA models **Length of trial/frequency of follow-up** 12 weeks; every 4 weeks during the pretrial phase and every 2 weeks during the randomised trial phase (including the titration phase)	**Ongoing concurrent medication** Number of participants taking 1 concurrent AED: Total = 81/174 (47%); placebo = 19/45 (42%); VGB (1 g) = 24/45 (53%); VGB (3 g) = 23/43 (53%); VGB (6 g) = 15/41 (37%) Number of participants taking 2 concurrent AEDs: Total = 92/174 (53%); placebo = 26/45 (58%); VGB (1 g) = 20/44 (53%); VGB (3 g) = 20/43 (47%); VGB (6 g) = 26/41 (63%) Number of participants taking 3 concurrent AEDs: Total = 1/174 (1%); placebo = 0/45 (1%); VGB (1 g) = 1/45 (1%); VGB (3 g) = 0/43 (0%); VGB (6 g) = 0/41 (0%) AEDs used by the participants as a whole population included (n = 174): barbiturates 25 (14%); benzodiazepine 16 (9%); CBZ 120 (69%); hydantoin 64 (37%); VPA 31 (18%); other AEDs 12 (7%). There were no significant differences between the four study groups in terms of the number of participants taking each of the drugs **Co-morbidities** None stated **Baseline seizure frequency** See Outcome 1 **Other characteristics** Not stated		**Intervention 2** VGB 3 g (n = 44): fatigue (n = 13), drowsiness (n = 11), dizziness (n = 11), nystagmus (n = 7), agitation (n = 6), headache (n = 6), tremor (n = 7), amnesia (n = 5), abnormal vision (n = 7), ataxia (n = 4), weight increase (n = 3), confusion (n = 5), depression (n = 2), abnormal coordination (n = 2), diarrhoea (n = 2), paraesthesia (n = 3), hyporeflexia (n = 3), nausea (n = 1), asthenia (n = 2), diplopia (n = 1); abnormal gait (n = 1), abnormal thinking (n = 2), chest pain (n = 1), impaired concentration (n = 3), menstrual disorder (n = 2), rash (n = 4), vertigo (n = 0), vomiting (n = 0) **Intervention 3** VGB 6 g (n = 44): fatigue (n = 19), drowsiness (n = 13), dizziness (n = 11), nystagmus (n = 8), agitation (n = 8), headache (n = 8), tremor (n = 7), amnesia (n = 7), abnormal vision (n = 6), ataxia (n = 7), weight increase (n = 5), confusion (n = 4) depression (n = 6), abnormal coordination (n = 3), diarrhoea (n = 6), paraesthesia (n = 4), hyporeflexia (n = 3), nausea (n = 2), asthenia (n = 3), diplopia (n = 5), abnormal gait (n = 5), abnormal thinking (n = 5), chest pain (n = 4), impaired concentration (n = 2),	number omitted increased (ANOVA, p = 0.0083; ANCOVA, p = 0.0007), suggesting a slight and clinically insignificant decrease in cognitive performance The authors also report data relating to the plasma concentrations of VGB and concomitant AEDs, but these data have not been extracted. In addition, it is not reported how the time of testing and mood effects on cognitive performance were accounted for in the design and analysis of the study

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
	Inclusion/exclusion criteria Inclusion: aged 18–60 years; uncontrolled (at least 6 seizures plus a seizure-free interval of <28 days during the preceding 8 weeks) CPSs or partial seizures with secondary generalisation; receiving at least one but not more than two concomitant AEDs; previously participated in adequate therapeutic trials of PHT or CBZ; history of abnormal EEG documenting focal abnormalities, including focal rhythmic, slow, sharps or spikes Exclusion: treatable cases of seizures (metabolic or neoplastic causes, active infection, etc.); history of more than one episode of status epilepticus within previous 6 months; progressive neurological disorders (multiple sclerosis, brain tumours); surgery for epilepsy (previous 6 months) or brain tumour (previous 12 months); alcoholism; drug addiction; major depression or other serious psychiatric disorder; clinically significant hepatic, renal, haematological, endocrine or gastrointestinal disease; verbal/performance IQ < 65 [Wechsler Adult Intelligence Scale – Revised (WAIS-R)]		menstrual disorder (n = 0), rash (n = 0), vertigo (n = 4), vomiting (n = 4) **Comparator** Placebo (n = 45): fatigue (n = 9), drowsiness (n = 12), dizziness (n = 5), nystagmus (n = 3), agitation (n = 2), headache (n = 6), tremor (n = 7), amnesia (n = 0), abnormal vision (n = 3), ataxia (n = 3), weight increase (n = 2), confusion (n = 0), depression (n = 1), abnormal coordination (n = 1), diarrhoea (n = 1), paraesthesia (n = 1), hyporeflexia (n = 1), nausea (n = 5), asthenia (n = 0), diplopia (n = 0), abnormal gait (n = 0), abnormal thinking (n = 1), chest pain (n = 2), impaired concentration (n = 0), menstrual disorder (n = 1), rash (n = 1), vertigo (n = 1), vomiting (n = 0).	

continued

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Seizure frequency; the median number of complex partial plus partial secondarily generalised seizures per 28 days **Intervention 1** Baseline (n = 45): 8.5 (95% CI: 6.0 to 12.3) Follow-up (n = 45): 7.7 (95% CI: 4.1 to 11.5) Placebo vs VGB (1 g) p = 0.1263 **Intervention 2** Baseline (n = 43): 8.0 (95% CI: 7.0 to 10.5) Follow-up (n = 43): 3.7 (95% CI: 2.5 to 6.0) Placebo vs VGB (3 g) p = 0.0001 VGB (3 g) vs VGB (6 g) p = 0.8145 **Intervention 3** Baseline: 9.0 (95% CI: 7.0 to 14.5) Follow-up: 4.5 (95% CI: 3.3 to 6.0) Placebo vs VGB (6 g) p = 0.0001 **Comparator** Baseline: 9.0 (95% CI: 7.0 to 10.5) Follow-up: 8.8 (95% CI: 6.0 to 12.1) Placebo and VGB (1 g) vs VGB (3 g) and VGB (6 g) p = 0.0001	**Outcome** Proportion of responders; responders were defined as having achieved at least a 50% reduction in seizure frequency at the end-point **Intervention 1** n = 11/45 (24%) Placebo vs VGB (1 g) p = 0.0248 **Intervention 2** n = 22/43 (51%) Placebo vs VGB (3 g) $p \leq 0.0001$ **Intervention 3** n = 22/41 (54%) Placebo vs VGB (6 g) $p \leq 0.0001$ VGB (3 g) vs VGB (6 g) p = 0.9655 **Comparator** n = 3/45 (7%) Placebo vs VGB (3 g) and VGB (6 g) $p \leq 0.0001$ Placebo and VGB (1 g) vs VGB (3 g) and VGB (6 g) $p \leq 0.0001$	**Outcome** Proportion of seizure-free patients; the number of seizure-free patients at the end of the trial period **Intervention 1** 0/45 (0%) **Intervention 2** 4/43 (9.3%) **Intervention 3** 5/41 (12.2%) **Comparator** 0/45 (0%)	**Outcome** Physicians' global evaluation of improvement/efficacy/tolerability; data presented for the percentage of participants (absolute numbers not reported) classified as showing a moderate or better improvement in their epilepsy. A global assessment which also included AEs did not differ significantly **Intervention 1** 32% **Intervention 2** 40% **Intervention 3** 56% **Comparator** 20%

Outcome 5

Outcome Seizure-free days; the adjusted mean change in seizure-free days from baseline to end of follow-up **Intervention 1** +1.2 days **Intervention 2** +2.0 days	**Intervention 3** +3.2 days **Comparator** –0.1 days

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Dodrill, 1993[169] **Related publications** Efficacy and safety data,[155] abstracts[421,422] **Country** USA **Source** Literature search **Aim** To investigate the effect of 3 g VGB as an add-on therapy compared with placebo on cognitive functioning, mood and adjustment in patients with CPSs or partial seizures with secondary generalisations **Type of publication** Full paper (final analysis) **Funding** Marion Merrell Dow **Trial ID** Study 024 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** The study consisted of a 12-week baseline period in which seizures and medications	**Number of participants** 203 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total: 34.39 years (SD 8.66); VGB: 34.53 years (SD 9.12); placebo: 34.25 years (SD 8.24); Not stated **Gender** Total: men = 74, women = 94; VGB: men = 34, women = 49; placebo: men = 40, women = 45 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** No more than two concurrent AEDs (no further details) **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated	**Intervention 1** VGB; 3 g/day; 12 weeks No. randomised: 92 No. completed: 83 **Comparator** Placebo; 12 weeks No. randomised: 90 No. completed: 85	**Withdrawals prerandomisation** 21 individuals originally screened were not randomised (reasons not stated) **Withdrawals postrandomisation** VGB: excluded (n = 9) [2 dropped out owing to AEs (reasons not stated)] Placebo: excluded (n = 14) [AEs (n = 6), administrative reasons (n = 2), incomplete data (n = 2), WAIS-R scores <65 (n = 4)] **Adverse events** **Intervention 1** Suicide (n = 1), emotional response including nervousness, apprehension, emotional lability, paranoia with grandiose thoughts (n = 6), cognitive change such as forgetfulness (n = 2), drowsiness (n = 2) **Comparator** Drowsiness (n = 2), 2 dropped out owing to AEs (reasons not stated)	**Authors' conclusions** There were no differences between the VGB and placebo groups on any of the neuropsychological variables, mood or adjustment. VGB appears to be a useful AED with little impact upon tests of either cognitive abilities or QoL **Comments** There is reference to a further 9 patients being dropped from the overall study, 3 of whom were retained in the neuropsychological analyses. It is not clear how many of the remaining 6 were in VGB and placebo groups, therefore the number noted above as completing the trial is an overestimate. The exclusion criteria did not define how many episodes of status epilepticus were required to meet the 'frequent' threshold. No information is provided on why only 182 of the 203 patients screened for the study were randomised All p-values relate to treatment × time interactions The authors also present data relating to variables with statistically significant interaction effects on the two-factor ANOVA and correlations of VGB serum levels (five single subscales of five tests) and changes in test

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
were monitored and WAIS-R administered prior to randomisation There was a 4-week titration after randomisation followed by a maintenance period of 12 weeks **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Differential changes in scores from baseline were analysed by time × group interactions on one-way repeated measures ANOVA. This allowed the evaluation of differential responses of the groups over time to compare VGB with placebo. Changes on the tests with the groups in relation to whether or not there had been significant seizure relief in comparison to baseline were also carried out using ANOVA. ANOVA was applied to each test variable individually and to all interaction effects **Length of trial/frequency of follow-up** 12 weeks; end of treatment period at 12 weeks	**Inclusion/exclusion criteria** Inclusion: difficult to control complex partial or partial with secondary generalisation seizures; at least 6 seizures in the 8 weeks prior to end of baseline; fewer than 28 days between seizures; no more than two concurrent AEDs; no other experimental agents were allowed Exclusion: history of progressive neurological disorder; frequent episodes of status epilepticus; WAIS-R score<65; ongoing psychiatric disorder; any other condition that might adversely impact on results			performance (only one subscale of the WPSI showed a significant correlation). The authors state that these significant findings are likely to be chance occurrences The possible effect of mood state on neuropsychological performance was not accounted for and there was no indication of how possible time of day effects on cognitive performance were dealt with AEs were not consistently reported and information was provided only about those who dropped out owing to AEs

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Lafayette Pegboard Test: a measure of the manual dexterity, visual-motor coordination and motor speed of participants. Consists of a pegboard into which 25 keyed pegs are required to be placed in a required alignment as fast as possible. Reported as mean scores (in seconds) for the preferred hand and non-preferred hand **Intervention 1** Preferred hand Baseline data: mean = 81.64 (SD 16.61). Follow-up data: mean = 82.37 (SD 18.06), $p = 0.188$ (treatment × time interaction) Non-preferred hand Baseline data: mean = 89.86 (SD 15.70). Follow-up data: mean = 88.95 (SD 16.47), $p = 0.734$ (treatment × time interaction) **Comparator** Preferred hand Baseline data: mean = 80.07 (SD 16.55). Follow-up data: mean = 77.75 (SD 18.63) Non-preferred hand Baseline data: mean = 87.31 (SD 18.22). Follow-up data: mean = 85.58 (SD 24.27)	**Outcome** Stroop Test: colour names are printed in incongruous colours and the participant must first read the names ignoring the colour of the print and then give the colour of the print ignoring the colour names. Reported as mean reading speed (in seconds) and the number of errors for both sections **Intervention 1** Reading speed (seconds): baseline data: mean = 56.28 (SD 20.25); follow-up data: mean = 57.42 (SD 20.12), $p = 0.255$ Reading speed (no. of errors): baseline data: mean = 0.87 (SD 1.44); follow-up data: mean = 0.80 (SD 1.45), $p = 0.594$ Interference (seconds): baseline data: mean = 144.05 (SD 59.62); follow-up data: mean = 141.13 (SD 57.18), $p = 0.889$ Interference (no. of errors): baseline data: mean = 4.52 (SD 4.02); follow-up data: mean = 4.68 (SD 3.91), $p = 0.805$ **Comparator** Reading speed (seconds): baseline data: mean = 54.30 (SD 16.59); follow-up data: mean = 57.95 (SD 24.33) Reading speed (no. of errors): baseline data: mean = 0.96 (SD 1.28); follow-up data: mean = 0.76 (SD 1.23) Interference (seconds): baseline data: mean = 133.63 (SD 40.59); follow-up data: mean = 130.07 (SD 46.59) Interference (no. of errors): baseline data: mean = 4.18 (SD 3.38); follow-up data: mean = 4.20 (SD 3.88)	**Outcome** Benton Visual Retention (Form F and Form G); for form F the participant sees 15 drawings each for 5 seconds (15 items for 10 seconds for Form G). Another card with four drawings is then shown immediately (after a 15-second delay with Form G) and the participant must identify the drawing from the previous card. Reported as mean number of correct responses **Intervention 1** Form F (no. correct): baseline data: mean = 11.52 (SD 1.95); follow-up data: mean = 11.74 (SD 2.01), $p = 0.499$ Form G (no. correct): baseline data: mean = 13.76 (SD 1.56); follow-up data: mean = 13.45 (SD 1.97), $p = 1.97$ **Comparator** Form F (no. correct): baseline data: mean = 11.47 (SD 2.23); follow-up data: mean = 11.92 (SD 2.20) Form G (no. correct): baseline data: mean = 13.88 (SD 1.58); follow-up data: mean = 13.95 (SD 1.38)	**Outcome** Controlled Oral Word Association Test: in a 1-minute period the participant must recall as many words as possible beginning with each of three specified letters. Reported as mean total number of correct responses **Intervention 1** Total no. correct: baseline data: mean = 26.68 (SD 11.77); follow-up data: mean = 27.49 (SD 11.39), $p = 0.594$ **Comparator** Total no. correct: baseline data: mean = 24.99 (SD 11.15); follow-up data: mean = 26.44 (SD 11.54)

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome Symbol Digit Modalities: similar to the Digit Symbol subtest from WAIS-R except that numbers rather than symbols are written. Reported as number of items correct in 90 seconds **Intervention 1** No. right (written): baseline data: mean = 39.84 (SD 11.92); follow-up data: mean = 41.73 (SD 13.42), $p = 0.374$ **Comparator** No. right (written): baseline data: mean = 40.93 (SD 12.53); follow-up data: mean = 41.55 (SD 12.26)	**Outcome** Rey Auditory–Verbal Learning Test: a list of 15 words is read five times and a recall is obtained after each reading. The total number of correct items is recorded. Then a second list of 15 different words is read and recalled. The participant is then asked to recall the first list and again after a 20-minute delay **Intervention 1** Trials 1–5, 1st list, recall: baseline data: mean = 44.25 (SD 10.33); follow-up data: mean = 44.60 (SD 11.26), $p = 0.834$ Trial 6, 2nd list, recall: baseline data: mean = 5.26 (SD 2.18); follow-up data: mean = 5.10 (SD 2.08), $p = 0.990$ Trial 7, 1st list, recall: baseline data: mean = 7.65 (SD 3.63); follow-up data: mean = 8.41 (SD 3.54), $p = 0.275$ Trial 8, 1st list, delayed recall: baseline data: mean = 7.52 (SD 3.61); follow-up data: mean = 7.82 (SD 3.87), $p = 0.991$ Trial 9, 1st list, delayed recognition: baseline data: mean = 13.25 (SD 2.08); follow-up data: mean = 13.52 (SD 2.12), $p = 0.332$ **Comparator** Trials 1–5, 1st list, recall: baseline data: mean = 46.33 (SD 9.10); follow-up data: mean = 46.93 (SD 9.71) Trial 6, 2nd list, recall: baseline data: mean = 5.47 (SD 1.94); follow-up data: mean = 5.31 (SD 2.13) Trial 7, 1st list, recall: baseline data: mean = 8.59 (SD 3.30); follow-up data: mean = 8.87 (SD 3.25) Trial 8, 1st list, delayed recall: baseline data: mean = 8.24 (SD 3.61); follow-up data: mean = 8.54 (SD 3.49)	**Outcome** Wonderlic Personnel Test: a written test of mental abilities that renders an IQ score closely approximating that of the WAIS FIQ. The number of items wrong and an IQ score are reported **Intervention 1** IQ: baseline data: mean = 85.93 (SD 14.89); follow-up data: mean = 88.81 (SD 14.44), $p = 0.147$ No. of items wrong: baseline data: mean = 7.07 (SD 5.16); follow-up data: mean = 6.95 (SD 4.89), $p = 0.721$ **Comparator** IQ: baseline data: mean = 88.84 (SD 15.13); follow-up data: mean = 90.68 (SD 15.93) No. of items wrong: baseline data: mean = 7.42 (SD 5.82); follow-up data: mean = 7.05 (SD 3.93)	**Outcome** Digit Cancellation Test: a page of random one-digit numbers is presented and the participant cancels with a single stroke as many as possible of two single digits in a 4-minute period. The number right and the number omitted are reported **Intervention 1** No. right: baseline data: mean = 155.53 (SD 62.09); follow-up data: mean = 149.55 (SD 53.42), $p = 0.644$ No. omitted: baseline data: mean = 6.76 (SD 20.74); follow-up data: mean = 8.48 (SD 21.17), $p = 0.292$ **Comparator** No. right: baseline data: mean = 159.63 (SD 52.23); follow-up data: mean = 157.58 (SD 51.26) No. omitted: baseline data: mean = 6.11 (SD 20.64); follow-up data: mean = 3.96 (SD 5.01)

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
	Trial 9, 1st list, delayed recognition: baseline data: mean = 13.35 (SD 2.00); follow-up data: mean = 13.88 (SD 1.64)		

Outcome 9	Outcome 10	Outcome 11
Outcome POMS: a score is obtained from each scale and a single overall score of 'mood disturbance' is also recorded **Intervention 1** Tension–anxiety: baseline data: mean = 12.42 (SD 6.48); follow-up data: mean = 12.02 (SD 7.20), $p = 0.855$ Depression–dejection: baseline data: mean = 13.02 (SD 12.02); follow-up data: mean = 11.87 (SD 10.23), $p = 0.943$ Anger–hostility: baseline data: mean = 9.92 (SD 8.54); follow-up data: mean = 9.58 (SD 8.90), $p = 0.785$ Vigour–activity: baseline data: mean = 15.86 (SD 6.06); follow-up data: mean = 15.49 (SD 6.82), $p = 0.166$ Fatigue–inertia: baseline data: mean = 9.94 (SD 6.02); follow-up data: mean = 10.40 (SD 6.70), $p = 0.224$ Confusion–bewilderment: baseline data: mean = 8.96 (SD 5.24); follow-up data: mean = 9.64 (SD 5.16), $p = 0.175$ Total mood disturbance: baseline data: mean = 38.41 (SD 36.51); follow-up data: mean = 38.01 (SD 37.65), $p = 0.406$ **Comparator** Tension–anxiety: baseline data: mean = 10.85 (SD 5.96); follow-up data: mean = 10.26 (SD 5.72)	**Outcome** WPSI: a 132-item inventory of psychosocial adjustment in epilepsy which provides indications of functioning in each of seven areas, plus an index of overall adjustment and three validity scales **Intervention 1** Family background: baseline data: mean = 2.17 (SD 2.22); follow-up data: mean = 2.17 (SD 2.30), $p = 0.662$ Emotional adjustment: baseline data: mean = 12.36 (SD 6.68); follow-up data: mean = 12.23 (SD 6.33), $p = 0.795$ Interpersonal adjustment: baseline data: mean = 5.53 (SD 4.39); follow-up data: mean = 5.49 (SD 4.17), $p = 0.834$ Vocational adjustment: baseline data: mean = 6.64 (SD 3.30); follow-up data: mean = 6.78 (SD 3.25), $p = 0.556$ Financial status: baseline data: mean = 2.35 (SD 2.03); follow-up data: mean = 2.39 (SD 2.15), $p = 0.693$ Adjustment to seizures: baseline data: mean = 5.20 (SD 3.66); follow-up data: mean = 5.18 (SD 3.49), $p = 0.784$ Medicine and medicine management: baseline data: mean = 1.82 (SD 1.38); follow-up data: mean = 1.60 (SD 1.24), $p = 0.161$ Overall functioning: baseline data: mean = 18.57 (SD 10.90); follow-up data: mean = 18.52 (SD 9.96), $p = 0.635$	**Outcome** Mood Rating Scale: consists of a 100-mm visual analogue scale for 15 dimensions most commonly reported in the literature to be sensitive to drug effects. Distance in mm is measured and average score for the 15 dimensions is given. Higher scores correspond to better mood **Intervention 1** Total score (average): baseline data: mean = 59.97 (SD 16.75); follow-up data: mean = 57.13 (SD 17.72), $p = 0.078$ **Comparator** Total score (average): baseline data: mean = 59.08 (SD 17.02); follow-up data: mean = 64.17 (SD 14.98)

continued

Outcome 9	Outcome 10	Outcome 11
Depression–dejection: baseline data: mean = 11.32 (SD 8.98); follow-up data: mean = 10.05 (SD 8.98) Anger–hostility: baseline data: mean = 8.38 (SD 7.37); follow-up data: mean = 7.71 (SD 7.09) Vigour–activity: baseline data: mean = 15.78 (SD 5.28); follow-up data: mean = 16.74 (SD 5.45) Fatigue–inertia: baseline data: mean = 8.49 (SD 5.68); follow-up data: mean = 7.88 (SD 5.19) Confusion–bewilderment: baseline data: mean = 8.25 (SD 4.52); follow-up data: mean = 8.00 (SD 4.26) Total mood disturbance: baseline data: mean = 31.53 (SD 28.83); follow-up data: mean = 27.15 (SD 27.11)	Lie scale: baseline data: mean = 2.40 (SD 1.81); follow-up data: mean = 2.35 (SD 1.95), $p = 0.919$ Rare items: baseline data: mean = 1.46 (SD 1.44); follow-up data: mean = 1.32 (SD 1.34), $p = 0.904$ **Comparator** Family background: baseline data: mean = 2.26 (SD 2.29); follow-up data: mean = 2.15 (SD 2.03) Emotional adjustment: baseline data: mean = 11.42 (SD 5.69); follow-up data: mean = 11.09 (SD 5.41) Interpersonal adjustment: baseline data: mean = 5.28 (SD 3.69); follow-up data: mean = 5.35 (SD 4.48) Vocational adjustment: baseline data: mean = 6.99 (SD 2.84); follow-up data: mean = 6.96 (SD 2.86) Financial status: baseline data: mean = 2.40 (SD 2.15); follow-up data: mean = 2.33 (SD 2.04) Adjustment to seizures: baseline data: mean = 5.52 (SD 3.34); follow-up data: mean = 5.38 (SD 3.65) Medicine and medicine management: baseline data: mean = 1.45 (SD 1.13); follow-up data: mean = 1.54 (SD 1.26) Overall functioning: baseline data: mean = 18.69 (SD 8.77); follow-up data: mean = 18.13 (SD 9.26) Lie scale: baseline data: mean = 2.47 (SD 1.94); follow-up data: mean = 2.45 (SD 1.91) Rare items: baseline data: mean = 1.39 (SD 2.08); follow-up data: mean = 1.29 (SD 1.86)	

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Dodrill, 1995[168] **Related publications** None **Country** USA **Source** Literature search **Aim** To evaluate the cognitive and QoL effects VGB in a double-blinded, add-on, placebo-controlled, parallel group dose–response study of patients with focal epilepsy whose CPSs were difficult to control **Type of publication** Full paper (final analysis) **Funding** Marion Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** Seizures and medications were monitored during a 12-week baseline period and the	**Number of participants** 174 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 146): 34.19 years (SD 9.18); VGB (1 g) (n = 36): 34.89 years (SD 8.38); VGB (3 g) (n = 38): 34.26 years (SD 9.18); VGB (6 g) (n = 32): 33.72 years (SD 9.66); placebo (n = 40): 33.88 years (SD 9.77); total (n = 146): 18–63 years; VGB (1 g) (n = 36): 18–54 years; VGB (3 g) (n = 38): 18–53 years; VGB (6 g) (n = 32): 19–63 years; placebo (n = 40): 20–60 years **Gender** Total (n = 146): men = 69, women = 77; VGB (1 g) (n = 36): men = 17, women = 19; VGB (3 g) (n = 38): men = 21, women = 17; VGB (6 g) (n = 32): men = 17, women = 15; placebo (n = 40): men = 14, women = 26 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** No more than 2 other AEDs	**Intervention 1** VGB; 1 g/day; 12 weeks No. randomised: 45 No. completed: 36 **Intervention 2** VGB; 3 g/day; 12 weeks No. randomised: 43 No. completed: 38 **Intervention 3** VGB; 6 g/day; 12 weeks No. randomised: 41 No. completed: 32 **Comparator** Placebo; NA; 12 weeks No. randomised: 45 No. completed: 40	**Withdrawals prerandomisation** All withdrawals were discussed together (see below) **Withdrawals postrandomisation** VGB (1 g): baseline neuropsychological data not obtained (n = 2), did not undergo follow-up assessment (n = 6) VGB (3 g): baseline neuropsychological data not obtained (n = 2), did not undergo follow-up assessment (n = 3) VGB (6 g): baseline neuropsychological data not obtained (n = 1), did not undergo follow-up assessment (n = 9) (note that 1 patient is counted twice as data were not obtained at baseline or follow-up) Placebo: did not undergo follow-up assessment (n = 3) In addition, 1 patient (treatment group not specified) was excluded because they had a WAIS-R score <65 Reasons for not obtaining baseline data: scheduling problems (n = 5), lost data (n = 1); reasons for not obtaining follow-up data: drop-outs due to AEs (n = 10), drop-outs for administrative reasons (n = 5), lack of efficacy (n = 1), lost to follow-up (n = 2), discontinued medication (n = 1), unknown (n = 1)	**Authors' conclusions** VGB is a useful AED that has little impact on tests of either cognitive abilities or QoL, even at a high dose **Comments** The authors do not state how the data regarding seizure frequency were gathered. The exclusion criteria did not define how many episodes of status epilepticus were required to meet the stated 'frequent' threshold. The inclusion criteria do not specify the minimum number of seizures required for entry into the trial Although the authors do not explicitly state whether or not they carried out an ITT analysis, given that only those participants who completed all aspects of the trial were included in the analysis, it is unlikely that the analysis was performed on an ITT basis The 6-g dose of VGB is higher than the usual maximum dose of 3 g The only outcome which showed significance for trend was the digit cancellation test. Data were also presented in terms of the means (SD) of people who did and who did not experience significant relief from seizures (not shown in this table). None of these

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
WAIS-R was administered prior to randomisation. After randomisation a titration phase (6 weeks maximum) was initiated. VGB was administered beginning with 1 g/day for 1 week, with 500-mg increments on days 1 and 5 of each subsequent week until the predetermined dosage level was achieved. This was then followed by a 12-week maintenance phase **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** None stated **Analysis methods** The changes across treatment groups (from baseline to 12-week follow-up) in terms of seizure frequency and the relationship to significant relief from seizures was analysed using an ANOVA model. The Pearson correlation coefficient was used to examine the association between VGB blood serum levels and test results and also the change in serum levels from baseline to 12 weeks follow-up **Length of trial/frequency of follow-up** 12 weeks; end of treatment follow-up period (12 weeks)	**Co-morbidities** Not stated **Baseline seizure frequency** Seizures per 28 days at the end of the baseline period Total (n = 146): median = 9 (95% CI: 7.0 to 12.0); VGB (1 g) (n = 36): median = 8 (95% CI: 6.0 to 11.5); VGB (3 g) (n = 38): median = 8.5 (95% CI: 7.0 to 12.5); VGB (6 g) (n = 32): median = 8.5 (95% CI: 6.5 to 14.5); placebo (n = 40): median = 9 (95% CI: 7.0 to 10.5) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: complex partial or partial secondarily generalised seizures; EEG documented focal abnormalities; already receiving one or two marketed AEDs; no other experimental agents Exclusion: history of progressive neurological disorder; frequent episodes of status epilepticus; WAIS-R score < 65; ongoing or recent psychiatric disorder; any other condition that may affect study results		**Adverse events** **Intervention 1** AEs are not consistently reported. The only information provided is that 10 patients dropped out owing to AEs **Intervention 2** No data **Intervention 3** No data **Comparator** No data	interactions was found to be statistically significant Although patients were recruited from 14 sites, site was not used as an independent variable in the analysis. In addition, the possible effects of mood state on neuropsychological performance was not accounted for. No indication was given of how possible time of day effects on cognitive performance were dealt with

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Lafayette Pegboard Test: a measure of manual dexterity, visuomotor coordination and motor speed. The score is defined as the number of seconds required to perform the task with each hand (120 maximum for each hand) **Intervention 1** (n = 36) Baseline data: mean = 82.48 (SD 20.43); follow-up data: mean = 76.55 (SD 16.05) **Intervention 2** (n = 38) Baseline data: mean = 81.39 (SD 17.74); follow-up data: mean = 78.44 (SD 18.55) **Intervention 3** (n = 32) Baseline data: mean = 80.84 (SD 14.27); follow-up data: mean = 79.42 (SD 15.63) **Comparator** (*n* = 40) Baseline data: mean = 84.42 (SD 16.25); follow-up data: mean = 80.94 (SD 16.09)	**Outcome** Stroop Test: the test uses a colour plate in which colour names are printed. In the first part of the test the person reads the words as quickly as possible, ignoring the colours; and in the second part of the test the person reads the colours of print ignoring the words. The time (150 and 300 seconds maximum for the first and second parts, respectively) and errors for both parts are recorded **Intervention 1** (*n* = 36) Reading speed (s): baseline data: mean = 53.03 (SD 21.71); follow-up data: mean = 53.31 (SD 19.01) Reading speed errors: baseline data: mean = 0.97 (SD 1.23); follow-up data: mean = 0.92 (SD 1.32) Interference (s): baseline data: mean = 135.56 (SD 45.80); follow-up data: mean = 129.19 (SD 46.70) Interference errors: baseline data: mean = 5.11 (SD 4.69); follow-up data: mean = 4.81 (SD 3.93) **Intervention 2** (*n* = 38) Reading speed (s): baseline data: mean = 56.03 (SD 15.14); follow-up data: mean = 64.60 (SD 25.53) Reading speed errors: baseline data: mean = 1.08 (SD 1.30); follow-up data: mean = 1.24 (SD 1.57) Interference (s): baseline data: mean = 134.60 (SD 46.35); follow-up data: mean = 145.37 (SD 61.09)	**Outcome** Benton Visual Retention Test: for each of 15 items a drawing is shown for 15 seconds. Another card with four drawings is then shown immediately and the patient must pick out the drawing from the previous card. The score for each form is the number of items correctly recognised **Intervention 1** Form F, no. correct: baseline data: mean = 11.81 (SD 1.92); follow-up data: mean = 11.94 (SD 2.24) Form G, no. correct: baseline data: mean = 13.11 (SD 2.49); follow-up data: mean = 13.86 (SD 1.55) **Intervention 2** Form F, no. correct: baseline data: mean = 11.26 (SD 1.77); follow-up data: mean = 12.08 (SD 1.89) Form G, no. correct: baseline data: mean = 13.66 (SD 1.34); follow-up data: mean = 13.47 (SD 1.67) **Intervention 3** Form F, no. correct: baseline data: mean = 11.47 (SD 1.93); follow-up data: mean = 11.66 (SD 2.12) Form G, no. correct: baseline data: mean = 13.50 (SD 1.92); follow-up data: mean = 13.66 (SD 1.72) **Comparator** Form F, no. correct: baseline data: mean = 11.28 (SD 2.32); follow-up data: mean = 11.80 (SD 2.07)	**Outcome** Proportion of responders; responders were defined as having at least a 50% improvement in seizure frequency in last 8 weeks of treatment compared to last 8 weeks of baseline (all VGB groups and placebo collapsed). Non-responders had no improvement in their seizure rate **Intervention 1** Responders (*n* = 38); (total *n* = 144; explanation not given for the 2 missing data points) **Intervention 2** No data **Intervention 3** No data **Comparator** Non-responders (*n* = 96)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
	Interference errors: baseline data: mean = 5.26 (SD 4.43); follow-up data: mean = 5.50 (SD 4.86) **Intervention 3** (*n* = 32) Reading speed (s): baseline data: mean = 54.62 (SD 17.47); follow-up data: mean = 56.50 (SD 15.59) Reading speed errors: baseline data: mean = 1.03 (SD 1.56); follow-up data: mean = 1.19 (SD 1.31) Interference (s): baseline data: mean = 133.16 (SD 52.64); follow-up data: mean = 138.47 (SD 44.46) Interference errors: baseline data: mean = 4.53 (SD 4.20); follow-up data: mean = 5.09 (SD 4.12) 934 **Comparator (*n* = 40)** Reading speed (s): baseline data: mean = 53.81 (SD 19.88); follow-up data: mean = 54.24 (SD 19.08) Reading speed errors: baseline data: mean = 0.78 (SD 1.16); follow-up data: mean = 0.81 (SD 1.15) Interference (s): baseline data: mean = 128.08 (SD 56.02); follow-up data: mean = 125.76 (SD 49.47) Interference errors: baseline data: mean = 4.81 (SD 3.89); follow-up data: mean = 3.97 (SD 3.83)	Form G, no. correct: baseline data: mean = 13.18 (SD 2.17); follow-up data: mean = 13.55 (SD 1.87)	

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Outcome Controlled Oral Word Association Test: the participants say as quickly as possible as many words beginning with each of three chosen letters (CFL or PRW). The score is the total number of words correct for the three letters combined **Intervention 1** (*n* = 36) Total no. correct: baseline data: mean = 26.19 (SD 13.52); follow-up data: mean = 29.19 (SD 15.56) **Intervention 2** (*n* = 38) Total no. correct: baseline data: mean = 25.63 (SD 10.11); follow-up data: mean = 29.11 (SD 12.08) **Intervention 3** (*n* = 32) Total no. correct: baseline data: mean = 26.38 (SD 10.11); follow-up data: mean = 26.31 (SD 10.14) **Comparator** (*n* = 40) Total no. correct: baseline data: mean = 26.18 (SD 9.68); follow-up data: mean = 26.23 (SD 8.29)	**Outcome** Symbol Digit Modalities Test: uses symbols and is similar to the WAIS-R subtest. The number of correct items is scored in 90 seconds **Intervention 1** (*n* = 36) Total no. correct: baseline data: mean = 40.69 (SD 13.52); follow-up data: mean = 41.14 (SD 12.52) **Intervention 2** (*n* = 38) Total no. correct: baseline data: mean = 39.76 (SD 10.73); follow-up data: mean = 40.18 (SD 10.96) **Intervention 3** (*n* = 32) Total no. correct: baseline data: mean = 41.72 (SD 11.76); follow-up data: mean = 41.31 (SD 11.38) **Comparator** (*n* = 40) Total no. correct: baseline data: mean = 42.56 (SD 11.03); follow-up data: mean = 43.51 (SD 12.23)	**Outcome** Rey Auditory Verbal Learning Test: a list of 15 words is read five separate times and recall is noted after each reading. The total number of items correctly recalled for the five times is recorded **Intervention 1** (*n* = 36) Trials 1–5, first list, recall: baseline data: mean = 40.89 (SD 11.54); follow-up data: mean = 40.69 (SD 9.84) Trial 6, second list, recall: baseline data: mean = 5.00 (SD 2.10); follow-up data: mean = 4.69 (SD 1.88) Trial 7, first list, recall: baseline data: mean = 7.53 (SD 3.55); follow-up data: mean = 7.58 (SD 3.86) Trial 8, first list, delayed recall: baseline data: mean = 7.28 (SD 3.45); follow-up data: mean = 6.78 (SD 3.62) Trial 9, first list, delayed recognition: baseline data: mean = 14.58 (SD 4.74); follow-up data: mean = 14.47 (SD 4.69) **Intervention 2** (*n* = 38) Trials 1–5, first list, recall: baseline data: mean = 41.87 (SD 9.24); follow-up data: mean = 40.05 (SD 10.27) Trial 6, second list, recall: baseline data: mean = 5.24 (SD 1.85); follow-up data: mean = 5.08 (SD 2.29) Trial 7, first list, recall: baseline data: mean = 7.63 (SD 3.30); follow-up data: mean = 7.55 (SD 3.45) Trial 8, first list, delayed recall: baseline data: mean = 7.16 (SD 3.23); follow-up data: mean = 7.21 (SD 332)	**Outcome** Wonderlic Personnel Test: a written test of mental abilities which yields an IQ score closely approximately the WAIS FIQ test. The IQ score and number of incorrect items are scored **Intervention 1** (*n* = 36) IQ: baseline data: mean = 89.69 (SD 14.07); follow-up data: mean = 89.75 (SD 14.22) Items correct: baseline data: mean = 6.67 (SD 4.60); follow-up data: mean = 8.03 (SD 5.99) **Intervention 2** (*n* = 38) IQ: baseline data: mean = 88.05 (SD 14.98); follow-up data: mean = 87.10 (SD 12.79) Items correct: baseline data: mean = 6.66 (SD 4.75); follow-up data: mean = 7.95 (SD 4.74) **Intervention 3** (*n* = 32) IQ: baseline data: mean = 93.31 (SD 17.93); follow-up data: mean = 91.03 (SD 16.07) Items correct: baseline data: mean = 6.41 (SD 3.82); follow-up data: mean = 6.69 (SD 3.48) **Comparator** (*n* = 40) IQ: baseline data: mean = 93.49 (SD 16.61); follow-up data: mean = 92.67 (SD 17.76)

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
		Trial 9, first list, delayed recognition: baseline data: mean = 13.90 (SD 4.42); follow-up data: mean = 13.08 (SD 3.97) **Intervention 3** (*n* = 32) Trials 1–5, first list, recall: baseline data: mean = 44.28 (SD 11.15); follow-up data: mean = 43.28 (SD 9.79) Trial 6, second list, recall: baseline data: mean = 5.66 (SD 2.01); follow-up data: mean = 5.16 (SD 1.67) Trial 7, first list, recall: baseline data: mean = 7.72 (SD 3.92); follow-up data: mean = 8.06 (SD 3.57) Trial 8, first list, delayed recall: baseline data: mean = 7.58 (SD 4.09); follow-up data: mean = 7.84 (SD 4.30) Trial 9, first list, delayed recognition: baseline data: mean = 14.10 (SD 4.45); follow-up data: mean = 14.61 (SD 3.64) **Comparator** (*n* = 40) Trials 1–5, first list, recall: baseline data: mean = 45.92 (SD 10.88); follow-up data: mean = 45.58 (SD 9.18) Trial 6, second list, recall: baseline data: mean = 5.75 (SD 2.05); follow-up data: mean = 5.03 (SD 1.73) Trial 7, first list, recall: baseline data: mean = 8.58 (SD 3.38); follow-up data: mean = 8.20 (SD 3.25) Trial 8, first list, delayed recall: baseline data: mean = 8.33 (SD 3.62); follow-up data: mean = 7.70 (SD 3.44) Trial 9, first list, delayed recognition: baseline data: mean = 14.33 (SD 3.41); follow-up data: mean = 14.50 (SD 3.26)	Items correct: baseline data: mean = 6.23 (SD 4.02); follow-up data: mean = 7.23 (SD 4.22)

continued

Outcome 9	Outcome 10	Outcome 11	Outcome 12
Outcome Digit Cancellation: a page of random one-digit numbers is presented and the patient cancels with a single stroke as many two single digits as possible in a 4-minute period. The number of items correct and the number of items omitted are recorded **Intervention 1** (*n* = 36) No. correct: baseline data: mean = 153.06 (SD 53.18); follow-up data: mean = 161.94 (SD 59.19) No. omitted: baseline data: mean = 4.50 (SD 5.39); follow-up data: mean = 2.86 (SD 4.33) **Intervention 2** (*n* = 38) No. correct: baseline data: mean = 147.45 (SD 49.20); follow-up data: mean = 141.58 (SD 55.39) No. omitted: baseline data: mean = 2.79 (SD 4.10); follow-up data: mean = 4.16 (SD 4.77) **Intervention 3** (*n* = 32) No. correct: baseline data: mean = 163.58 (SD 53.18); follow-up data: mean = 150.48 (SD 43.03) No. omitted: baseline data: mean = 3.94 (SD 9.43); follow-up data: mean = 9.58 (SD 21.22) **Comparator** (*n* = 40) No. correct: baseline data: mean = 140.82 (SD 48.77); follow-up data: mean = 175.44 (SD 59.18)	**Outcome** POMS: this has scales of tension–anxiety, depression–dejection, anger–hostility, vigour–activity, fatigue–inertia and confusion–bewilderment. A single score for 'mood disturbance' is also given **Intervention 1** (*n* = 36) Tension–anxiety: baseline data: mean = 12.28 (SD 6.57); follow-up data: mean = 12.16 (SD 6.29) Depression–dejection: baseline data: mean = 11.25 (SD 9.42); follow-up data: mean = 11.30 (SD 9.05) Anger–hostility: baseline data: mean = 10.14 (SD 8.45); follow-up data: mean = 15.23 (SD 5.17) Vigour–activity: baseline data: mean = 14.31 (SD 5.45); follow-up data: mean = 15.23 (SD 5.17) Fatigue–inertia: baseline data: mean = 8.47 (SD 6.50); follow-up data: mean = 8.94 (SD 6.33) Confusion–bewilderment: baseline data: mean = 8.94 (SD 4.53); follow-up data: mean = 9.02 (SD 4.63) Total mood disturbance: baseline data: mean = 36.78 (SD 29.75); follow-up data: mean = 36.14 (SD 28.08) **Intervention 2** (*n* = 38) Tension–anxiety: baseline data: mean = 11.58 (SD 6.58); follow-up data: mean = 12.26 (SD 6.86) Depression–dejection: baseline data: mean = 12.24 (SD 10.28); follow-up data: mean = 14.21 (SD 10.97)	**Outcome** WPSI: a 132-item inventory of psychosocial adjustment providing indicators of functioning in 7 areas: family background, emotional adjustment, interpersonal adjustment, vocational adjustment, financial status, adjustment to seizures, medicine and medical management, along with an overall score and three validity scales **Intervention 1** (*n* = 36) Family background: baseline data: mean = 1.89 (SD 1.83); follow-up data: mean = 1.81 (SD 1.88) Emotional adjustment: baseline data: mean = 12.67 (SD 6.00); follow-up data: mean = 12.14 (SD 5.59) Interpersonal adjustment: baseline data: mean = 6.08 (SD 4.14); follow-up data: mean = 6.67 (SD 4.76) Vocational adjustment: baseline data: mean = 6.94 (SD 2.66); follow-up data: mean = 7.08 (SD 2.96) Financial status: baseline data: mean = 2.08 (SD 2.30); follow-up data: mean = 2.00 (SD 2.07) Adjustment to seizures: baseline data: mean = 6.03 (SD 3.39); follow-up data: mean = 5.83 (SD 3.85) Medicine and medical management: baseline data: mean = 1.83 (SD 1.32); follow-up data: mean = 1.61 (SD 1.32) Overall functioning: baseline data: mean = 19.86 (SD 9.12); follow-up data: mean = 19.69 (SD 9.88) Lie scale: baseline data: mean = 1.92 (SD 1.73); follow-up data: mean = 1.94 (SD 1.43)	**Outcome** Mood Rating Scale: a visual analogue scale used to measure 15 mood dimensions during the previous week. The test score is the average distance in mm along the scale for all of the dimensions **Intervention 1** (*n* = 36) Total score (average): baseline data: mean = 58.95 (SD 14.79); follow-up data: mean = 58.29 (SD 13.95) **Intervention 2** (*n* = 38) Total score (average): baseline data: mean = 62.74 (SD 17.29); follow-up data: mean = 59.41 (SD 18.22) **Intervention 3** (*n* = 32) Total score (average): baseline data: mean = 59.79 (SD 18.54); follow-up data: mean = 52.20 (SD 18.76) **Comparator** (*n* = 40) Total score (average): baseline data: mean = 57.69 (SD 18.71); follow-up data: mean = 55.09 (SD 17.23)

continued

Outcome 9	Outcome 10	Outcome 11	Outcome 12
No. omitted: baseline data: mean = 3.54 (SD 3.69); follow-up data: mean = 2.67 (SD 4.02)	Anger–hostility: baseline data: mean = 8.62 (SD 6.77); follow-up data: mean = 11.33 (SD 8.68) Vigour–activity: baseline data: mean = 16.87 (SD 6.64); follow-up data: mean = 17.03 (SD 6.58) Fatigue–inertia: baseline data: mean = 8.51 (SD 6.03); follow-up data: mean = 8.82 (SD 5.77) Confusion–bewilderment: baseline data: mean = 9.97 (SD 5.66); follow-up data: mean = 9.77 (SD 5.14) Total mood disturbance: baseline data: mean = 34.05 (SD 35.92); follow-up data: mean = 39.37 (SD 34.85) **Intervention 3** (*n* = 32) Tension–anxiety: baseline data: mean = 12.04 (SD 8.37); follow-up data: mean = 12.91 (SD 6.93) Depression–dejection: baseline data: mean = 11.59 (SD 10.32); follow-up data: mean = 14.16 (SD 10.52) Anger–hostility: baseline data: mean = 10.67 (SD 8.03); follow-up data: mean = 10.38 (SD 8.35) Vigour–activity: baseline data: mean = 15.78 (SD 5.70); follow-up data: mean = 15.75 (SD 6.45) Fatigue–inertia: baseline data: mean = 9.70 (SD 6.72); follow-up data: mean = 10.44 (SD 6.88) Confusion–bewilderment: baseline data: mean = 9.72 (SD 5.65); follow-up data: mean = 11.09 (SD 5.86) Total mood disturbance: baseline data: mean = 37.94 (SD 36.24); follow-up data: mean = 43.22 (SD 38.06)	Rare items: baseline data: mean = 1.08 (SD 1.23); Follow-up data: mean = 1.00 (SD 1.22) **Intervention 2** (*n* = 38) Family background: baseline data: mean = 2.06 (SD 2.37); follow-up data: mean = 2.22 (SD 2.61) Emotional adjustment: baseline data: mean = 13.61 (SD 7.00); follow-up data: mean = 14.50 (SD 6.14) Interpersonal adjustment: baseline data: mean = 6.44 (SD 4.46); follow-up data: mean = 7.78 (SD 5.31) Vocational adjustment: baseline data: mean = 7.06 (SD 2.79); follow-up data: mean = 6.61 (SD 2.84) Financial status: baseline data: mean = 2.67 (SD 2.48); follow-up data: mean = 2.67 (SD 2.20) Adjustment to seizures: baseline data: mean = 6.11 (SD 3.64); follow-up data: mean = 6.03 (SD 3.62) Medicine and medical management: baseline data: mean = 2.03 (SD 1.56); follow-up data: mean = 2.06 (SD 1.64) Overall functioning: baseline data: mean = 21.31 (SD 10.95); follow-up data: mean = 22.50 (SD 10.93) Lie scale: baseline data: mean = 2.17 (SD 1.58); follow-up data: mean = 2.25 (SD 1.71) Rare items: baseline data: mean = 1.33 (SD 1.39); follow-up data: mean = 1.81 (SD 1.56) **Intervention 3** (*n* = 32) Family background: baseline data:	

continued

Outcome 9	Outcome 10	Outcome 11	Outcome 12
	Comparator (*n* = 40) Tension–anxiety: baseline data: mean = 12.00 (SD 7.14); follow-up data: mean = 11.60 (SD 5.34) Depression–dejection: baseline data: mean = 11.40 (SD 9.89); follow-up data: mean = 11.83 (SD 9.27) Anger–hostility: baseline data: mean = 9.95 (SD 8.61); follow-up data: mean = 10.75 (SD 7.20) Vigour–activity: baseline data: mean = 13.59 (SD 5.62); follow-up data: mean = 14.98 (SD 6.25) Fatigue–inertia: baseline data: mean = 9.64 (SD 7.09); follow-up data: mean = 10.25 (SD 6.88) Confusion–bewilderment: baseline data: mean = 8.97 (SD 5.59); follow-up data: mean = 9.65 (SD 5.18) Total mood disturbance: baseline data: mean = 38.35 (SD 37.35); follow-up data: mean = 39.10 (SD 31.92)	mean = 2.26 (SD 2.03); follow-up data: mean = 1.90 (SD 1.81) Emotional adjustment: baseline data: mean = 13.00 (SD 6.87); follow-up data: mean = 14.00 (SD 7.46) Interpersonal adjustment: baseline data: mean = 6.55 (SD 4.78); follow-up data: mean = 6.74 (SD 4.80) Vocational adjustment: baseline data: mean = 6.13 (SD 3.34); follow-up data: mean = 6.58 (SD 3.09) Financial status: baseline data: mean = 2.32 (SD 2.29); follow-up data: mean = 2.58 (SD 2.23) Adjustment to seizures: baseline data: mean = 5.65 (SD 4.10); follow-up data: mean = 5.52 (SD 3.93) Medicine and medical management: baseline data: mean = 1.84 (SD 1.49); follow-up data: mean = 1.74 (SD 1.37) Overall functioning: baseline data: mean = 19.87 (SD 11.06); follow-up data: mean = 21.29 (SD 11.95) Lie scale: baseline data: mean = 2.32 (SD 1.83); follow-up data: mean = 1.97 (SD 1.72) Rare items: baseline data: mean = 1.61 (SD 1.65); follow-up data: mean = 1.26 (SD 1.00) **Comparator** (*n* = 40) Family background: baseline data: mean = 2.23 (SD 2.21); follow-up data: mean = 2.08 (SD 1.76) Emotional adjustment: baseline data: mean = 12.08 (SD 5.14); follow-up data: mean = 13.25 (SD 5.99)	

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Outcome 9	Outcome 10	Outcome 11	Outcome 12
		Interpersonal adjustment: baseline data: mean = 6.05 (SD 4.31); follow-up data: mean = 5.95 (SD 3.97) Vocational adjustment: baseline data: mean = 6.10 (SD 3.50); follow-up data: mean = 6.50 (SD 3.37) Financial status: baseline data: mean = 2.05 (SD 1.87); follow-up data: mean = 2.23 (SD 2.03) Adjustment to seizures: baseline data: mean = 5.63 (SD 3.48); follow-up data: mean = 6.08 (SD 3.55) Medicine and medical management: baseline data: mean = 1.68 (SD 1.33); follow-up data: mean = 1.58 (SD 1.53) Overall functioning: baseline data: mean = 18.25 (SD 8.91); follow-up data: mean = 19.85 (SD 10.31) Lie scale: baseline data: mean = 1.93 (SD 1.70); follow-up data: mean = 1.63 (SD 1.53) Rare items: baseline data: mean = 1.18 (SD 1.26); follow-up data: mean = 1.08 (SD 1.14)	

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
French, 1996[155] **Related publications** Cognitive outcome data,[169] abstracts[421,422] **Country** USA **Source** Literature search **Aim** To compare the efficacy and tolerability of VGB as add-on therapy with that of placebo in patients with focal epilepsy whose CPSs are difficult to control **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** Study 024 **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** Seizures and medications were monitored during an initial 12-week period. The WAIS-R was administered prior to randomisation.	**Number of participants** 203 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 182): 34 years (no further information stated; not possible to extract from related paper Ref. 169 as baseline information is only given on the 168 patients who participated in the neuropsychological component of study); total (n = 182): 18–60 years (no further information) **Gender** Total (n = 182): men = 80, women = 102 (no further information) **Age at onset of seizures** Not stated **Pretrial medication** Prior treatment with PHT or CBZ required **Ongoing concurrent medication** 113/182 (62%) participants received two concurrent AEDs **Co-morbidities** Not stated **Baseline seizure frequency** See seizure frequency outcome data	**Intervention 1** VGB; 3 g/day; 12 weeks No. randomised: 92 No. completed: 82 **Comparator** Placebo; NA; 12 weeks No. randomised: 90 No. completed: 88	**Withdrawals prerandomisation** Discontinued (n = 20) (no reasons given) **Withdrawals postrandomisation** VGB: discontinued before receiving medication (n = 1), AE (n = 7), change in MRI not related to drug therapy (n = 1), concomitant cannabis use (n = 1);, pregnancy (n = 1) Placebo: AE (n = 2) **Adverse events** **Intervention 1** Drowsiness (n = 27), light-headedness (n = 20), headache (n = 20), fatigue (n = 18), tremor (n = 12). One or more possibly drug-related AEs were reported by 87% (80/92) of VGB-treated patients **Comparator** Drowsiness (n = 12), light-headedness (n = 13), headache (n = 15), fatigue (n = 12), tremor (n = 4). One or more possibly drug-related AEs were reported by 86% (77/90) of placebo-treated patients	**Authors' conclusions** The results indicate that 3 g/day VGB is more effective than placebo as add-on therapy. VGB was well tolerated, compliance was high with twice-daily administration and therapy did not result in clinically relevant drug interactions **Comments** At the time of randomisation, 93 participants were assigned to VGB and 90 to placebo. However, one participant in the VGB group withdrew before receiving any treatment and so only 182 participants were considered in the analysis Other analyses dealing with pharmacokinetics are detailed in the paper, but not reported in this data extraction table. However, there were no significant interactions between pharmokinetic measures and seizure frequency Tables 1 and 2 refer to subcategories <50% increase and 1–50% increase which are almost equivalent. It is likely that the <50% may have been misquoted in the original publication. Very limited information is available in terms of the CIs and SDs for the measurements. However, the authors indicate that two pages of

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
The last 8 weeks of this period were considered as the baseline period. Postrandomisation a 4-week titration period occurred followed by a maintenance period of 12 weeks **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** An ANCOVA model was used to compare end-of-study seizure frequencies (adjusting for investigative site and baseline seizure frequency). The same model was also used for the by-visit analysis and for the secondary efficacy analysis. Mantel–Haenszel procedure stratified by investigative site was used to analyse therapeutic success and the physicians' evaluations and the Wilcoxon test to analyse the % reduction in seizure frequency **Length of trial/frequency of follow-up** 12 weeks; weeks 2 and 4 during the titration period and weeks 2, 4, 8 and 12 from beginning of maintenance period	**Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 18–60 years; complex partial or partial with/without secondary generalisation difficult to control with current AEDs; at least 6 seizures in 8 weeks prior to end of baseline period; fewer than 28 days between seizures in 8 weeks prior to end of baseline period; no more than 2 current AEDs; prior treatment with PHT or CBZ; no other experimental agents; abnormal EEG; MRI assessment; WAIS-R assessment Exclusion: history of progressive neurological disorder; frequent episodes of status epilepticus; WAIS-R score <65; ongoing psychiatric disorder; any other condition that might adversely impact on results; alcoholism/drug addition; epilepsy surgery within preceding 6 months, history of depression			supplementary material are available (although they do not specify what this contains)

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Seizure frequency; the median number of seizures in the preceding 28-day period. The last 8 weeks of the baseline period were compared with the last 8 weeks of the follow-up period **Intervention 1** CPSs plus partial seizures with secondary generalisation: baseline: median = 8.3; follow-up: median = 5.3 CPSs: baseline: median = 8.5; follow-up: median = 5.0 Partial seizures with secondary generalisation: baseline: median = 4.0; follow-up: median = not stated **Comparator** CPSs plus partial seizures with secondary generalisation: baseline: median = 8.3; follow-up: median = 7.5 CPSs: baseline: median = 8.0; follow-up: median = 7.0 Partial seizures with secondary generalisation: baseline: median = 1.5; follow-up: median = 2.5	**Outcome** Proportion of responders; the number of patients experiencing the specified changes in seizure frequency (CPSs plus partial seizures with secondary generalisation) **Intervention 1** Responders 0–49% reduction: 34/92 (36.9) 50–99% reduction: 34/92 (36.9%) At least 50% reduction: 40/92 (43%), $p < 0.001$ **Non-responders** <50% increase: 4/92 (4.4%) 1–50% increase: 14/92 (15.2%) **Comparator** Responders 0–49% reduction: 38/90 (42.2%) 50–99% reduction: 16/90 (17.8%) At least 50% reduction: 17/90 (19%) Non-responders <50% increase: 14/90 (15.6%) 1–50% increase: 21/90 (23.3%)	**Outcome** Proportion of seizure-free patients; the number of participants having 100% reduction in seizure frequency **Intervention 1** 6/92 (6.5%) **Comparator** 1/90 (1.1%)	**Outcome** Change in seizure frequency; median percentage reduction in the number of seizures experienced **Intervention 1** 39.5% ($p > 0.001$, vs placebo) **Comparator** 7.5%

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Grunewald, 1994[38] **Related publications** Abstract[423] **Country** UK **Source** Literature search **Aim** To assess the effects of VGB on memory, cognition, motor speed and seizures **Type of publication** Full paper (final analysis) **Funding** Marion Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Random number generated code; after pretrial period **Details of pretrial period** On trial entry IQ and linguistic competence were assessed and time allowed for the participants to familiarise themselves with the testing procedure. This was followed by	**Number of participants** 45 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 45): not stated; VGB (n = 22): median = 29; placebo (n = 23): median = 27; total (n = 45): 15–61; VGB (n = 22): 17–59 years; placebo (n = 23): 16–55 years (note inconsistency between total and individual group ranges) **Gender** Total (n = 45): men = 24, women = 21 (no further details) **Age at onset of seizures** Total (n = 45): not stated; VGB (n = 22): median = 11 years (range 2–34); placebo (n = 23): median = 10 years (range 1–22) **Pretrial medication** Concurrent AEDs during baseline period CBZ: total 33/45; VGB 17/22; placebo 16/23 VPA: total 4/45; VGB 1/22; placebo 3/23 PHT: total 9/45; VGB 3/22; placebo 6/23 PB: total 3/45; VGB 2/22; placebo 1/23	**Intervention 1** VGB; 3 g/day; 18 weeks No. randomised: 22 No. completed: 20 **Comparator** Placebo; 18 weeks No. randomised: 23 No. completed: 23	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** VGB: severe depressive symptoms (n = 2) **Adverse events** **Intervention 1** VGB (n = 22): severe depressive symptoms (n = 2), weight gain (n = 4), headache (n = 1), constipation (n = 5), fatigue (n = 4), mild depression (n = 4), dizziness (n = 3), double vision (n = 3), tremor (n = 2), impaired memory (n = 2) **Comparator** Placebo (n = 23): weight gain (n = 2), headache (n = 4), constipation (n = 1), fatigue (n = 3), mild depression (n = 2);, dizziness (n = 1), double vision (n = 2), tremor (n = 3)	**Authors' conclusions** VGB was effective in reducing CPS frequency in a group of patients with refractory partial epilepsy. It was associated with a small but statistically significant reduction in motor speed and a modest impairment of performance on a visual memory task. The influence of long-term treatment and reversibility of these effects on withdrawal of VGB remains to be established **Comments** The authors include the 2-week titration period in their assessment of the treatment period, giving a total of 20 weeks of treatment. The 2-week titration period has been excluded in our stated length of follow-up as all of the participants may not have been receiving the optimum therapeutic dose of drug during the 2-week titration period After 20 weeks patients entered the open phase of the trial. All patients were offered open treatment with VGB without breaking the blinding. 16/22 patients originally allocated VGB and 18/23 originally placebo underwent neuropsychological assessment between 44 and 68 weeks. The results of this open phase of the trial have not been reported in this extraction table

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
an 8-week baseline period during which MRI was performed and at the end of the period an assessment of cognitive function was carried out. This was followed by a 14-day titration period (1 g twice daily, then 1.5 g twice daily after 14 days) **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Seizure scores were normalised by using a log transformation (normality confirmed by data inspection and statistical tests) and an ANOVA model was used to analyse serum AED concentrations and transformed seizure scores. Baseline data were analysed using Student's *t*-test or the Wilcoxon test. Change in cognitive test scores from baseline to follow-up was analysed using ANOVA and Wilcoxon or χ^2 tests were used to analyse factors possibly predictive of response to VGB. Changes on the mood checklist scores were analysed using the Mann–Whitney test **Length of trial/frequency of follow-up** 18 weeks; clinically assessed every 4 weeks, psychological testing occurred 20 weeks after beginning of titration phase; seizure frequency was assessed between 4–12 weeks and 12–20 weeks from beginning of titration phase	PRM: total 3/45; VGB 2/22; placebo 1/23 **Ongoing concurrent medication** Concurrent AEDs during the double-blind trial period CBZ: total 25/45; VGB 13/22; placebo 12/23 VPA: total 4/45; VGB 1/22; placebo 3/23 PHT: total 8/45; VGB 2/22; placebo 6/23 PB: total 3/45; VGB 2/22; placebo 1/23 PRM: total 3/45; VGB 2/22; placebo 1/23 **Co-morbidities** Not stated **Baseline seizure frequency** See Outcome 1 **Other characteristics** Minor modifications of concomitant AEDs occurred (VGB $n = 2$ and placebo $n = 2$, in each case $n = 1$ increased medication and $n = 1$ decreased medication in each group) **Inclusion/exclusion criteria** Not stated			The authors also report data relating to possible predictors (age, site of epileptic focus, presence of hippocampal sclerosis, site of EEG seizure focus, duration of epilepsy, age at onset of seizures, history of febrile convulsion) of response to VGB. None of the factors were found to be significant. Data concerning the Mood Adjective Checklist scores from baseline to 20 weeks were also presented according to whether participants were classified as responders (at least a 50% in seizure frequency) or non-responders (all others). Depression ($p = 0.01$), fatigue ($p = 0.03$) and aggression ($p = 0.04$) scores were shown to have significant improvement in responders compared with non-responders The denominator was not specified for the mean seizure frequency data The authors do not appear to take into account the possible impact of mood on neuropsychological performance, and do not mention the order in which the cognitive tests were performed

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Seizure frequency; the median number of seizures recorded in an 8-week period, subdivided into seizure type **Intervention 1** SPSs: Baseline: median = 4 (range 0–91) Follow-up 4–12 weeks: median = 2.5 (range 0–156) Follow-up 12–20 weeks: median = 4 (range 0–196) CPSs: Baseline: median = 15 (range 0–38) Follow-up 4–12 weeks: median = 5 (range 0–26) Follow-up 12–20 weeks: median = 5 (range 0–47) Secondary generalised seizures: Baseline: median = 0 (range 0–17) Follow-up 4–12 weeks: median = 0 (range 0–17) Follow-up 12–20 weeks: median = 0 (range 0–10) **Comparator** SPSs: Baseline: median = 2 (range 0–55) Follow-up 4–12 weeks: median = 2 (range 0–178) Follow-up 12–20 weeks: median = 0 (range 0–249) CPSs: Baseline: median = 8 (range 0–124)	**Outcome** Proportion of responders; a responder was defined as having at least a 50% decrease in seizure frequency and a non-responder as having at least a 50% increase in seizure frequency **Intervention 1** Responders (at least 50% decrease): 4–12 weeks: *n* = 9/22 12–20 weeks: *n* = 10/22 Non-responders (at least a 50% increase): 4–12 weeks: *n* = 1/22 12–20 weeks: *n* = 0/22 **Comparator** Responders (at least 50% decrease): 4–12 weeks: *n* = 4/23 8–12 weeks: *n* = 3/23 Non-responders (at least a 50% increase): 4–12 weeks: *n* = 7/23 8–12 weeks: *n* = 7/23	**Outcome** Memory scores; comprises the following tests: Digit Span (from the WAIS-R, scores reflect the maximum number of digits forwards and backwards and the total number repeated correctly), Verbal Learning (from the Adult Memory and Information Processing Battery (AMIPB), scores reflect the total number of items recalled), Verbal Recall (participant has to recall immediately and after 30 minutes the main contents of a short paragraph read aloud; the number of items recalled is recorded), Design Learning (non-verbal analogue of the list learning task but using a simple geometric shape drawn on paper; the number of correct design segments drawn is recorded) **Intervention 1** List A trials 1–5: baseline: mean = 44.9 (SD 7.5); follow-up 20 weeks: mean = 42.9 (SD 9.5) List B: baseline: mean = 5.3 (SD 1.4); follow-up 20 weeks: mean = 4.8 (SD 1.7) Trial 6: baseline: mean = 8.3 (SD 3.2); follow-up 20 weeks: mean = 8.3 (SD 2.8) Immediate story recall: baseline: mean = 14.2 (SD 7.4); follow-up 20 weeks: mean = 19.5 (SD 8.9) % retained: baseline: mean = 73.0 (SD 27.0); follow-up 20 weeks: mean = 80.3 (SD 26.6) Design A trials 1–5: baseline: mean = 31.4 (SD 11.1); follow-up 20 weeks: mean = 30.0 (SD 10.0) ($p < 0.04$) Design B: baseline: mean = 5.2 (SD 2.2); follow-up 20 weeks: mean = 4.5 (SD 2.6)	**Outcome** Mental speed and flexibility; comprising the following tests: Information Processing Speed (tasks involving rapid repetitive mental activity and memory are performed and the number of correct items and the errors made in 2 minutes are recorded), Cognitive Flexibility (a modified version of the Stoop Test where a measure of interference is derived by subtracting performance on the experimental task from that of the baseline task) and Fluency (participant is asked to say as many words as possible beginning with the letter D in 60 seconds and to name as many different animals as possible. The score reflects the number of novel word produced for each task) **Intervention 1** Processing task A time: baseline: mean = 30.8 (SD 9.2); follow-up 20 weeks: mean = 27.9 (SD 9.2) Processing task B time: baseline: mean = 25.3 (SD 10.1); follow-up 20 weeks: mean = 26.2 (SD 7.9) Stroop colours: baseline: mean = 159.6 (SD 89.0); follow-up 20 weeks: mean = 113.1 (SD 31.7) Fluency (words): baseline: mean = 8.7 (SD 5.6); follow-up 20 weeks: mean = 9.8 (SD 6.8) Fluency (animals): baseline: mean = 16.3 (SD 5.3); follow-up 20 weeks: mean = 15.5 (SD 5.5)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Follow-up 4–12 weeks: median = 12 (range 0–108) Follow-up 12–20 weeks: median = 10 (range 0–111) Secondary generalised seizures: Baseline: median = 0 (range 0–13); Follow-up 4–12 weeks: median = 0 (range 0–7) Follow-up 12–20 weeks: median = 0 (range 0–3)		Trial 6: baseline: mean = 6.5 (SD 2.7); follow-up 20 weeks: mean = 6.7 (SD 2.6) **Comparator** List A trials 1–5: baseline: mean = 41.7 (SD 8.9); follow-up 20 weeks: mean = 43.0 (SD 8.0) List B: baseline: mean = 4.9 (SD 2.1); follow-up 20 weeks: mean = 5.3 (SD 1.5) Trial 6: baseline: mean = 7.4 (SD 3.3); follow-up 20 weeks: mean = 8.6 (SD 2.3) Immediate story recall: baseline: mean = 14.3 (SD 7.0); follow-up 20 weeks: mean = 20.7 (SD 9.2) % retained: baseline: mean = 76.8 (SD 29.7); follow-up 20 weeks: mean = 69.8 (SD 28.7) Design A trials 1–5: baseline: mean = 29.3 (SD 9.2); follow-up 20 weeks: mean = 33.8 (SD 8.4) Design B: baseline: mean = 5.5 (SD 2.3); follow-up 20 weeks: mean = 4.1 (SD 1.8) Trial 6: baseline: mean = 6.3 (SD 2.5); follow-up 20 weeks: mean = 7.5 (SD 2.3)	**Comparator** Processing task A time: baseline: mean = 31.0 (SD 8.7); follow-up 20 weeks: mean = 28.5 (SD 9.2) Processing task B time: baseline: mean = 26.3 (SD 9.4); follow-up 20 weeks: mean = 26.6 (SD 9.0) Stroop colours: baseline: mean = 136.8 (SD 58.4); follow-up 20 weeks: mean = 98.9 (SD 20.3) Fluency (words): baseline: mean = 10.6 (SD 5.0); follow-up 20 weeks: mean = 10.5 (SD 5.2) Fluency (animals): baseline: mean = 17.1 (SD 4.8); follow-up 20 weeks: mean = 16.9 (SD 4.0)

Outcome 5	
Outcome Motor speed; comprises two subtests: bilateral hand movements (participant asked to alternate between fist and flat hand as many times as possible in 20 seconds; the number of successful alternations is recorded) and tapping rate (records speed of hand movements between two steel plates in one practice and three trial runs with each hand) **Intervention 1** Bilateral hand movements: baseline: mean = 40.0 (SD 12.8); follow-up 20 weeks: mean = 41.3 (SD 12.1) Tapping task (dominant hand): baseline: mean = 77.0 (SD 15.0); follow-up 20 weeks: mean = 72.1 (SD 14.5) ($p < 0.01$) Tapping task (non-dominant hand): baseline: mean = 67.6 (SD 13.8); follow-up 20 weeks: mean = 67.5 (SD 13.7)	**Comparator** Bilateral hand movements: baseline: mean = 44.6 (SD 16.3); follow-up 20 weeks: mean = 42.7 (SD 14.8) Tapping task (dominant hand): baseline: mean = 85.6 (SD 14.3); follow-up 20 weeks: mean = 92.0 (SD 19.1) Tapping task (non-dominant hand): baseline: mean = 74.0 (SD 9.7); follow-up 20 weeks: mean = 78.2 (SD 12.7)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Provinciali, 1996[152] **Related publications** None **Country** Italy **Source** Literature search **Aim** To evaluate changes in cognitive performances, mood and QoL in drug-resistant epileptic patients after the introduction of 2–3 g of VGB as additional treatment **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** After baseline neuropsychological assessment (T0), all participants received	**Number of participants** 40 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 40): not stated; VGB (n = 20): median = 34.8 years; placebo (n = 20): median = 38.2 years; total (n = 40): 17–66 years; VGB (n = 20): 17–66 years; placebo (n = 20): 20–66 years **Gender** Total (n = 40): men = 21, women = 19; VGB (n = 20): men = 10, women = 10; placebo (n = 20): men = 11, women = 19 **Age at onset of seizures** Total (n = 40): median = not stated (range not stated); VGB (n = 20): median = 16.7 (range 1–36); placebo (n = 20): median = 22.6 (range 1–60) **Pretrial medication** Not stated **Ongoing concurrent medication** Concurrent AEDs (maximum 4): total (n = 40): median = not stated (range not stated); VGB (n = 20): median = 2.4 (range 1–22); placebo (n = 20): median = 2.2 (range 1–19).	**Intervention 1** VGB; 2–3 g/day; 4 months No. randomised: 20 No. completed: not stated **Comparator** Placebo; 4 months No. randomised: 20 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** None stated **Comparator** None stated	**Authors' conclusions** The results support the experience that VGB therapy does not produce any negative psychic effect in the short term, but it is considered that further investigation could clarify the long-term effects of VGB treatment in the cognitive and behaviour domains **Comments** The paper (published in 1996) reports that this is an ongoing study; however, further trial reports were not identified It is not clear from the paper whether the 1- and 4-month follow-up times include/exclude the 3-week titration period. Also, it is not clear whether or not all participants completed the trial The minimum inclusion requirement of 1 seizure/month is lower than that of many other studies There are few data regarding seizure frequency. There is no indication of the denominator used in many of the data sets or which follow-up point is being referred to. In addition, it is not clear whether the information regarding seizure frequency was used from the patient or the caregiver checklist or a

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
placebo. 4 weeks later a second assessment was carried out to assess the re-test reproducibility of the tests. Participants were then randomised to either placebo or VGB and this was followed by a 3-week titration period. Follow-up assessments were made after 1 and 4 months, although it is not clear whether these time points include the 3-week titration period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Neuropsychological assessment scores were logistically transformed and an ANOVA was used to compare group differences over time and the effects of re-test differences. The two-way Friedman test was used to analyse intra- and inter-group trends on measures of mood and QoL. Pearson's correlation was used to evaluate the relationship between cognitive performance and reaction time **Length of trial/frequency of follow-up** 4 months; 1 and 4 months	Drugs included the following: CBZ (VGB $n = 18$, placebo $n = 17$), PHT (VGB $n = 7$, placebo $n = 8$), PB (VGB $n = 11$, placebo $n = 13$), PRM (VGB $n = 7$, placebo $n = 7$), VPA (VGB $n = 2$, placebo $n = 4$), CLB (VGB $n = 2$, placebo $n = 1$), CZP (VGB $n = 2$, placebo $n = 1$) **Co-morbidities** Not stated **Baseline seizure frequency** Number of seizures/month: total ($n = 40$): median = not stated (range not stated); VGB ($n = 20$): median = 2.4 (range 1–22); placebo ($n = 20$): median = 2.2 (range 1–19) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: epilepsy duration of >3 years; drug-resistant CPSs; at least 1 seizure/month; current treatment of ≥2 AEDs with plasma levels within the therapeutic range Exclusion: physical impairment that may impact on execution of tests; IQ < 70; history of psychiatric disorders			combination of both and whether this was decided *a priori* There is no discussion of the problems of using caregiver-reported data and data for only three participants in the placebo group are reported. The authors also fail to take into account the possible effect of mood on cognitive performance No significant differences in cognitive performance were identified except for the Trail Making Test B and the learning tests, where VGB participants showed worse performances than placebo participants. No re-test changes were observed in any group

continued

Results			
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**
Outcome Proportion of responders; responders were classified according to four categories: seizure-free, >50% reduction in seizure frequency, no change and increase in seizure frequency **Intervention 1** >50% reduction: 16/20 (including totally seizure free *n* = 2); no change (3/20); increase in frequency (*n* = 1) **Comparator** Slight improvement is seizure frequency (3/20); no further details	**Outcome** Proportion of seizure-free patients **Intervention 1** 2/20 **Comparator** 0/20	**Outcome** Italian Matrix Test; participants have to cross out a target number among other numbers. The number of correct cancellations is reported **Intervention 1** Baseline: mean = 52.8 (SD 6.8); 1-month follow-up: mean = 53.0 (SD 4.4); 4-month follow-up: mean = 53.4 (SD 5.3) **Comparator** Baseline: mean = 52.9 (SD 7.2); 1-month follow-up: mean = 52.7 (SD 6.2); 4-month follow-up: mean = 52.1 (SD 9.1)	**Outcome** Bells Test; participants must cross out bells drawn at random among other pictures of the same size. The number of correct items cancelled is reported **Intervention 1** Baseline: mean = 27.9 (SD 4.4); 1-month follow-up: mean = 29.4 (SD 4.7); 4-month follow-up: mean = 29.7 (SD 4.7) **Comparator** Baseline: mean = 30.6 (SD 9.5); 1-month follow-up: mean = 28.6 (SD 7.2); 4-month follow-up: mean = 26.2 (SD 7.1)
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome H Barrage Test; participants must cross out the letter H among other pictures of the same size. The number of correct items cancelled is reported **Intervention 1** Baseline: mean = 90.1 (SD 13.3); 1-month follow-up: mean = 96.4 (SD 9.6); 4-month follow-up: mean = 97.6 (SD 8.9) **Comparator** Baseline: mean = 80.0 (SD 28.1); 1-month follow-up: mean = 85.2 (SD 15.7); 4-month follow-up: mean = 88.4 (SD 19.9)	**Outcome** Tolouse Pieron; a target symbol must be crossed out among other symbols of the same size (max. of 120 seconds allowed). The number of correct cancellations is reported **Intervention 1** Baseline: mean = 57.9 (SD 14.5); 1-month follow-up: mean = 62.0 (SD 15.5); 4-month follow-up: mean = 64.8 (SD 14.9) **Comparator** Baseline: mean = 55.7 (SD 20.3); 1-month follow-up: mean = 56.3 (SD 19.1); 4-month follow-up: mean = 57.4 (SD 19.1)	Outcome Trial Making Test A; counts the time taken to join up the numbers from 1 to 25 randomly written on a sheet of paper. Trial Making Test B; counts the time taken to join up the numbers from 1 to 13 randomly written on a sheet of paper **Intervention 1** Trial Making Test A Baseline: mean = 52.7 (SD 25.5); 1-month follow-up: mean = 49.9 (SD 18.5); 4-month follow-up: mean = 47.8 (SD 17.0) Trial Making Test B Intervention 1: baseline: mean = 134.4 (SD 85.7); 1-month follow-up: mean = 125.9 (SD 107.0); 4-month follow-up: mean = 98.5 (SD 33.7)	Outcome Digit Symbol Test; the participant has to match symbols to numbers from 1 to 9 according to definite rules. The number of correct associations made in 90 seconds is reported **Intervention 1** Baseline: mean = 36.0 (SD 9.2); 1-month follow-up: mean = 39.8 (SD 11.2); 4-month follow-up: mean = 43.3 (SD 12.5) **Comparator** Baseline: mean = 41.7 (SD 18.6); 1-month follow-up: mean = 43.6 (SD 17.8); 4-month follow-up: mean = 45.8 (SD 16.7)

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
		Comparator Trial Making Test A Baseline: mean = 49.8 (SD 25.6); 1-month follow-up: mean = 50.3 (SD 30.2); 4-month follow-up: mean = 51.5 (SD 38.1) Trial Making Test B Baseline: mean = 112.5 (SD 64.7); 1-month follow-up: mean = 112.3 (SD 66.4); 4-month follow-up: mean = 112.5 (SD 72.7)	
Outcome 9	**Outcome 10**	**Outcome 11**	**Outcome 12**
Outcome Reaction Times; dedicated software randomly projects a visual stimulus on a screen and the participant has to push any key **Intervention 1** Baseline: mean = 338.5 (SD 69.7); 1-month follow-up: mean = 326.7 (SD 65.7); 4-month follow-up: mean = 332.9 (SD 73.6) **Comparator** Baseline: mean = 328.8 (SD 66.2); 1-month follow-up: mean = 330.7 (SD 70.3); 4-month follow-up: mean = 336.4 (SD 71.9)	**Outcome** Forward Digit Span; counts the maximum number of digits a participant can recall following an oral list **Intervention 1** Baseline: mean = 4.4 (SD 1.2); 1-month follow-up: mean = 4.8 (SD 0.9); 4-month follow-up: mean = 5.0 (SD 1.0) **Comparator** Baseline: mean = 5.4 (SD 1.2); 1-month follow-up: mean = 5.4 (SD 0.9); 4-month follow-up: mean = 5.9 (SD 0.8)	**Outcome** Corsi's Blocks; evaluates spatial span and spatial learning abilities by the participant having to touch an increasingly difficult sequence of blocks in the same order as the investigator. The number of correct items is recorded **Intervention 1** Baseline: mean = 4.3 (SD 1.1); 1-month follow-up: mean = 4.6 (SD 0.9); 4-month follow-up: mean = 4.8 (SD 0.6) **Comparator** Baseline: mean = 4.8 (SD 0.9); 1-month follow-up: mean = 5.1 (SD 0.6); 4-month follow-up: mean = 5.2 (SD 1.0)	**Outcome** Buschke–Fuld Test; counts the number of trials a participant requires to learn a word list **Intervention 1** Baseline: mean = 8.5 (SD 5.6); 1-month follow-up: mean = 9.2 (SD 4.3); 4-month follow-up: mean = 10.4 (SD 4.4) **Comparator** Baseline: mean = 10.7 (SD 4.9); 1-month follow-up: mean = 10.4 (SD 5.1); 4-month follow-up: mean = 10.3 (SD 5.4)

continued

Outcome 13	Outcome 14	Outcome 15
Outcome Zung Depression Scale; a personal inventory of 30 items about mood and feelings. The number of items applicable to the participant is recorded **Intervention 1** Baseline: mean = 8.4 (SD 6.0); 1-month follow-up: mean = 7.9 (SD 5.1); 4-month follow-up: mean = 8.6 (SD 5.0) **Comparator** Baseline: mean = 12.1 (SD 4.5); 1-month follow-up: mean = 11.3 (SD 4.2); 4-month follow-up: mean = 10.5 (SD 4.9)	**Outcome** Life Satisfaction Index; an inventory concerning work, family, daily activities, sexuality, social relations, leisure and economic situation. The patient scores each item 1 (lowest) to 4 (highest). The mean score is recorded **Intervention 1** Baseline: mean = 80.0 (SD 28.1); 1-month follow-up: mean = 85.2 (SD 15.7); 4-month follow-up: mean = 88.4 (SD 19.9) **Comparator** Baseline: mean = 80.0 (SD 28.1); 1-month follow-up: mean = 85.2 (SD 15.7); 4-month follow-up: mean = 88.4 (SD 19.9)	**Outcome** Goodrich Inventory; administered to all relatives of the participants to investigate the behavioural disturbances possibly arising from the treatments. Contains items about thinking, behaviour, physical condition and feeling **Intervention 1** Baseline: mean = 80.0 (SD 28.1); 1-month follow-up: mean = 85.2 (SD 15.7); 4-month follow-up: mean = 88.4 (SD 19.9) **Comparator** Baseline: mean = 80.0 (SD 28.1); 1-month follow-up: mean = 85.2 (SD 15.7); 4-month follow-up: mean = 88.4 (SD 19.9)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Reynolds, 1991[141] **Related publications** Report of interim data,[427] preliminary paper,[428] preliminary abstract[429] **Country** UK **Source** Literature search **Aim** To perform an open, double-blind and long-term study of VGB in patients with treatment-resistant epilepsy who were receiving only one or at most two standard AEDs **Type of publication** Full paper (final analysis) **Funding** Merrell Dow **Trial ID** Not stated **Study design** Add-on therapy; new vs placebo; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after open phase to identify responders	**Number of participants** 33 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Total (n = 33): mean = 29.7 years; Total (n = 33): 16–61 years **Gender** Total (n = 33): men = 16, women = 17 **Age at onset of seizures** Total (n = 33): 21.3 years (range 6–53 years) **Pretrial medication** See concurrent medications **Ongoing concurrent medication** No more than two concomitant AEDs were allowed. AEDs included the following: One drug (n = 20): Carbamazepine n = 17; Phenytoin n = 0; Valproate n = 1; Phenobarbital n = 1; Clobazam n = 1; Others n = 0 Two drugs (n = 13): Carbamazepine n = 10; Phenytoin n = 4; Valproate n = 3; Phenobarbital n = 3; Clobazam n = 3; Others n = 3	**Intervention 1** VGB; 2–3 g/day; 8 weeks No. randomised: 10 No. completed: 9 **Comparator** Placebo; NA; 8 weeks No. randomised: 10 No. completed: 8	**Withdrawals prerandomisation** Prior to randomisation, 13 patients withdrew: failure to achieve at least 50% reduction in seizure frequency (n = 6); unacceptable AEs (n = 7). The AEs were headache, abdominal pain (n = 1); depression (n = 1); increased lability of mood, unsteady gait, disturbed sleep (n = 1); headache, nocturia (n = 1); dizziness (n = 1); depression, swollen breasts (n = 1); depression, confusion (n = 1) **Withdrawals postrandomisation** VGB: increase in seizures associated with poor compliance (n = 1); placebo: development of status epilepticus (n = 1); severe exacerbation of epilepsy (n = 1) **Adverse events** **Intervention 1** The authors provide data for each of the phases of the trial. Below are the events reported for the double-blind phase which are divided into the two study groups (placebo and VGB). The remaining data do not distinguish between placebo and VGB. The data are reported in terms of events rather than participants experiencing events	**Authors' conclusions** The evidence confirms that VGB is a valuable new drug for many patients with chronic epilepsy, especially those with partial seizure disorders, who are usually the most drug resistant and who constitute most patients with chronic epilepsy. No serious or irreversible side-effects were found **Comments** The participants in this trial were selected based on their successful response to treatment in the previous phase (see Ref. 428, Reynolds, 1988) Length of follow-up in the double-blind placebo phase of the trial was 8 weeks. However, patients were also receiving VGB in the prior open phase. From the end of the titration phase to the end of the double-blind treatment phase was 14 weeks (16 weeks including titration). The double-blind trial was followed by an open-phase study lasting 1 year (these results are not presented in this data extraction table) Only participants who achieved at least a 50% reduction in seizure frequency in the previous phase were allowed to proceed to the double-blind phase of the trial. Therefore, the findings of this study are unlikely to reflect the

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period The pretrial period consisted of a 6-week baseline period for observation and assessing seizure frequency; followed by an 8-week open phase for the titration and maintenance of VGB (2 weeks of titration and 6-weeks of maintenance). At the end of this phase seizure frequency during the 6-week maintenance period was compared with the baseline period and patients with at least a 50% reduction in seizures (i.e. responders) were entered into the double-blind placebo phase of the trial **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** Student's *t*-test was used to compare seizure frequency in the open phase of the trial with baseline (no further details provided). Changes in seizure frequency during the double-blind phase of the trial were compared by parametric and non-parametric methods (no further details) **Length of trial/frequency of follow-up** 8 weeks; end of 8-week open phase; end of 8-week double-blind phase	**Co-morbidities** Neurologic or mental handicap (n = 10) **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: at least 4 complex partial seizures per month with or without secondarily generalised or at least 2 weeks of primary generalised seizures for previous 3 months; age 16–65 years; 1–2 concurrent AEDs Exclusion: women at risk of pregnancy; persons incapable of supplying a reliable seizure diary for intellectual, physical or psychological reasons; renal, hepatic, cardiovascular, gastrointestinal or other serious medical or psychiatric disease; drug or alcohol abusers		Double-blind period (n = 10): drowsiness (n = 2), depression/irritability (n = 0), headache (n = 0), behaviour disturbance (n = 0), confusion (n = 0), increased micturition (n = 0), dizziness (n = 1), increased appetite and weight (n = 0) **Comparator** Double-blind period (n = 10): Drowsiness (n = 0), depression/irritability (n = 0), headache (n = 1), behaviour disturbance (n = 1), confusion (n = 0), increased micturition (n = 0), dizziness (n = 0), increased appetite and weight (n = 0)	true effectiveness within the general population There were 7 additional withdrawals due to AEs All participants had their drug doses increased to 3 g/day. However, if AEs occurred or seizure frequency increased, the dose was reduced to 2.5 or 2 g The authors report that there were no significant changes in the plasma levels of the standard AEDs in the open, double-blind or long-term follow-up phases. Outcome data for the long-term follow-up phase are not reported in this data extraction table

continued

Results

Outcome 1

Outcome
Change in seizure frequency; mean % change in total seizure frequency from baseline (only data for those 'responders' who went through into the double-blind phase were considered)

Intervention 1
Total seizures
Baseline (open-phase) (n = 10): 70.0% reduction
Follow-up (double-blind) 1–4 weeks (n = 9): 50.3% reduction (p = 0.032)
Follow-up (double-blind) 5–8 weeks (n = 9): 59.6% reduction (p = 0.003)
Follow-up (double-blind) 1–8 weeks (n = 9): 54.7% reduction (p = 0.002)

CPSs
Baseline (open-phase) (n = 8): 68.5% reduction
Follow-up (double-blind) 1–4 weeks (n = 7): 45.1% reduction (p = 0.201)
Follow-up (double-blind) 5–8 weeks (n = 7): 59.0% reduction (p = 0.090)
Follow-up (double-blind) 1–8 weeks (n = 7): 51.9% reduction (p = 0.126)

Comparator
Total seizures
Baseline (open-phase) (n = 10): 60.0% reduction
Follow-up (double-blind) 1–4 weeks (n = 9): 20.9% increase
Follow-up (double-blind) 5–8 weeks (n = 8): 8.9% increase
Follow-up (double-blind) 1–8 weeks (n = 9): 18.9% increase

CPSs
Baseline (open-phase) (n = 7): 48.9% reduction
Follow-up (double-blind) 1–4 weeks (n = 6): 24.4% increase
Follow-up (double-blind) 5–8 weeks (n = 5): 42.8% increase
Follow-up (double-blind) 1–8 weeks (n = 6): 27.6% increase

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Specchio, 1999[61] **Related publications** None **Country** Italy **Source** Literature search **Aim** To assess the comparative efficacy and safety of new AEDs as 'add-on' therapy treatment in clinical practice **Type of publication** Abstract (interim analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Add-on therapy; new vs new; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** After 3 months of screening, patients were randomised and added VGB, LTG and GBP to current therapy for 18 months at doses tailored to single patient's needs	**Number of participants** 404 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; not stated **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** VGB: mean = 15.5; LTG: mean = 18.2; GBP: mean = 14.6 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: adult patients with partial epilepsy refractory to standard therapy	**Intervention 1** VGB; not stated; 18 months No. randomised: 131 No. completed: 62 **Intervention 2** LTG; not stated; 18 months No. randomised: 122 No. completed: 30 **Comparator** GBP; not stated; 18 months No. randomised: 151 No. completed: 49	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** VGB (n = 119): 39% **Intervention 2** LTG (n = 95): 36% **Comparator** GBP (n = 141): 29%	**Authors' conclusions** VGB, LTG and GBP showed similar effectiveness as add-on therapy in refractory epileptics GBP seemed to be slightly better tolerated. The presence of <6 seizures/month of baseline was a predictor of better response **Comments** These data are taken from an abstract rather than a full study report. It is therefore lacking in detail for study design, sample size calculations, randomisation, participants, intervention, statistical methods and outcomes. The quality of the study cannot be adequately assessed. It is not possible to say whether the drugs were used according to their licensed use since the drug dosages are not stated Results in ITT were presented for 119, 95 and 141 participants, respectively, who had 18 months of follow-up

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
ITT analysis performed/method Authors state yes; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 18 months; at 3-month intervals				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Proportion of responders; responders were defined as having at least a 50% reduction in seizure frequency **Intervention 1** (*n* = 119): 50% **Intervention 2** (*n* = 95): 44% **Comparator** (*n* = 141): 35%	**Outcome** Proportion of seizure-free patients; the percentage of seizure-free patients was reported (absolute numbers not reported). Data were stratified according to all patients and those experiencing more or less than 6 seizures per month at baseline **Intervention 1** Total (*n* = 119): 17% <6 seizures/month: 24% >6 seizures/month: 12% **Intervention 2** Total (*n* = 95): 18% <6 seizures/month: 24% >6 seizures/month: 12% **Comparator** (*n* = 141): 15% <6 seizures/month: 7% >6 seizures/month: 1%	**Outcome** Seizure frequency; not stated **Intervention 1** (*n* = 119): 8.8 **Intervention 2** (*n* = 95): 11.5 **Comparator** (*n* = 141): 12.6	**Outcome** Proportion of participants completing the study period; the percentage of participants completing the study period (absolute numbers not stated). Stratified according to all patients and those experiencing more or less than 6 seizures per month at baseline **Intervention 1** <6 seizures/month: 53% >6 seizures/month: 50% **Intervention 2** <6 seizures/month: 37% >6 seizures/month: 26% **Comparator** <6 seizures/month: 46% >6 seizures/month: 23%	

Vigabatrin (unlicensed use)

Crossover studies (*n* = 1)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Tanganelli, 1996[53] **Related publications** Abstract[431] **Country** Italy **Source** Literature search **Aim** To compare VGB with CBZ in a randomised response conditional crossover study **Type of publication** Full paper (final analysis) **Funding** None received **Trial ID** Not stated **Study design** Monotherapy; new vs old; crossover trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Random number tables; after pretrial period	**Number of participants** 58 **Type of epilepsy** Newly diagnosed **Type of seizures** Partial onset **Mean age/age range** Total (*n* = 51): 36.4 years (SD not stated); VGB (*n* = 26): 37.9 years; CBZ (*n* = 25): 34.8 years.; total (*n* = 51): 18–58 years; VGB (*n* = 26): not stated; CBZ (*n* = 25): not stated **Gender** Total (*n* = 51): men = 30, women = 21; VGB (*n* = 26): male/female ratio 1.5; CBZ (*n* = 25): male/female ratio 1.4 **Age at onset of seizures** Age at onset and years of seizure history not stated. The median duration of the seizure-free period before the end of phase 2 was 4 weeks (range 3–9 weeks) for VGB (*n* = 26) and 6 weeks (range 3–10 weeks) for CBZ (*n* = 25) **Pretrial medication** Not stated	**Intervention 1** VGB; max. 3500 mg/day; 16 weeks No. randomised: 37 No. completed: 37 **Comparator** CBZ; max. 1400 mg/day; 16 weeks No. randomised: 39 No. completed: 39	**Withdrawals prerandomisation** Total: a lack of collaboration or poor compliance (*n* = 7) **Withdrawals postrandomisation** None **Adverse events** **Intervention 1** VGB titration phase (4 weeks) (*n* = 37): generalised rash (*n* = 0), drowsiness (*n* = 7), weakness/fatigue (*n* = 4), dizziness (*n* = 1), transient diplopia (*n* = 0), headache (*n* = 3), weight gain (*n* = 1), decreased libido (*n* = 0), nausea (*n* = 1), leucopenia (*n* = 0) VGB maintenance phase (4 weeks) (*n* = 37): generalised rash (*n* = 0), drowsiness (*n* = 3), weakness/fatigue (*n* = 2), dizziness (*n* = 0), transient diplopia (*n* = 0), headache (*n* = 1), weight gain (*n* = 3), decreased libido (*n* = 0), nausea (*n* = 0), leucopenia (*n* = 0) **Comparator** CBZ titration phase (4 weeks) (*n* = 39): generalised rash (*n* = 1), drowsiness (*n* = 15), weakness/fatigue (*n* = 1), dizziness (*n* = 7), transient	**Authors' conclusions** The preliminary results for this small number of patients are encouraging and suggest that VGB may be considered as a first-line drug for epilepsy with CPSs and as a valid alternative when other monotherapies are ineffective or poorly tolerated **Comments** This study design is a conditional response design. Only those patients with persisting seizures or intolerable side-effects were switched to the crossover phase. This means that the findings of this study may not be applicable to the general population. In addition, the study findings should be treated with caution in view of the relatively small sample size and the lack of power The upper limit allowed for VGB (3.5 g/day) exceeds the UK recommendation of maximum 3 g/day. Monotherapy is not a licensed use for VGB in the UK Patients were evaluated every 4 weeks for seizure frequency, side-effects, EEG, routine haematology, blood chemistry, urinalysis tests and determination of serum levels in CBZ-treated

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Participants were randomised to either the VGB or the CBZ group and evaluated after an initial 8-week period. The crossover to the alternative drug was carried out, for another 4 months, only in cases with persisting seizures or in the presence of intolerable side-effects. Patients who did not respond to either drug were subsequently treated with a combination of VGB and CBZ. Patients who had no seizures during the maintenance period remained on the assigned therapy (rather than entering the crossover phase) and then entered the follow-up phase The starting dose for VGB was 1.0 g/day and for CBZ (controlled release) 0.2 g/day. The dose was progressively increased at weekly intervals (0.5 g at a time for VGB and 0.2 g for CBA), until seizures ceased or intolerable side-effects occurred, or serum levels (only for CBA) did not exceed the agreed upper limit of the therapeutic range (12 mg/l). For both drugs the doses prescribed could not exceed the recommended maximum dose (1.4 g/day for CBZ and 3.5 g/day for VGB) **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** The study sample allowed for 75% power to detect a difference of 20% in seizure frequency	**Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Mean number of seizures during run-in period: total (n = 51): 8.3; VGB (n = 26): 9.1; CBZ (n = 25): 7.4 **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 18–65 years; at least two untreated and unprovoked seizures, complex partial type, with or without secondary generalisation, in the previous 8 weeks (run-in) Exclusion: history of alcohol or drug abuse; the presence of a brain tumour or progressive neurological disease; IQ score <90; presence or history of psychiatric, cardiac, renal, hepatic or metabolic disease; pregnancy or the risk of pregnancy		diplopia (n = 1), headache (n = 0), weight gain (n = 0), decreased libido (n = 2), nausea (n = 3), leucopenia (n = 4) CBZ maintenance phase (4 weeks) (n = 39): generalised rash (n = 0), drowsiness (n = 9), weakness/fatigue (n = 2), dizziness (n = 2), transient diplopia (n = 0), headache (n = 0), weight gain (n = 1), decreased libido (n = 2), nausea (n = 1), leucopenia (n = 4)	patients. Side-effects were evaluated by means of a self-interview in order to avoid influence by the examiner. It consisted of a list of all possible side-effects, with a grading for their severity (0 = absence; 1 = slight; 2 = moderate; 3 = severe) Of the 14 patients resistant to both VGB and CBZ in monotherapy, a combined therapy of the two drugs stopped the seizures in 5 cases. In 5 additional cases with a poor response to monotherapy, a reduction in the frequency of seizures of >75% was observed

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Analysis methods Fisher's exact *p*-value was used. No further details reported **Length of trial/frequency of follow-up** 32 weeks; every 4 weeks				
Results				
Outcome 1	**Outcome 2**	**Outcome 3**	**Outcome 4**	
Outcome Proportion of seizure-free patients; number of participants experiencing total seizure control with acceptable tolerance **Intervention 1** VGB phase 1 (n = 26): 46.1% (n = 12). Fisher's exact *p*-value: 0.413; OR = 1.48 (95% CI: 0.49 to 4.48) VGB phase 2 (n = 11): 45.4% (n = 5). Fisher's exact *p*-value: >0.999; OR = 0.9 (95% CI: 0.18 to 4.41) Both phases together (n = 37): 45.9% (n = 17). Fisher's exact *p*-value: 0.647; OR = 1.24 (95% CI: 0.5 to 3.0) **Comparator** CBZ phase 1 (n = 25): 56.0% (n = 14) CBZ phase 2 (n = 14): 42.8% (n = 6) Both phases together (n = 39): 51.3% (n = 20)	**Outcome** Proportion of participants with persisting seizures **Intervention 1** VGB phase 1 (n = 26): 53.9% (n = 14). Fisher's exact *p*-value: 0.413; OR = 1.48 (95% CI: 0.49 to 4.48) VGB phase 2 (n = 11): 54.6% (n = 6). Fisher's exact *p*-value: >0.9999; OR = 0.9 (95% CI: 0.18 to 4.41) Both phases together (n = 37): 54.1% (n = 20). Fisher's exact *p*-value: 0.647; OR = 1.24 (95% CI: 0.5 to 3.0) **Comparator** CBZ phase 1 (n = 25): 40% (n = 10) CBZ phase 2 (n = 14): 57.2% (n = 8) Both phases together (n = 39): 46.2% (n = 18)			

Parallel studies (n = 4)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Chadwick, 1999[92] **Related publications** None **Country** European **Source** Literature search **Aim** VGB is a newly licensed drug for use in patients with epilepsy. It was investigated whether this drug was comparable to standard first-line monotherapy in efficacy and incidence of AEs **Type of publication** Full paper (final analysis) **Funding** Hoechst Marion Roussell **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; equivalence trial **Setting** Outpatient **Method/timing of randomisation** Computerised; after enrolment	**Number of participants** 459 **Type of epilepsy** Newly diagnosed **Type of seizures** Partial onset **Mean age/age range** VGB (n = 220): 35 years (SD 15); CBZ (n = 226): 36 years (SD 16); VGB (n = 220): 12–75 years; CBZ (n = 226): 13–72 years **Gender** VGB (n = 220): men = 117, women = 103; CBZ (n = 226): men = 122, women = 104 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Psychiatric history VGB (n = 220): n = 13; CBZ (n = 226): n = 9 **Baseline seizure frequency** Number of patients with seizures (median seizures; 25th–75th percentile)	**Intervention 1** VGB; 1–4 g/day; 52 weeks No. randomised: 229 No. completed: 130 **Comparator** CBZ; 200–1400 mg/day; 52 weeks No. randomised: 230 No. completed: 132	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** VGB: never took treatment drug (n = 1), no follow-up after randomisation (n = 8), AEs during titration (n = 12), lack of efficacy during titration (n = 3), other during titration (n = 3), AEs after titration (n = 31), lack of efficacy after titration (n = 20), other after titration (n = 21); CBZ: never took treatment drug (n = 1), no follow-up after randomisation (n = 3), AEs during titration (n = 22), lack of efficacy during titration (n = 1), other during titration (n = 1), AEs after titration (n = 39), lack of efficacy after titration (n = 8), other after titration (n = 33) **Adverse events** **Intervention 1** AEs with an overall incidence of 10% or an incidence of at least 5% in any randomised group reported Patients with at least one AE (n = 191/228) Deaths (n = 2): one experienced coronary infarction, stomach bleeding and a stomach ulcer and had increased liver transaminase 7 months after trial entry; one	**Authors' conclusions** VGB seems less effective but better tolerated than CBZ, which is the first-choice drug for the treatment of partial epilepsies. VGB cannot therefore be recommended as a first-line drug for monotherapy in this group of patients **Comments** Additional information on randomisation and concealment was supplied by the authors. The authors report that randomisation was by pre-prepared list for each centre in blocks of four; sealed envelopes kept by the pharmacy were used to conceal allocation VGB is not licensed for use as a monotherapy in the UK. The usual maximum dose of VGB is (as adjunctive therapy) 3 g. In this study, 25 patients received a dose >3 g. The usual minimum dose of CBZ is 800 g. In this study 173 patients received a dose less than this Although the authors state that the dose of VGB could be reduced to 1.5 g and CBZ to 400 mg, 11 patients on VGB received a lower dose of 1.0 g and 9 patients on CBZ received a dose of 200 mg

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period Participants were randomised to VGB or CBZ. In the first 6 weeks after randomisation an initial daily dose of 1 g VGB was increased to an initial maintenance dose of 2 g. The initial dose of 200 mg CBZ was increased to 600 mg. Increases of total daily dose of VGB to 4 g and CBZ to 1600 mg or decreases to 1.5 g VGB or 400 mg CBZ were permitted to allow maximum seizure control with minimum toxic effects. Double dummy dosing was used. After unmasking the treatment at 52 weeks, participants completing 1 year on VGB continued in an open follow-up study (not reported in the paper) **ITT analysis performed/method** Authors state yes; not stated **Sample size calculation** The study was designed to test for equivalence between VGB and CBZ (i.e. to exclude VGB being any greater than 15% less or more effective than CBZ) with the assumption of a treatment failure rate (owing to absence of efficacy or presence of AEs) on the two drugs of 40%. The sample size was calculated as 168 patients for each group with a significance level of 5% (two-sided) with a power of 80%. To allow for an expected drop-out rate of 20%, recruitment of 400 participants was planned **Analysis methods** The primary outcome was time to treatment failure which was defined as withdrawal because of lack of therapeutic effects or AEs. The secondary efficacy end-points were time to achieve 6 months of	SPSs: VGB (n = 220): n = 74 (5; 2–15); CBZ (n = 226): n = 63 (6; 2–36) CPSs: VGB (n = 220): n = 92 (6; 2–30); CBZ (n = 226): n = 91 (7; 2–26) Secondary generalised: VGB (n = 220): n = 139 (6; 2–3); CBZ (n = 226): n = 150 (2; 2–3) Not known: VGB (n = 220): n = 8 (2; 2–3); CBZ (n = 226): n = 8 (2; 1–3) **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 12–65 years; at least 2 seizures in the previous 12 months (SPSs or CPSs with or without secondary generalisation) Exclusion criteria: the occurrence of generalised seizure type		took treatment for 1 day and on drug withdrawal experienced shortness of breath and confusion, his heart disorder worsened, resulting in death Serious AE (n = 26/228) CNS: total (n = 141); amnesia (n = 16), drowsiness (n = 49), fatigue (n = 45), headache (n = 47) Psychiatry: total (n = 58); agitation (n = 16), depression (n = 15), insomnia (n = 15), other psychiatric (n = 12) Skin and appendages: total (n = 31), rash (n = 7), other skin and appendages (n = 27) Other events: asthenia (n = 5), weight increase (n = 25), dizziness (n = 29) **Comparator** Patients with at least one AE (n = 195/229) Serious AE (n = 21/229) Deaths (n = 1): one died following a bicycle accident caused by cerebral haemorrhage 2 months after trial entry CNS: total (n = 144); amnesia (n = 17), drowsiness (n = 63), fatigue (n = 50), headache (n = 48) Psychiatry: total (n = 34); agitation (n = 13), depression (n = 7), insomnia (n = 5), other psychiatric (n = 9) Skin and appendages: total (n = 52); rash (n = 22), other skin and appendages (n = 30)	Demographic data are provided for the ITT population. Excluded from the definition of the ITT population were 11 patients who had no follow-up after the start of therapy (VGB n = 8, CBZ n = 3) and 2 patients who never took the drug after randomisation (VGB n = 1, CBZ n = 1). The 52-week follow-up period includes a titration period of a minimum of 6 weeks, with individual patient doses being adjusted beyond this period The exclusion criteria were limited compared with other studies The Kaplan–Meier analysis of time to withdrawal was repeated for the 400 patients who completed the study according to protocol and found no change in estimates. (The reference to 400 patients completing the study according to protocol at this stage of the analysis contradicts the diagram for the trial profile, which indicates that 404 patients completed titration and a later analysis referring to the same group of patients gives n = 404) AEs showing significant between-group differences were psychiatric, skin and appendages and weight gain

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
remission after the first 6 weeks from randomisation and time to first seizure of any type after randomisation. Time to withdrawal owing to absence of therapeutic effect was also measured Kaplan–Meier plots and Cox's regression model of time were used for treatment failure and other time-related events. An adjusted model was fitted after initial log-rank test for differences between the groups. This model used covariates of centre, number of seizures in 12 months before randomisation, duration of epilepsy, age at randomisation and presence of SGTC seizures before randomisation. Patients who withdrew for reasons other than absence of therapeutic effect or presence of AEs or who completed the double-blind phase of the study were censored at the date of withdrawal or completion. Participants who completed the study according to protocol were also examined, which the authors state provided a more conservative method of testing equivalence **Length of trial/frequency of follow-up** 52 weeks; every 2 months after randomisation; haematological and biochemical variables at weeks 30 and 52			Other events: asthenia (n = 15), weight increase (n = 12), dizziness (n = 29)	

continued

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Time to exit/withdrawal; withdrawal because of lack of therapeutic effects or AEs **Intervention 1** VGB (n = 220) Number at risk: 2 months n = 192; 4 months n = 178; 6 months n = 166; 8 months n = 149; 10 months n = 137; 12 months n = 132 HR 0.83 (95% CI: 0.57 to 1.20) Adjusted HR 0.75 (95% CI: 0.52 to 1.10) **Comparator** CBZ (n = 226) Number at risk: 2 months n = 183; 4 months n = 171; 6 months n = 163; 8 months n = 142; 10 months n = 138; 12 months n = 129	**Outcome** Proportion of seizure-free patients; number achieving 6 months of remission (seizure freedom) **Intervention 1** VGB 107/202 HR 1.20 (95% CI: 0.93 to 1.57) Adjusted HR 1.15 (95% CI: 0.88 to 1.51) **Comparator** CBZ 116/202	**Outcome** Time to achieve 6 months of remission (seizure freedom); time to achieve 6 months of remission after maintenance dose was reached in the population who completed the study according to protocol **Intervention 1** VGB (n = 202) Number at risk: 6 months n = 202; 8 months n = 65; 8 months n = 46; 12 months n = 26 Log-rank p = 0.58 Adjusted HR 1.18 (95% CI: 0.89 to 1.55) **Comparator** CBZ (n = 202) Number at risk: 6 months n = 202; 8 months n = 47; 8 months n = 34; 12 months n = 25	**Outcome** Time to first seizure; time to first seizure after maintenance dose was reached **Intervention 1** VGB (n = 202) Number at risk: 2 months n = 150; 4 months n = 106; 6 months n = 86; 8 months n = 76; 10 months n = 67; 12 months n = 57 Log-rank p = 0.0001 HR 1.74 (95% CI: 1.31 to 2.33) Adjusted HR 1.79 (95% CI: 1.33 to 2.40) **Comparator** CBZ (n = 202) Number at risk: 2 months n = 161; 4 months n = 129; 6 months n = 109; 8 months n = 99; 10 months n = 89; 12 months n = 87

Outcome 5	Outcome 6
Outcome Time to first seizure **Intervention 1** Time to first seizure after randomisation was less for patients on VGB (p = 0.0003), adjusted and unadjusted HR 1.57 (95% CI: 1.23 to 2.02) Time to first seizure 6 months after randomisation, adjusted HR 1.58 (95% CI: 1.06 to 2.35) Time to withdrawal owing to absence of therapeutic effect alone (VGB n = 23; CBZ n = 9), adjusted HR 2.37 (95% CI: 1.09 to 5.18), p = 0.0298 **Comparator** See above	**Outcome** Survival analysis of time to withdrawal owing to AEs **Intervention 1** Survival analysis of time to withdrawal owing to AEs showed that CBZ patients withdrew earlier than those on VGB (adjusted HR 0.63 (95% CI: 0.43 to 0.94); unadjusted HR 0.70 (95% CI: 0.47 to 1.03) **Comparator** See above

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Czapinski, 1997[45] **Related publications** None **Country** Poland **Source** Literature search **Aim** Open randomised comparative study of VGB and LTG efficacy in monotherapy of patients with drug-resistant epilepsy with PCSs resistant to CBZ **Type of publication** Abstract (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Monotherapy; new vs new; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; after pretrial period **Details of pretrial period** There was 1-month baseline period during which CBZ was administered with stable serum drug levels. This was followed by randomisation to	**Number of participants** 40 **Type of epilepsy** Refractory **Type of seizures** Partial onset **Mean age/age range** Not stated; total: 20–55 years **Gender** Not stated **Age at onset of seizures** Not stated **Pretrial medication** CBZ (n = 40) **Ongoing concurrent medication** CBZ (n = 40) until the drug was withdrawn from responders to LTG and VGB treatment during the titration period of the trial **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: aged 20–55 years; CBZ-resistant PCSs with or	**Intervention 1** VGB; max. 4 g/day; 12 months No. randomised: not stated No. completed: not stated **Comparator** LTG; max. 600 mg/day; 12 months No. randomised: not stated No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** Approximately one-third of patients with drug-resistant epilepsy with PCSs can be successfully treated with VGB or LTG employed as monotherapy. The initially observed difference in drug effectiveness disappears in long-term therapy **Comments** This is an abstract and there are few details about the trial design and quality Monotherapy is not a licensed use for VGB in the UK. However, the comparison is included in the LTG meta-analyses. Current manufacturers' information provided for health professionals indicates that the usual dose of LTG as monotherapy is 200 mg daily with doses up to 500 mg being required. The maximum dose in this study of 500 mg is above that. For VGB, the usual range is 2–3 g daily and a maximum of 3 g daily. The maximum dose in this study is above that Length of time of follow-up was 12 months from randomisation; however, VGB and LTG were received as monotherapy for only 6 months The numbers randomised to each group are not given so it is not

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
VGB (at a dose of 2 g/day) or LTG (at a dose of 300 mg/day). These doses were administered for a period of 2 months. This was followed by a 4-month titration period during which the dose of VGB was increased to 4 g or LTG up to 600 mg, as needed with subsequent termination of CBZ in responders. The responders received 6 months of monotherapy with VGB or LTG **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** Not stated **Length of trial/frequency of follow-up** 12 months; not stated	without secondary generalisation; at least 4 seizures monthly Exclusion: criteria not stated			possible to use this data in the meta-analysis The responders' outcome is not defined so these data cannot be used in the meta-analyses
Results				
Outcome 1				
Outcome Proportion of responders; the authors did not define what was meant by the term 'responder' **Intervention 1** *n* = 10 (number of participants in intervention group not stated) **Comparator** *n* = 7 (number of participants in control group not stated)				

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Kälviäinen, 1995[71] **Related publications** Abstracts,[424,425] interim report[426] **Country** Finland **Source** Literature search **Aim** To evaluate the efficacy, safety and cognitive effects of initial VGB monotherapy compared with initial CBZ monotherapy in patients with newly diagnosed epilepsy **Type of publication** Full paper (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Outpatient **Method/timing of randomisation** Not stated; after enrolment **Details of pretrial period** Prior to randomisation, a full neurological examination, brain CT and/or MRI scan, laboratory tests, 21-channel EEG and visual	**Number of participants** 100 **Type of epilepsy** Newly diagnosed **Type of seizures** Combination of partial/generalised **Mean age/age range** VGB (n = 50): 33 years (SD 16); CBZ (n = 50): 37 years (SD 16); not stated **Gender** VGB (n = 50): men = 21, women = 29; CBZ (n = 50): men = 24, women = 26 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Seizure type: Partial seizures only: VGB (4/50), CBZ (4/50) Partial and secondarily generalised: VGB (10/50), CBZ (11/50)	**Intervention 1** VGB; individually titrated. mean = 50 mg/kg/day, 40–60 mg/kg/day; 12 months No. randomised: 50 No. completed: 43 **Comparator** CBZ; individually titrated. Mean = 28 μmol/l, range 22–34 μmol/l; 12 months No. randomised: 50 No. completed: 45	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** VGB: withdrawn owing to non-compliance (n = 7); CBZ: withdrawn owing to non-compliance (n = 5) **Adverse events** **Intervention 1** (n = 43): Some side-effects (n = 31) No side-effects (n = 12) Intolerable side-effects (n = 0) Tolerable side-effects: drowsiness (n = 19), dizziness (n = 3), visual disturbances (n = 7), myoclonic jerks (n = 6), gastrointestinal symptoms (n = 3), cognitive disturbance (n = 2), eczema (n = 1), increased appetite (n = 2), headache (n = 1), depressive mood (n = 1), insomnia (n = 1), loss of hair (n = 1), arthralgia (n = 1), feeling of thirst (n = 1) Generalised rashes were significantly more likely in CBZ than VGB patients (15 vs 0%, $p < 0.01$) Visual disturbances were significantly more likely in VGB than CBZ patients (16 vs 0%, $p < 0.01$)	**Authors' conclusions** VGB seems to be an effective and safe AED as primary monotherapy for epilepsy with fewer cognitive side-effects than CBZ **Comments** VGB is not licensed for monotherapy use in the UK One of the criteria for treatment success and failure was whether seizure control was acceptable or unacceptable. The authors do not report how acceptable and unacceptable were defined and whether these were patient defined or investigator defined The authors analyse and report the data on 12-month neuropsychological follow-up only for those patients in each drug group who were defined as treatment successes. It is possible that exclusion of treatment failures, specifically in relation to unacceptable seizure control and intolerable side-effects, may have affected the findings on neuropsychological performance. Given that there were differences between the VGB and CBZ groups in why treatment was classified as failure, it is possible that this could impact on between-group differences in neuropsychological performance

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Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
evoked potential (VEP) recordings and neuropsychological evaluation. After randomisation, there was a 2-month titration phase during which the daily dose of VGB was increased to a mean level of 50 mg/kg and the dose of CBZ to a plasma level of 35 μmol/l (therapeutic range, 20–50 μmol/l) or lower in cases of complete seizure control or dose related side-effects. If clinically necessary doses of CBZ were increased until seizures were controlled or toxic effects developed. VGB doses were not increased because doses of VGB in excess of 50 mg/kg usually provide no additional benefit. This was followed by a maintenance phase of 12 months. A non-placebo, non-randomised group was used as a control population for VEP recordings and neuropsychological evaluation. The 59 patients in this group had a single seizure before the baseline investigations and no relapse of seizures or AED treatment during the 12-month follow-up period **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** The differences between two group means were analysed by Student's two-tailed *t*-test and the covariance analyses and the differences between more than two group means by one-way ANOVA with Duncan's *post hoc* test. The χ^2 test with Yates' correction or Fishers' exact test for independent observations was used for comparison of frequencies. The drug	Secondarily generalised only: VGB (25/50), CBZ (27/50) Primary generalised: VHB (4/50), CBZ (1/50) Unclassified generalised: VGB (7/50), CBZ (7/50) **Inclusion/exclusion criteria** Inclusion: aged 15–64 years; at least 2 unprovoked epileptic seizures during the previous 2 years or 1 seizure and distinct EEG changes indicative of epilepsy; seizures classified according to the revised ICSs; IQ >85 according to the WAIS (using six subtests) Exclusion criteria: alcohol related seizures; current alcohol or other drug abuse; progressive neurological disorders; mental retardation; severe psychiatric problems; other severe medical disorders		Myoclonic jerks were significantly more likely in in VGB than CBZ patients (14 vs 2%, $p < 0.05$) **Comparator** ($n = 45$): Some side-effects ($n = 39$) No side-effects ($n = 6$) Intolerable side-effects: generalised rash ($n = 7$), hepatic toxic effects ($n = 3$), elevation of blood glucose level ($n = 1$), confusion and personality change ($n = 1$) Tolerable side-effects: drowsiness ($n = 28$), dizziness ($n = 9$), myoclonic jerks ($n = 1$), gastrointestinal symptoms ($n = 4$), cognitive disturbance ($n = 3$), eczema ($n = 4$), loss of appetite ($n = 2$), drug interactions ($n = 2$), headache ($n = 1$), gynecomastia ($n = 1$)	Although there were 30 treatment successes in the VGB group and 30 in the CBZ group, neuropsychological data are reported only for 25 in the VGB group and 24 in the CBZ group. No explanations are provided for the 5 participants missing in the VGB group and 6 in the CBZ group Possible effect of mood state on neuropsychological performance was not accounted for. There was no indication of how the possible time of day effect on cognitive performance was dealt with or how the tests were sequenced. However, the authors did examine the impact of psychomotor speed on test performance. When the variance in test scores between the groups that could be attributed to simple psychomotor speed (finger tapping) was factored out by MANCOVA, all statistically significant differences between groups remained at the same significance level Neuropsychological data are also reported for an untreated group, although these have not been extracted. Results from laboratory tests are also reported, but these have not been extracted

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
success rate after 12 months was used to evaluate the comparative efficacy and toxicity of VGB and CBZ. Drug success was defined as the proportion of patients continuing successful treatment with the randomly assigned drug. Treatment was defined as a failure when seizure control was unacceptable, intolerable side-effects developed or both. For follow-up data, continuous variables were analysed using MANOVA for repeated measures. MANCOVA was used to take into account the influence of age and IQ as covariates in evaluating the changes in neuropsychological test scores **Length of trial/frequency of follow-up** 12 months; during the maintenance phase, clinical examination and laboratory tests were performed every third month and VEP recordings and neuropsychological evaluations at 12 months				VEPs There was significant group effect on VEP P2 peak latency when the VGB, CBZ and untreated groups were compared ($F = 3.90$, df = 2.21, $p < 0.05$)

Results

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Outcome Proportion of responders; reported as the number of patients rated as follows: treatment success (patients continuing successful treatment) and treatment failure (seizure control was unacceptable, intolerable side-effects developed, or both) **Intervention 1** Responders $n = 30/50$ (includes seizure-free): Acceptable seizure control $n = 14/50$	**Outcome** Proportion of seizure-free patients **Intervention 1** $n = 16/50$; VGB vs CBZ ($p < 0.01$) **Comparator** $n = 26/50$	**Outcome** Verbal ability; two tests were used: the Object Naming Test and the Verbal Fluency Test. Object Naming was used to examine verbal ability and naming. 36 outline drawings of objects, including the 10 practice items, were presented to the participants to name. The score is the sum of the correct responses. The Verbal Fluency Test was used to evaluate word fluency and retrieval from semantic memory. The score is the sum of words beginning with the letter S written in	**Outcome** Memory; the Wechsler Memory Scale Logical Prose Subtest, Story A was used with immediate and delayed (90 minutes) recall **Intervention 1** Memory: Immediate Recall Baseline data: mean = 11.7 (SD 3.7). Follow-up data: mean = 12.0 (SD 3.3) Memory: Delayed Recall Baseline data: mean = 9.5 (SD 3.7). Follow-up data: mean = 10.1 (SD 3.4)

continued

Outcome 1	Outcome 2	Outcome 3	Outcome 4
Non-responders n = 20/50: Unacceptable seizure control n = 13/50 Intolerable side-effects n = 0/50; VGB vs CBZ ($p < 0.001$) Non-compliance n = 7/50 **Comparator** Responders n = 30/50 (includes seizure-free): Acceptable seizure control n = 4/50 Non-responders n = 20/50: Unacceptable seizure control n = 3/50 Intolerable side-effects n = 12/50 Non-compliance n = 5/50		5 minutes and four-letter words beginning with the letter K written in 4 minutes **Intervention 1** Object Naming Baseline data: mean = 21.9 (SD 2.4). Follow-up data: mean = 21.9 (SD 1.9) Verbal Fluency Baseline data: mean = 44.7 (SD 13.0). Follow-up data: mean = 52.4 (SD 17.2) MANCOVA for repeated measures found a significant group effect (F = 7.49, df = 2.10, $p < 0.01$). *Post hoc* analysis showed significant improvement in the VGB group (F = 17.59, df = 1.22, $p < 0.001$) but no change in the CBZ or untreated groups **Comparator** Object Naming Baseline data: mean = 21.2 (SD 2.7). Follow-up data: mean = 21.4 (SD 2.8) Verbal Fluency Baseline data: mean = 43.0 (SD 17.6). Follow-up data: mean = 39.4 (SD 18.5)	**Comparator** Memory: Immediate Recall Baseline data: mean = 9.7 (SD 3.9). Follow-up data: mean = 11.0 (SD 5.1) Memory: Delayed Recall Baseline data: mean = 8.4 (SD 4.3). Follow-up data: mean = 8.8 (SD 4.9)
Outcome 5	**Outcome 6**	**Outcome 7**	**Outcome 8**
Outcome List Learning Test (Modified from the Rey Auditory Verbal Learning Test); consists of the oral presentation of 15 semantically unrelated words which the participant learns and recalls across 4 consecutive trials. Seven subscores were used. The number of words recalled is reported **Intervention 1** Trial 1 Baseline data: mean = 4.6 (SD 1.6). Follow-up data: mean = 5.3 (SD 1.7)	**Outcome** Forward Digit Span; this was used as a test of verbal attention span. The length of the longest correctly repeated number sequence is reported **Intervention 1** Baseline data: mean = 10.3 (SD 1.4). Follow-up data: mean = 10.6 (SD 1.3) **Comparator** Baseline data: mean = 10.1 (SD 1.4). Follow-up data: mean = 10.1 (SD 1.2)	**Outcome** Corsi Block Span; this was used a a measure of non-verbal attention. The length of the longest correctly repeated block tapping sequence is reported **Intervention 1** Baseline data: mean = 6.0 (SD 0.9). Follow-up data: mean = 5.9 (SD 0.8) **Comparator** Baseline data: mean = 5.7 (SD 0.9). Follow-up data: mean = 5.6 (SD 0.8)	**Outcome** The Letter Cancellation Test; this was used as a measure of visual attention and visual scanning. The number of letters is reported **Intervention 1** Baseline data: mean = 45.6 (SD 12.3). Follow-up data: mean = 44.3 (SD 10.1) **Comparator** Baseline data: mean = 40.5 (SD 6.8). Follow-up data: mean = 37.5 (SD 9.1)

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Trial 4 Baseline data: mean = 9.1 (SD 2.0). Follow-up data: mean = 9.6 (SD 2.8) Primacy Score (the sum of the words recalled from the first 4 words of the list) Baseline data: mean = 1.7 (SD 0.7). Follow-up data: mean = 1.6 (SD 0.8) Recency Score (the sum of the words recalled from the last 4 words of the list) Baseline data: mean = 1.5 (SD 1.2). Follow-up data: mean = 2.0 (SD 1.1) Immediate Recall (the sum of correctly recalled words) Baseline data: mean = 29.1 (SD 7.5). Follow-up data: mean = 30.8 (SD 8.1) Delayed Recall (the number of correctly recalled words after 90mins) Baseline data: mean = 4.0 (SD 2.8). Follow-up data: mean = 6.0 (SD 3.2). MANCOVA for repeated measures found a significant group effect ($F = 5.27$, df = 1.47, $p < 0.05$). *Post hoc* analysis showed significant improvement in the VGB group ($F = 24.24$, df = 1.11, $p < 0.001$) and the untreated group ($F = 18.08$, df = 1.11, $p < 0.001$) but no change in the CBZ group. Delayed Recognition (the number of correctly recognised words after 90 minutes) Baseline data: mean = 11.9 (SD 2.3). Follow-up data: mean = 12.7 (SD 1.5) **Comparator** Trial 1 Baseline data: mean = 5.4 (SD 1.8). Follow-up data: mean = 5.4 (SD 2.0) Trial 4 Baseline data: mean = 9.2 (SD 2.1). Follow-up data: mean = 9.0 (SD 2.9)			

continued

Outcome 5	Outcome 6	Outcome 7	Outcome 8
Primacy Score Baseline data: mean = 2.0 (SD 0.8). Follow-up data: mean = 1.8 (SD 1.2) Recency Score Baseline data: mean = 1.7 (SD 0.8). Follow-up data: mean = 1.8 (SD 0.9) Immediate recall Baseline data: mean = 30.3 (SD 7.7). Follow-up data: mean = 30.1 (SD 8.8) Delayed recall Baseline data: mean = 4.5 (SD 3.6). Follow-up data: mean = 5.1 (SD 3.4) Delayed recognition Comparator: baseline data: mean = 11.1 (SD 3.3). Follow-up data: mean = 11.9 (SD 2.2)			

Outcome 9	Outcome 10	Outcome 11
Outcome The Stroop Test C; this test was used to evaluate sustained attention, resistance to interference and response inhibition. The length of time to complete the task in minutes is reported **Intervention 1** Baseline data: mean = 60.4 (SD 18.1). Follow-up data: mean = 56.7 (SD 17.4) **Comparator** Baseline data: mean = 64.0 (SD 18.6). Follow-up data: mean = 61.2 (SD 22.6)	**Outcome** The Alternating S Task; this was used to evaluate the flexibility of mental processing. The participant is asked to write the letter S and the reversed letter S alternately for 60 seconds. The sum of correct items is reported **Intervention 1** Baseline data: mean = 54.3 (SD 21.7). Follow-up data: mean = 70.5 (SD 27.0) MANCOVA for repeated measures found a significant group effect ($F = 5.15$, df = 2.12, $p < 0.051$. *Post hoc* analysis showed significant improvement in the VGB group ($F = 40.22$, df = 2.46, $p < 0.001$) and the Untreated group ($F = 17.46$, df = 1.11, $p < 0.001$) but no change in the CBZ group **Comparator** Baseline data: mean = 46.5 (SD 22.2). Follow-up data: mean = 53.1 (SD 25.8)	**Outcome** The Finger Tapping Test; this test was used to assess psychomotor speed. Tapping rate was determined during a 10-second period in two trials for each hand. The mean number of taps for both hands is reported **Intervention 1** Baseline data: mean = 45.6 (SD 4.5). Follow-up data: mean = 46.0 (SD 4.4) MANCOVA for repeated measures found a significant group effect ($F = 3.35$, df = 1.45, $p < 0.05$). *Post hoc* analysis showed significant deterioration in the CBZ group ($F = 5.37$, df = 1.99, $p < 0.05$) and the untreated group ($F = 18.08$, df = 1.11, $p < 0.001$) but no change in the VGB and untreated groups **Comparator** Baseline data: mean = 44.7 (SD 5.8). Follow-up data: mean = 43.5 (SD 6.9)

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Riekkinen, 1997[59] **Related publications** Prior study[71] **Country** Finland **Source** Literature search **Aim** To determine (1) whether there are changes in prospective cognitive testings and quantitative MRI associated with a specific AED used and (2) whether treatment with VGB is associated with changes in white matter tracts indicating intramyelinic oedema (The authors used the abbreviation GVG to refer to vigabatrin) **Type of publication** Abstract (final analysis) **Funding** Not stated **Trial ID** Not stated **Study design** Monotherapy; new vs old; parallel trial; superiority trial **Setting** Not stated **Method/timing of randomisation** Not stated; not stated	**Number of participants** 27 **Type of epilepsy** Newly diagnosed **Type of seizures** Partial onset **Mean age/age range** VGB (n = 13): 28 years (SD 13); CBZ (n = 14): 32 years (SD 17); not stated **Gender** VGB (n = 13): male = 6, women = 7; CBZ (n = 14): men = 7, women = 7 **Age at onset of seizures** Not stated **Pretrial medication** Not stated **Ongoing concurrent medication** Not stated **Co-morbidities** Not stated **Baseline seizure frequency** Not stated **Other characteristics** Not stated **Inclusion/exclusion criteria** Inclusion: newly diagnosed patients with partial epilepsy	**Intervention 1** VGB; not stated.; 1 year No. randomised: 13 No. completed: not stated **Comparator** CBZ; not stated; 1 year No. randomised: 14 No. completed: not stated	**Withdrawals prerandomisation** Not stated **Withdrawals postrandomisation** Not stated **Adverse events** **Intervention 1** Not stated **Comparator** Not stated	**Authors' conclusions** During 1-year follow-up there are no changes indicating progression of epilepsy independent of the drug used. However, VGB seems to be a safe AED also as initial monotherapy with favourable cognitive profile **Comments** Monotherapy is not a licensed use for VGB in the UK. These data are taken from an abstract rather than a full study report. It is therefore lacking in detail for study design, randomisation, participants, intervention, statistical methods and outcomes. The quality of the study cannot be adequately assessed. Sample size calculations are not reported so it is not possible to determine whether an adequate number of participants were enrolled The dosages of drugs administered to participants are not stated, so it is not possible to state whether the doses given were within the recommended licensed limits The authors state that when an earlier open-label study population[71] was combined with the present study population, the VGB group (n = 38) performed better in verbal fluency and memory tasks, in flexible mental

continued

Study details and design	Participant details	Intervention details	Withdrawals/adverse events	Conclusions and comments
Details of pretrial period There was a baseline period, but the length of this period is not stated **ITT analysis performed/method** Authors do not state yes or no; not stated **Sample size calculation** Not stated **Analysis methods** MANCOVA was used to assess performance in the learning of a word list **Length of trial/frequency of follow-up** 1 year; baseline and after 1 year of successful drug treatment				processing and in simple psychomotor speed than the CBZ group (n = 38)
Results				
Outcome 1				
Outcome Change in functional capacity; measured using cognitive test battery and quantitative MRI **Intervention 1** VGB had no detrimental effects on cognition. The performance in the learning of word list improved on VGB patients but not in CBZ patients, $p < 0.05$ There were no changes in hippocampal or amygdalar volumes or T2 relaxation times independent of the drug used. VGB did not cause any changes in parietal, temporal or thalamic white matter T2 relaxation times **Comparator** The performance in the learning of word list did not improve in CBZ patients				

Appendix 24

Adverse events results tables

Note. Entries in bold represent statistically significant results.

Any adverse event (total)

Drug	Comparator	Study	RR (95% CI)
GBP	VGB	Lindberger, 2000[132]	0.878 (95% CI: 0.710 to 1.061)
	VGB	Specchio, 1999[61]	0.748 (95% CI: 0.539 to 1.038)
	LTG	Specchio, 1999[61]	0.987 (95% CI: 0.685 to 1.432)
	LTG	Crawford, 2001[131]	1.231 (95% CI: 0.834 to 1.830)
	Placebo	Leach, 1997[90]	1.267 (95% CI: 0.836 to 1.982)
	Placebo	**UK Gabapentin Study Group, 1990[73]**	**1.523 (95% CI: 1.081 to 2.183)**
	Placebo	**US Gabapentin Study Group, 1993[138] (600 mg)**	**1.198 (95% CI: 1.006 to 1.412)**
	Placebo	**US Gabapentin Study Group, 1993[138] (1200 mg)**	**1.216 (95% CI: 1.061 to 1.419)**
	Placebo	**US Gabapentin Study Group, 1993[138] (1800 mg)**	**1.252 (95% CI: 1.070 to 1.465)**
	Placebo	**Anhut, 1994[156] (1200 mg)**	**1.309 (95% CI: 1.055 to 1.642)**
	Placebo	Anhut, 1994[156] (900 mg)	1.214 (95% CI: 0.908 to 1.581)
LTG	Conv.	**GlaxoSmithKline, 2000[118]**	**0.809 (95% CI: 0.730 to 0.894)**
	Conv.	**Martinez, 2002[114]**	**0.663 (95% CI: 0.480 to 0.888)**
	CBZ	Brodie, 1995[121]	0.959 (95% CI: 0.869 to 1.055)
	CBZ	Brodie, 1999[117]	1.044 (95% CI: 0.925 to 1.236)
	CBZ	Kerr, 2001[122]	0.972 (95% CI: 0.869 to 1.095)
	CBZ	Nieto Barrera, 2001[119]	0.920 (95% CI: 0.767 to 1.118)
	PHT	**Steiner, 1999[75]**	**0.789 (95% CI: 0.629 to 0.974)**
	VPA	**Kerr, 2001[122]**	**0.911 (95% CI: 0.831 to 0.999)**
	VPA	Gilliam, 1998[112]	0.961 (95% CI: 0.830 to 1.104)
	VPA	Biton, 2001[116]	1.029 (95% CI: 0.923 to 1.154)
	VPA	GlaxoSmithKline, 2001[62] (Tamhe)	0.883 (95% CI: 0.717 to 1.106)
	Placebo	Schmidt, 1993[91]	0.955 (95% CI: 0.760 to 1.171)
	GBP	Crawford, 2001[131]	0.813 (95% CI: 0.546 to 1.199)
	GBP	**Specchio, 1999[61]**	**1.772 (95% CI: 1.314 to 2.405**)
	TGB	Chmielewska, 2001[133]	0.657 (95% CI: 0.258 to 1.587)
	VGB	**Specchio, 1999[61]**	**1.326 (95% CI: 1.010 to 1.751)**
LEV	Placebo	Cereghino, 2000[143] (1000 mg)	1.004 (95% CI: 0.902 to 1.120)
	Placebo	Shorvon, 2000[145] (1000 mg)	0.978 (95% CI: 0.823 to 1.159)
	Placebo	Shorvon, 2000[145] (2000 mg)	1.044 (95% CI: 0.888 to 1.227)
	Placebo	Betts, 2000[139] (2000 mg)	0.985 (95% CI: 0.799 to 1.217)
	Placebo	Cereghino, 2000[143] (3000 mg)	1.008 (95% CI: 0.907 to 1.123)
	Placebo	Betts, 2000[139] (4000 mg)	0.995 (95% CI: 0.802 to 1.230)
	Placebo	Ben-Menachem, 2000[144] (3000 mg)	1.040 (95% CI: 0.840 to 1.300)
OXC	CBZ	Reinikainen, 1987[115]	0.711 (95% CI: 0.345 to 1.376)
	CBZ	Loiseau, 1998[72]	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Barcs, 2000[70] (600 mg)	1.365 (95% CI: 0.732 to 2.554)
	Placebo	**Barcs, 2000[70] (1200 mg)**	**4.147 (95% CI: 2.497 to 6.993)**
	Placebo	Sachdeo, 1998[111] (1200 mg)	0.911 (95% CI: 0.699 to 1.154)
	Placebo	Barcs, 2000[70] (2400 mg)	7.689 (95% CI: 4.766 to 12.650)
	Placebo	Schachter, 1999[78] (2400 mg)	1.310 (95% CI: 0.988 to 1.780)

continued

Drug	Comparator	Study	RR (95% CI)
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Richens, 1995[146]	0.808 (95% CI: 0.542 to 1.183)
	Placebo	Crawford, 2001[147]	0.800 (95% CI: 0.361 to 1.754)
	Placebo	Sachdeo, 1997[140] (16 mg b.d.)	1.064 (95% CI: 0.969 to 1.178)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s)	0.997 (95% CI: 0.892 to 1.113)
	Placebo	Uthman, 1998[163] (16 mg)	1.082 (95% CI: 0.970 to 1.204)
	Placebo	Uthman, 1998[163] (32 mg)	1.021 (95% CI: 0.914 to 1.143)
	Placebo	Uthman, 1998[163] (56 mg)	1.018 (95% CI: 0.886 to 1.146)
	Placebo	Kälviäinen, 1998[164]	1.106 (95% CI: 0.997 to 1.252)
	LTG	Chmielewska, 2001[133]	1.523 (95% CI: 0.630 to 3.874)
TPM	Placebo	Barrett, 1997[76]	1.088 (95% CI: 0.920 to 1.319)
	Placebo	**Korean Topiramate Study Group, 1999[149]**	**1.665 (95% CI: 1.330 to 2.144)**
	Placebo	Yen, 2000[165]	1.286 (95% CI: 0.589 to 2.870)
VGB	LTG	Specchio, 1999[61] (LTG)	1.079 (95% CI: 0.786 to 1.488)
	GBP	Specchio, 1999[61] (GBP)	1.336 (95% CI: 0.963 to 1.856)
	VGB	Lindberger, 2000[132]	1.139 (95% CI: 0.942 to 1.408)
	Placebo	**Rimmer, 1984[49]**	**2.286 (95% CI: 1.213 to 4.674)**
	Placebo	**Beran, 1996[87] (2 g) per protocol**	**1.385 (95% CI: 1.021 to 1.930)**
	Placebo	Beran, 1996[87] (3 g) per protocol	1.286 (95% CI: 0.891 to 1.898)
	Placebo	Dean, 1999[154] (1 g)	1.062 (95% CI: 0.858 to 1.330)
	Placebo	Dean, 1999[154] (3 g)	1.140 (95% CI: 0.940 to 1.414)
	Placebo	Dean, 1999[154] (6 g)	1.169 (95% CI: 0.974 to 1.445)
	Placebo	French, 1996[155]	1.016 (95% CI: 0.900 to 1.151)

Serious adverse events

Drug	Comparator	Study	RR (95% CI)
GBP	VGB	Lindberger, 2000[132] (VGB)	0.780 (95% CI: 0.203 to 2.977)
	LTG	Crawford, 2001[131] (LTG)	0.903 (95% CI: 0.277 to 2.907)
LTG	GBP	Crawford, 2001[131] (GBP)	1.108 (95% CI: 0.344 to 3.609)
	Placebo	Schapel, 1993[161]	3.000 (95% CI: 0.253 to 36.101)
	Placebo	Binnie, 1989[159]	0.321 (95% CI: 0.082 to 1.130)
	Placebo	Schachter, 1995[56]	1.118 (95% CI: 0.341 to 3.733)
	Placebo	Matsuo, 1993[142] (500 mg)	9.123 (95% CI: 0.900 to 94.675)
	Placebo	Matsuo, 1993[142] (300 mg)	3.083 (95% CI: 0.257 to 37.268)
	CBZ	GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)	1.680 (95% CI: 0.875 to 3.263)
	VPA	GlaxoSmithKline, 2001 (Kerr)[122] (VPA)	0.891 (95% CI: 0.545 to 1.458)
	CBZ	Nieto-Barrera, 2001[119]	0.851 (95% CI: 0.378 to 1.943)
	PHT	Steiner, 1999[75]	0.442 (95% CI: 0.150 to 1.276)
	VPA	Gilliam, 1998[112]	1.053 (95% CI: 0.297 to 3.726)
	CBZ	Reunanen, 1996[120] (100 mg)	1.017 (95% CI: 0.182 to 5.694)
	CBZ	Reunanen, 1996[120] (200 mg)	2.108 (95% CI: 0.460 to 9.715)
	CBZ	Brodie, 1995[121]	0.438 (95% CI: 0.146 to 1.304)
	Conv.	GlaxoSmithKline, 2000[118]	1.006 (95% CI: 0.481 to 2.103)
	CBZ	Brodie, 1999[117]	0.659 (95% CI: 0.380 to 1.170)
	VPA	GlaxoSmithKline, 2001[62] (Tamhe)	0.604 (95% CI: 0.180 to 2.049)
	GBP	Brodie, 2002[93]	1.046 (95% CI: 0.416 to 2.629)

continued

Drug	Comparator	Study	RR (95% CI)
LEV	Placebo	Cereghino, 2000[143] (1000 mg)	0.679 (95% CI: 0.277, 1.655)
	Placebo	**Cereghino, 2000[143] (3000 mg)**	**0.188 (95% CI: 0.047, 0.738)**
	Placebo	Shorvon, 2000[145] (1000 mg)	0.704 (95% CI: 0.143, 3.463)
	Placebo	Shorvon, 2000[145] (2000 mg)	2.818 (95% CI: 0.836, 9.611)
	Placebo	Betts, 2000[139] (2000 mg)	0.929 (95% CI: 0.225, 3.843)
	Placebo	Betts, 2000[139] (4000 mg)	1.368 (95% CI: 0.363, 5.197)
	Placebo	Ben Menachem, 2000[144] (3000 mg)	2.320 (95% CI: 0.530, 1.400)
OXC	Placebo	Barcs, 2000[70] (600 mg)	1.365 (95% CI: 0.605 to 3.088)
	Placebo	Barcs, 2000[70] (1200 mg)	0.972 (95% CI: 0.406 to 2.325)
	Placebo	Barcs, 2000[70] (2400 mg)	1.989 (95% CI: 0.939 to 4.240)
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Crawford, 2001[147]	0.333 (95% CI: 0.028 to 3.935)
	Placebo	Sachdeo, 1997[140] (16 mg b.d.)	1.009 (95% CI: 0.181 to 5.644)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s.)	1.019 (95% CI: 0.182 to 5.697)
	Placebo	Uthman, 1998[163] (16 mg)	0.249 (95% CI: 0.040 to 1.510)
	Placebo	Uthman, 1998[163] (32 mg)	0.689 (95% CI: 0.215 to 2.200)
	Placebo	Uthman, 1998[163] (56 mg)	1.064 (95% CI: 0.332 to 3.352)
	Placebo	Kälviäinen, 1998[164]	1.286 (95% CI: 0.521 to 3.188)
TPM	Placebo	Barrett, 1997[76]	0.500 (95% CI: 0.170 to 1.433)
	Placebo	Biton, 1999[79]	2.103 (95% CI: 0.476 to 9.467)
	Placebo	Faught, 1996[67] (400 mg)	5.000 (95% CI: 0.465 to 55.112)
VGB	GBP	Lindberger, 2000[132]	1.282 (95% CI: 0.336 to 4.932)
	Placebo	Dean, 1999[154] (1 g)	3.913 (95% CI: 0.617 to 25.569)
	Placebo	Dean, 1999[154] (3 g)	5.114 (95% CI: 0.836 to 32.404)
	Placebo	**Dean, 1999[154] (6 g)**	**7.159 (95% CI: 1.223 to 43.782)**
	Placebo	Grunewald, 1994[38]	5.217 (95% CI: 0.500 to 56.962)
	VPA	Brodie, 1999[66]	1.090 (95% CI: 0.493 to 2.411)

Asthenia

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	Placebo	Schapel, 1993[161]	0.444 (95% CI: 0.154 to 1.246)
	Placebo	Schmidt, 1993[91]	1.000 (95% CI: 0.487 to 2.054)
	Placebo	Boas, 1996[136]	0.619 (95% CI: 0.229 to 1.647)
	Placebo	Smith, 1993[55]	0.571 (95% CI: 0.257 to 1.254)
	Placebo	Binnie, 1989[159]	1.500 (95% CI: 0.496 to 4.620)
	Placebo	Jawad, 1989[160]	1.111 (95% CI: 0.554 to 2.249)
	CBZ	GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)	0.582 (95% CI: 0.318 to 1.065)
	VPA	**GlaxoSmithKline, 2001 (Kerr)[122] (VPA)**	**0.430 (95% CI: 0.263 to 0.701)**
	CBZ	Nieto Barrera, 2001[119]	0.660 (95% CI: 0.348 to 1.265)
	PHT	**Steiner, 1999[75]**	**0.552 (95% CI: 0.311 to 0.963)**
	VPA	Gilliam, 1998[112]	1.158 (95% CI: 0.532 to 2.523)
	CBZ	Reunanen, 1996[120] (100 mg)	0.619 (95% CI: 0.337 to 1.128)
	CBZ	Reunanen, 1996[120] (200 mg)	0.642 (95% CI: 0.350 to 1.167)
	VPA	Biton, 2001[116]	1.617 (95% CI: 0.835 to 3.169)
	CBZ	Brodie, 1995[121]	0.745 (95% CI: 0.486 to 1.136)
	CBZ	Brodie, 1999[117]	0.392 (95% CI: 0.133 to 1.165)
	Conv.	Martinez, 2002[114]	0.452 (95% CI: 0.154 to 1.301)

continued

Drug	Comparator	Study	RR (95% CI)
LEV	Placebo	Cereghino, 2000[143] (1000 mg)	1.410 (95% CI: 0.703 to 2.851)
	Placebo	Cereghino, 2000[143] (3000 mg)	1.112 (95% CI: 0.533 to 2.326)
	Placebo	Shorvon, 2000[145] (1000 mg)	0.939 (95% CI: 0.387 to 2.275)
	Placebo	Shorvon, 2000[145] (2000 mg)	1.644 (95% CI: 0.760 to 3.579)
	Placebo	Betts, 2000[139] (2000 mg)	2.012 (95% CI: 0.885 to 4.741)
	Placebo	Betts, 2000[139] (4000 mg)	0.855 (95% CI: 0.297 to 2.442)
	Placebo	Ben-Menachem, 2000[144] (3000 mg)	2.070 (95% CI: 0.960 to 4.570)
OXC	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Richens, 1995[146]	5.000 (95% CI: 0.820 to 31.654)
	Placebo	Sachdeo, 1997[140] (16 mg b.d)	1.586 (95% CI: 0.870 to 2.917)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s.)	1.601 (95% CI: 0.666 to 2.483)
	Placebo	Uthman, 1998[163] (32 mg)	1.034 (95% CI: 0.543 to 1.967)
	Placebo	Uthman, 1998[163] (56 mg)	1.596 (95% CI: 0.850 to 2.974)
	Placebo	Kälviäinen, 1998[164]	1.333 (95% CI: 0.687 to 2.608)
TPM	Placebo	Sharief, 1996[148]	4.174 (95% CI: 0.686 to 26.807)
VGB	–	No data	

Ataxia

Drug	Comparator	Study	RR (95% CI)
GBP	LTG	**Crawford, 2001[131] (LTG)**	**10.125 (95% CI: 1.019 to 104.554)**
	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	1.009 (95% CI: 0.406 to 2.461)
	Placebo	US Gabapentin Study Group, 1993[138] (1200 mg)	2.293 (95% CI: 1.224 to 4.371)
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.650 (95% CI: 0.757 to 3.545)
	Placebo	**Anhut, 1994[156] (1200 mg)**	**3.532 (95% CI: 1.112 to 11.437)**
LTG	GBP	**Crawford, 2001[131] (GBP)**	**0.099 (95% CI: 0.010 to 0.981)**
	Placebo	Schapel, 1993[161]	3.500 (95% CI: 0.889 to 14.311)
	Placebo	Sander, 1990[135]	1.667 (95% CI: 0.498 to 5.764)
	Placebo	**Messenheimer, 1994[158]**	**5.000 (95% CI: 2.264 to 11.332)**
	Placebo	Beran, 1998[134]	7.000 (95% CI: 0.703 to 73.587)
	Placebo	**Smith, 1993[55]**	**4.143 (95% CI: 1.996 to 8.860)**
	Placebo	Binnie, 1987[50]	0.143 (95% CI: 0.014 to 1.281)
	Placebo	**Jawad, 1989[160]**	**11.000 (95% CI: 1.179 to 111.133)**
	Placebo	**Schachter, 1995[56]**	**4.471 (95% CI: 2.087 to 9.869)**
	Placebo	**Veendrick-Meekes, 2000[137]**	**5.455 (95% CI: 1.017 to 32.377)**
	Placebo	**Matsuo, 1993[142] (500 mg)**	**2.897 (95% CI: 1.351 to 6.371)**
	Placebo	Matsuo, 1993[142] (300 mg)	1.028 (95% CI: 0.394 to 2.683)
	PHT	Steiner, 1999[75]	0.048 (95% CI: 0.005 to 0.459)
LEV	–	No data	
OXC	Placebo	Barcs, 2000[70] (600 mg)	1.820 (95% CI: 0.845 to 3.939)
	Placebo	**Barcs, 2000[70] (1200 mg)**	**3.348 (95% CI: 1.678 to 6.760)**
	Placebo	**Barcs, 2000[70] (2400 mg)**	**6.186 (95% CI: 3.231 to 12.042)**

continued

Drug	Comparator	Study	RR (95% CI)
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Uthman, 1998[163] (16 mg)	0.597 (95% CI: 0.136 to 2.565)
	Placebo	Uthman, 1998[163] (32 mg)	1.241 (95% CI: 0.416 to 3.714)
	Placebo	Uthman, 1998[163] (56 mg)	1.916 (95% CI: 0.645 to 5.665)
TPM	Placebo	Barrett, 1997[76]	0.750 (95% CI: 0.197 to 2.829)
	Placebo	Faught, 1996[67] (200 mg)	2.250 (95% CI: 0.796 to 6.535)
	Placebo	**Faught, 1996[67] (400 mg)**	**3.250 (95% CI: 1.225 to 8.979)**
	Placebo	**Faught, 1996[67] (600 mg)**	**2.935 (95% CI: 1.092 to 8.194)**
	Placebo	Privitera, 1996[68] (600 mg)	1.714 (95% CI: 0.573 to 5.216)
	Placebo	Privitera, 1996[68] (800 mg)	2.203 (95% CI: 0.776 to 6.418)
	Placebo	Privitera, 1996[68] (1000 mg)	2.250 (95% CI: 0.793 to 6.550)
VGB	Placebo	Dean, 1999[154] (1 g)	0.140 (95% CI: 0.013 to 1.434)
	Placebo	Dean, 1999[154] (3 g)	1.364 (95% CI: 0.359 to 5.214)
	Placebo	Dean, 1999[154] (6 g)	2.386 (95% CI: 0.721 to 8.107)

Dizziness

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	Sivenius, 1991[157] (1200 mg)	4.000 (95% CI: 0.572 to 28.114)
	Placebo	**US Gabapentin Study Group, 1993[138] (600 mg)**	**2.671 (95% CI: 1.242 to 5.730)**
	Placebo	**US Gabapentin Study Group, 1993[138] (1200 mg)**	**2.695 (95% CI: 1.359 to 5.448)**
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	2.016 (95% CI: 0.888 to 4.540)
	Placebo	**Anhut, 1994[156] (1200 mg)**	**2.510 (95% CI: 1.245 to 5.135)**
	Placebo	Anhut, 1994[156] (900 mg)	1.630 (95% CI: 0.656 to 3.975)
LTG	TGB	Chmielewska, 2001[133] (TGB)	0.788 (95% CI: 0.262 to 2.287)
	Placebo	**Schapel, 1993[161]**	**15.00 (95% CI: 1.587 to 149.843)**
	Placebo	Sander, 1990[135]	2.000 (95% CI: 0.476 to 8.730)
	Placebo	**Messenheimer, 1994[158]**	**2.900 (95% CI: 1.530 to 5.608)**
	Placebo	Schmidt, 1993[91]	1.125 (95% CI: 0.533 to 2.401)
	Placebo	Boas, 1996[136]	1.625 (95% CI: 0.853 to 3.271)
	Placebo	Smith, 1993[55]	1.438 (95% CI: 0.831 to 2.511)
	Placebo	Binnie, 1987[50]	3.000 (95% CI: 0.272 to 35.055)
	Placebo	Binnie, 1989[159]	0.600 (95% CI: 0.168 to 2.105)
	Placebo	**Schachter, 1995[56]**	**2.800 (95% CI: 1.893 to 4.268)**
	Placebo	Veendrick-Meekes, 2000[137]	8.333 (95% CI: 0.915 to 83.244)
	Placebo	**Matsuo, 1993[142] (500 mg)**	**1.977 (95% CI: 1.305 to 3.068)**
	Placebo	Matsuo, 1993[142] (300 mg)	1.131 (95% CI: 0.682 to 1.880)
	CBZ	GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)	0.884 (95% CI: 0.545 to 1.444)
	VPA	GlaxoSmithKline, 2001 (Kerr)[122] (VPA)	1.536 (95% CI: 0.968 to 2.452)
	CBZ	Nieto-Barrera, 2001[119]	1.865 (95% CI: 0.808 to 4.383)
	PHT	Steiner, 1999[75]	0.803 (95% CI: 0.346 to 1.851)
	VPA	Gilliam, 1998[112]	0.902 (95% CI: 0.524 to 1.546)
	CBZ	Reunanen, 1996[120] (100 mg)	0.593 (95% CI: 0.248 to 1.409)
	CBZ	Reunanen, 1996[120] (200 mg)	0.439 (95% CI: 0.165 to 1.152)
	VPA	Biton, 2001[116]	1.395 (95% CI: 0.644 to 3.042)
	CBZ	Brodie, 1995[121]	0.716 (95% CI: 0.397 to 1.287)

continued

Drug	Comparator	Study	RR (95% CI)
	Conv.	GlaxoSmithKline, 2000[118]	0.619 (95% CI: 0.382 to 1.001)
	CBZ	Brodie, 1999[117]	0.588 (95% CI: 0.256 to 1.377)
	Conv.	Martinez, 2002[114]	0.509 (95% CI: 0.191 to 1.330)
LEV	Placebo	**Cereghino, 2000[143] (1000 mg)**	**2.354 (95% CI: 1.055 to 5.337)**
	Placebo	**Cereghino, 2000[143] (3000 mg)**	**2.687 (95% CI: 1.229 to 5.988)**
	Placebo	Betts, 2000[139] (2000 mg)	4.651 (95% CI: 0.434 to 51.229)
	Placebo	Betts, 2000[139] (4000 mg)	9.231 (95% CI: 0.934 to 95.285)
OXC	Placebo	**Barcs, 2000[70] (600mg)**	**1.954 (95% CI: 1.231 to 3.127)**
	Placebo	**Barcs, 2000[70] (1200mg)**	**2.474 (95% CI: 1.598 to 3.873)**
	Placebo	**Barcs, 2000[70] (2400mg)**	**3.344 (95% CI: 2.206 to 5.142)**
	PHT	Bill, 1997[124] (PHT)	0.824 (95% CI: 0.465 to 1.456)
	CBZ	Reinikainen, 1987[115] (CBZ)	0.186 (95% CI: 0.031 to 1.010)
	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	**Sachdeo, 1998[111]**	**8.750 (95% CI: 1.550 to 52.556)**
	Placebo	Schachter, 1999[78]	1.500 (95% CI: 0.598 to 3.809)
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Sachdeo, 1997[140] (16 mg b.d)	1.442 (95% CI: 0.891 to 2.351)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s)	0.971 (95% CI: 0.563 to 1.672)
	Placebo	Uthman, 1998[163] (16 mg)	1.790 (95% CI: 0.985 to 3.249)
	Placebo	**Uthman, 1998[163] (32 mg)**	**1.999 (95% CI: 1.169 to 3.470)**
	Placebo	Uthman, 1998[163] (56 mg)	1.809 (95% CI: 0.988 to 3.300)
	Placebo	**Kälviäinen, 1998[164]**	**2.750 (95% CI: 1.344 to 5.761)**
	LTG	Chmielewska, 2001[133]	1.269 (95% CI: 0.437 to 3.810)
TPM	Placebo	Barrett, 1997[76]	1.000 (95% CI: 0.366 to 2.729)
	Placebo	Biton, 1999[79]	0.701 (95% CI: 0.225 to 2.147)
	Placebo	Rosenfeld, 1996[41]	1.572 (95% CI: 0.852 to 3.110)
	Placebo	Faught, 1996[67] (200 mg)	1.231 (95% CI: 0.679 to 2.254)
	Placebo	Faught, 1996[67] (400 mg)	1.154 (95% CI: 0.628 to 2.136)
	Placebo	Faught, 1996[67] (600 mg)	1.204 (95% CI: 0.664 to 2.208)
	Placebo	Korean Topiramate Study Group, 1999[149]	0.945 (95% CI: 0.531 to 1.683)
	Placebo	Tassinari, 1996[42]	2.333 (95% CI: 0.730 to 7.766)
	Placebo	**Ben-Menachem, 1996[151]**	**6.000 (95% CI: 1.043 to 36.856)**
	Placebo	Yen, 2000[165]	2.000 (95% CI: 0.472 to 8.781)
	Placebo	**Privitera, 1996[68] (600 mg)**	**2.238 (95% CI: 1.051 to 4.925)**
	Placebo	**Privitera, 1996[68] (800 mg)**	**2.378 (95% CI: 1.128 to 5.194)**
	Placebo	**Privitera, 1996[68] (1000 mg)**	**2.571 (95% CI: 1.232 to 5.573)**
VGB	Placebo	McKee, 1993[54]	3.000 (95% CI: 0.463 to 20.242)
	Placebo	Tassinari, 1987[85]	7.000 (95% CI: 0.695 to 73.776)
	Placebo	Dean, 1999[154] (1 g)	0.783 (95% CI: 0.240 to 2.541)
	Placebo	Dean, 1999[154] (3 g)	2.250 (95% CI: 0.894 to 5.825)
	Placebo	Dean, 1999[154] (6 g)	2.250 (95% CI: 0.894 to 5.825)
	Placebo	Reynolds, 1991[141]	3.000 (95% CI: 0.272 to 35.055)
	Placebo	Grunewald, 1994[38]	3.136 (95% CI: 0.486 to 21.102)
	Placebo	Bruni, 2000[153]	1.697 (95% CI: 0.757 to 3.886)
	Placebo	Brodie, 1999[66]	1.431 (95% CI: 0.654 to 3.152)

Drowsiness

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	Sivenius, 1991[157] (900 mg)	1.125 (95% CI: 0.215 to 5.856)
	Placebo	**Sivenius, 1991[157] (1200 mg)**	**4.000 (95% CI: 1.002 to 16.289)**
LTG	Placebo	Sander, 1990[135]	1.333 (95% CI: 0.372 to 4.864)
	Placebo	Matsuo, 1996[328]	1.250 (95% CI: 0.473 to 4.482)
	Placebo	Veendrick-Meekes, 2000[137]	0.545 (95% CI: 0.186 to 1.634)
LEV	–	No data	
OXC	CBZ	Reinikainen, 1987[115] (CBZ)	0.958 (95% CI: 0.400 to 2.247)
TGB	–	No data	
TPM	–	No data	
VGB	Placebo	**Tartara, 1986[86]**	**7.000 (95% CI: 1.288 to 41.956)**
	Placebo	Rimmer, 1984[49]	3.500 (95% CI: 0.938 to 13.968)
	Placebo	Beran, 1996[87] (2 g) per protocol	1.750 (95% CI: 0.584 to 5.334)
	Placebo	Beran, 1996[87] (3 g) per protocol	1.800 (95% CI: 0.692 to 4.789)
	Placebo	Loiseau, 1986[83]	2.000 (95% CI: 0.472 to 8.781)
	Placebo	**Tassinari, 1987[85]**	**1.800 (95% CI: 1.023 to 3.322)**
	Placebo	Dean, 1999[154] (1 g)	0.815 (95% CI: 0.395 to 1.668)
	Placebo	Dean, 1999[154] (3 g)	0.938 (95% CI: 0.467 to 1.874)
	Placebo	Dean, 1999[154] (6 g)	1.108 (95% CI: 0.575 to 2.143)
	Placebo	Reynolds, 1991[141]	5.000 (95% CI: 0.517 to 53.466)
	Placebo	Bruni, 2000[153]	1.142 (95% CI: 0.500 to 2.631)
	Placebo	**French, 1996[155]**	**2.032 (95% CI: 1.140 to 3.681)**
	VPA	Brodie, 1999[66]	1.415 (95% CI: 0.874 to 2.309)

Fatigue

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	**UK Gabapentin Study Group, 1990[73]**	**18.371 (95% CI: 1.912 to 183.043)**
	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	1.585 (95% CI: 0.580 to 4.263)
	Placebo	US Gabapentin Study Group, 1993[138] (1200 mg)	1.525 (95% CI: 0.636 to 3.682)
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.815 (95% CI: 0.692 to 4.703)
	Placebo	Anhut, 1994[156] (900 mg)	2.515 (95% CI: 0.844 to 7.423)
LTG	TGB	Chmielewska, 2001[133] (TGB)	0.657 (95% CI: 0.258 to 1.587)
	Placebo	Beran, 1998[134]	0.200 (95% CI: 0.032 to 1.177)
	Placebo	Matsuo, 1996[328]	0.111 (95% CI: 0.011 to 1.015)
LEV	–	No data	
OXC	Placebo	**Barcs, 2000[70] (600 mg)**	**2.133 (95% CI: 1.125 to 4.074)**
	Placebo	Barcs, 2000[70] (1200 mg)	1.701 (95% CI: 0.877 to 3.318)
	Placebo	**Barcs, 2000[70] (2400 mg)**	**2.154 (95% CI: 1.141 to 4.101)**
	Placebo	Sachdeo, 1998[111]	1.531 (95% CI: 0.565 to 4.205)
	Placebo	Schachter, 1999[78]	5.000 (95% CI: 0.812 to 31.762)
TGB	LTG	Chmielewska, 2001[133]	1.523 (95% CI: 0.630 to 3.874)

continued

Drug	Comparator	Study	RR (95% CI)
TPM	Placebo	Barrett, 1997[76]	1.143 (95% CI: 0.471 to 2.788)
	Placebo	Biton, 1999[79]	2.453 (95% CI: 0.746 to 8.290)
	Placebo	**Rosenfeld, 1996[41]**	**3.018 (95% CI: 1.255 to 7.830)**
	Placebo	Faught, 1996[67] (200 mg)	1.000 (95% CI: 0.329 to 3.042)
	Placebo	Faught, 1996[67] (400 mg)	0.600 (95% CI: 0.165 to 2.145)
	Placebo	Faught, 1996[67] (600 mg)	1.761 (95% CI: 0.671 to 4.717)
	Placebo	Tassinari, 1996[42]	2.333 (95% CI: 0.730 to 7.766)
	Placebo	Sharief, 1996[148]	1.565 (95% CI: 0.537 to 4.671)
	Placebo	**Ben-Menachem, 1996[151]**	**2.200 (95% CI: 1.351 to 3.894)**
	Placebo	**Privitera, 1996[68] (600 mg)**	**4.406 (95% CI: 1.728 to 11.814)**
	Placebo	Privitera, 1996[68] (800 mg)	2.693 (95% CI: 0.984 to 7.619)
	Placebo	**Privitera, 1996[68] (1000 mg)**	**2.750 (95% CI: 1.005 to 7.775)**
VGB	Placebo	**McKee, 1993[54]**	**7.000 (95% CI: 1.265 to 42.157)**
	Placebo	Beran, 1996[87] (2 g) per protocol	1.400 (95% CI: 0.501 to 3.951)
	Placebo	Beran, 1996[87] (3 g) per protocol	2.500 (95% CI: 0.595 to 10.784)
	Placebo	Dean, 1999[154] (1 g)	1.196 (95% CI: 0.559 to 2.578)
	Placebo	Dean, 1999[154] (3 g)	1.477 (95% CI: 0.719 to 3.085)
	Placebo	**Dean, 1999[154] (6 g)**	**2.159 (95% CI: 1.130 to 4.269**)
	Placebo	Grunewald, 1994[38]	1.394 (95% CI: 0.386 to 5.111)
	Placebo	Bruni, 2000[153]	1.523 (95% CI: 0.746 to 3.170)
	Placebo	French, 1996[155]	1.467 (95% CI: 0.763 to 2.849)
	VPA	Brodie, 1999[66]	1.062 (95% CI: 0.546 to 2.067)

Headache

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	Sivenius, 1991[157] (900 mg)	0.562 (95% CI: 0.077 to 3.948)
	Placebo	Sivenius, 1991[157] (1200 mg)	0.380 (95% CI: 0.035 to 3.660)
	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	1.541 (95% CI: 0.719 to 3.246)
	Placebo	US Gabapentin Study Group, 1993[138] (1200 mg)	0.728 (95% CI: 0.327 to 1.612)
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.664 (95% CI: 0.794 to 3.439)
LTG	TGB	Chmielewska, 2001[133] (TGB)	0.886 (95% CI: 0.364 to 2.095)
	Placebo	Schapel, 1993[161]	3.000 (95% CI: 0.741 to 12.548)
	Placebo	Sander, 1990[135]	2.000 (95% CI: 0.476 to 8.730)
	Placebo	Messenheimer, 1994[158]	1.143 (95% CI: 0.598 to 2.192)
	Placebo	Schmidt, 1993[91]	0.688 (95% CI: 0.400 to 1.124)
	Placebo	Boas, 1996[136]	0.722 (95% CI: 0.373 to 1.381)
	Placebo	**Smith, 1993[55]**	**13.000 (95% CI: 2.273 to 76.822)**
	Placebo	Binnie, 1987[50]	3.000 (95% CI: 0.272 to 35.055)
	Placebo	Binnie, 1989[159]	2.500 (95% CI: 0.603 to 10.708)
	Placebo	**Jawad, 1989[160]**	**6.000 (95% CI: 1.060 to 36.680)**
	Placebo	Matsuo, 1996[328]	0.833 (95% CI: 0.371 to 2.275)
	Placebo	Matsuo, 1993[142] (500 mg)	1.227 (95% CI: 0.739 to 2.050)
	Placebo	Matsuo, 1993[142] (300 mg)	1.245 (95% CI: 0.750 to 2.077)
	CBZ	GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)	0.758 (95% CI: 0.477 to 1.208)
	VPA	GlaxoSmithKline, 2001 (Kerr)[122] (VPA)	1.349 (95% CI: 0.950 to 1.925)
	CBZ	Nieto Barrera, 2001[119]	1.123 (95% CI: 0.618 to 2.072)
	PHT	Steiner, 1999[75]	0.552 (95% CI: 0.264 to 1.136)
	VPA	Gilliam, 1998[112]	0.855 (95% CI: 0.445 to 1.635)
	CBZ	Reunanen, 1996[120] (100 mg)	1.942 (95% CI: 0.999 to 3.815)
	CBZ	Reunanen, 1996[120] (200 mg)	1.916 (95% CI: 0.980 to 3.783)
	VPA	Biton, 2001[116]	1.517 (95% CI: 0.968 to 2.409)
	CBZ	Brodie, 1995[121]	1.200 (95% CI: 0.808 to 1.790)

continued

Drug	Comparator	Study	RR (95% CI)
	Conv.	GlaxoSmithKline, 2000[118]	1.399 (95% CI: 0.989 to 1.983)
	CBZ	Brodie, 1999[117]	0.529 (95% CI: 0.225 to 1.266)
	VPA	**GlaxoSmithKline, 2001[62] (Tamhe)**	**2.336 (95% CI: 1.042 to 5.374)**
	Conv.	Martinez, 2002[114]	0.509 (95% CI: 0.170 to 1.497)
LEV	Placebo	Cereghino, 2000[143] (1000 mg)	1.071 (95% CI: 0.621 to 1.854)
	Placebo	Cereghino, 2000[143] (3000 mg)	1.040 (95% CI: 0.602 to 1.801)
	Placebo	Shorvon, 2000[145] (1000 mg)	1.479 (95% CI: 0.701 to 3.138)
	Placebo	Shorvon, 2000[145] (2000 mg)	1.796 (95% CI: 0.879 to 3.702)
	Placebo	**Ben-Menachem, 2000[144] (3000 mg)**	**0.320 (95% CI: 0.120 to 0.800)**
OXC	Placebo	Barcs, 2000[70] (600 mg)	1.348 (95% CI: 0.957 to 1.908)
	Placebo	Barcs, 2000[70] (1200 mg)	1.138 (95% CI: 0.795 to 1.631)
	Placebo	Barcs, 2000[70] (2400 mg)	0.970 (95% CI: 0.663 to 1.418)
	PHT	Bill, 1997[124] (PHT)	0.746 (95% CI: 0.441 to 1.257)
	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Sachdeo, 1998[111]	1.367 (95% CI: 0.429 to 4.381)
	Placebo	Schachter, 1999[78]	1.000 (95% CI: 0.463 to 2.159)
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Richens, 1995[146]	2.000 (95% CI: 0.452 to 9.025)
	Placebo	Sachdeo, 1997[140] (16 mg b.d)	0.721 (95% CI: 0.340 to 1.520)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s.)	0.873 (95% CI: 0.430 to 1.771)
	Placebo	Uthman, 1998[163] (16 mg)	0.895 (95% CI: 0.421 to 1.863)
	Placebo	Uthman, 1998[163] (32 mg)	1.103 (95% CI: 0.587 to 2.075)
	Placebo	Uthman, 1998[163] (56 mg)	0.745 (95% CI: 0.327 to 1.653)
	Placebo	Kälviäinen, 1998[164]	1.154 (95% CI: 0.597 to 2.240)
	LTG	Chmielewska, 2001[133]	1.128 (95% CI: 0.477 to 2.745)
TPM	Placebo	Barrett, 1997[76]	1.125 (95% CI: 0.494 to 2.577)
	Placebo	Biton, 1999[79]	0.657 (95% CI: 0.242 to 1.748)
	Placebo	Rosenfeld, 1996[41]	0.844 (95% CI: 0.534 to 1.413)
	Placebo	Faught, 1996[67] (200 mg)	1.000 (95% CI: 0.526 to 1.900)
	Placebo	Faught, 1996[67] (400 mg)	1.077 (95% CI: 0.577 to 2.018)
	Placebo	Faught, 1996[67] (600 mg)	0.978 (95% CI: 0.514 to 1.862)
	Placebo	Korean Topiramate Study Group, 1999[149]	1.575 (95% CI: 0.622 to 4.029)
	Placebo	Tassinari, 1996[42]	2.667 (95% CI: 0.858 to 8.687)
	Placebo	Sharief, 1996[148]	0.626 (95% CI: 0.179 to 2.120)
	Placebo	Ben-Menachem, 1996[151]	0.600 (95% CI: 0.253 to 1.375)
	Placebo	Yen, 2000[165]	0.333 (95% CI: 0.049 to 2.152)
	Placebo	Privitera, 1996[68] (600 mg)	1.044 (95% CI: 0.589 to 1.860)
	Placebo	Privitera, 1996[68] (800 mg)	0.849 (95% CI: 0.456 to 1.571)
	Placebo	Privitera, 1996[68] (1000 mg)	0.600 (95% CI: 0.292 to 1.205)
VGB	Placebo	Beran, 1996[87] (2 g) per protocol	1.250 (95% CI: 0.384 to 4.100)
	Placebo	Tassinari, 1987[85]	3.000 (95% CI: 0.455 to 20.395)
	Placebo	Dean, 1999[154] (1 g)	0.815 (95% CI: 0.280 to 2.357)
	Placebo	Dean, 1999[154] (3 g)	1.023 (95% CI: 0.372 to 2.811)
	Placebo	Dean, 1999[154] (6 g)	1.364 (95% CI: 0.535 to 3.512)
	Placebo	Reynolds, 1991[141]	0.333 (95% CI: 0.029 to 3.674)
	Placebo	Grunewald, 1994[38]	0.261 (95% CI: 0.041 to 1.579)
	Placebo	Bruni, 2000[153]	1.447 (95% CI: 0.792 to 2.695)
	Placebo	French, 1996[155]	1.304 (95% CI: 0.722 to 2.374)
	VPA	Brodie, 1999[66]	0.859 (95% CI: 0.434 to 1.694)

Nausea

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	TGB	Chmielewska, 2001[133] (TGB)	0.591 (95% CI: 0.134 to 2.503)
	Placebo	Schapel, 1993[161]	2.333 (95% CI: 0.709 to 7.900)
	Placebo	Messenheimer, 1994[158]	1.455 (95% CI: 0.724 to 2.942)
	Placebo	Schmidt, 1993[91]	3.500 (95% CI: 0.943 to 13.932)
	Placebo	Boas, 1996[136]	3.467 (95% CI: 0.565 to 22.430)
	Placebo	**Smith, 1993[55]**	**2.556 (95% CI: 1.293 to 5.159)**
	Placebo	Binnie, 1989[159]	0.333 (95% CI: 0.049 to 2.207)
	Placebo	Jawad, 1989[160]	5.000 (95% CI: 0.478, to 54.669)
	Placebo	Schachter, 1995[56]	1.440 (95% CI: 0.905 to 2.348)
	Placebo	**Matsuo, 1993[142] (500 mg)**	**6.083 (95% CI: 2.033 to 18.826)**
	Placebo	**Matsuo, 1993[142] (300 mg)**	**4.455 (95% CI: 1.439 to 14.180)**
	CBZ	GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)	0.898 (95% CI: 0.491 to 1.655)
	VPA	**GlaxoSmithKline, 2001 (Kerr)[122] (VPA)**	**0.471 (95% CI: 0.301 to 0.734)**
	VPA	Gilliam, 1998[112]	0.921 (95% CI: 0.487 to 1.736)
	VPA	Biton, 2001[116]	0.800 (95% CI: 0.425 to 1.493)
	CBZ	Brodie, 1995[121]	1.416 (95% CI: 0.793 to 2.541)
	Conv.	GlaxoSmithKline, 2000[118]	0.734 (95% CI: 0.458 to 1.173)
	Conv.	Martinez, 2002[114]	1.018 (95% CI: 0.467 to 2.217)
LEV	Placebo	Betts, 2000[139] (2000 mg)	0.310 (95% CI: 0.026 to 3.675)
	Placebo	Betts, 2000[139] (4000 mg)	5.132 (95% CI: 0.846 to 32.424)
OXC	Placebo	**Barcs, 2000[70] (600 mg)**	**2.943 (95% CI: 1.387 to 6.306)**
	Placebo	**Barcs, 2000[70] (1200 mg)**	**6.560 (95% CI: 3.298 to 13.270)**
	Placebo	**Barcs, 2000[70] (2400 mg)**	**8.451 (95% CI: 4.296 to 16.929)**
	PHT	Bill, 1997[124] (PHT)	0.818 (95% CI: 0.413, 1.615)
	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Sachdeo, 1998[11]	0.729 (95% CI: 0.237 to 2.200)
	Placebo	**Schachter, 1999[78]**	**3.333 (95% CI: 1.063 to 10.809)**
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Uthman, 1998[163] (16 mg)	1.492 (95% CI: 0.641 to 3.448)
	Placebo	Uthman, 1998[163] (32 mg)	0.689 (95% CI: 0.264 to 1.783)
	Placebo	Uthman, 1998[163] (56 mg)	0.887 (95% CI: 0.323 to 2.383)
	Placebo	Kälviäinen, 1998[164]	1.125 (95% CI: 0.471 to 2.693)
	LTG	Chmielewska, 2001[133]	1.692 (95% CI: 0.400 to 7.467)
TPM	Placebo	Barrett, 1997[76]	2.000 (95% CI: 0.453 to 9.010)
	Placebo	**Biton, 1999[79]**	**11.55 (95% CI: 1.190 to 117.472)**
	Placebo	Tassinari, 1996[42]	4.000 (95% CI: 0.646 to 25.895)
VGB	Placebo	Dean, 1999[154] (1 g)	0.978 (95% CI: 0.321 to 2.979)
	Placebo	Dean, 1999[154] (3 g)	0.205 (95% CI: 0.032 to 1.251)
	Placebo	Dean, 1999[154] (6 g)	0.409 (95% CI: 0.095 to 1.726)

Nausea and/or vomiting

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	1.438 (95% CI: 0.580 to 3.505)
	Placebo	US Gabapentin Study Group, 1993[138] (1200 mg)	0.647 (95% CI: 0.247 to 1.681)
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.008 (95% CI: 0.367 to 2.704)
LTG	–	No data	
LEV	–	No data	
OXC	–	No data	
TGB	–	No data	
TPM	Placebo	Barrett, 1997[76]	1.000 (95% CI: 0.331 to 3.020)
	Placebo	Korean Topiramate Study Group, 1999[149]	2.025 (95% CI: 0.896 to 4.650)
VGB	–	No data	

Paraesthesia

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	TGB	Chmielewska, 2001[133] (TGB)	1.182 (95% CI: 0.294 to 4.715)
LEV	–	No data	
OXC	Placebo	Sachdeo, 1998[111]	7.636 (95% CI: 0.754 to 80.524)
TGB	TGB	Chmielewska, 2001[133] (LTG)	0.846 (95% CI: 0.212 to 3.400)
TPM	Placebo	**Rosenfeld, 1996[41]**	**2.578 (95% CI: 1.063 to 6.729)**
	Placebo	**Faught, 1996[67] (200 mg)**	**8.000 (95% CI: 1.387 to 48.388)**
	Placebo	**Faught, 1996[67] (400 mg)**	**9.000 (95% CI: 1.580 to 53.952)**
	Placebo	Faught, 1996[67] (600 mg)	3.913 (95% CI: 0.617 to 25.569)
	Placebo	Ben-Menachem, 1996[151]	5.000 (95% CI: 0.844 to 31.351)
	Placebo	**Privitera, 1996[68] (600 mg)**	**3.590 (95% CI: 1.168 to 11.479)**
	Placebo	Privitera, 1996[68] (800 mg)	2.938 (95% CI: 0.926 to 9.633)
	Placebo	Privitera, 1996[68] (1000 mg)	2.000 (95% CI: 0.583 to 7.003)
VGB	–	No data	

Rash

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	Placebo	Schapel, 1993[161]	1.500 (95% CI: 0.488 to 4.674)
	Placebo	Messenheimer, 1994[158]	2.333 (95% CI: 0.970 to 5.691)
	Placebo	Schachter, 1995[56]	1.844 (95% CI: 0.825 to 4.226)
	Placebo	Matsuo, 1993[142] (500 mg)	1.014 (95% CI: 0.388 to 2.647)
	Placebo	Matsuo, 1993[142] (300 mg)	1.763 (95% CI: 0.760 to 4.140)
	CBZ	**GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)**	**1.895 (95% CI: 1.057 to 3.445)**
	CBZ	Nieto Barrera, 2001[119]	0.932 (95% CI: 0.489 to 1.803)
	PHT	Steiner, 1999[75]	1.473 (95% CI: 0.668 to 3.263)
	CBZ	Brodie, 1995[121]	0.985 (95% CI: 0.601 to 1.614)
	CBZ	**Brodie, 1999[66]**	**0.366 (95% CI: 0.150 to 0.902)**
	Conv.	**Martinez, 2002[114]**	**7.123 (95% CI: 1.200 to 43.743)**
	Conv,	**Brodie, 2002[93]**	**2.392 (95% CI: 1.042 to 5.534)**
LEV	–	No data	
OXC	PHT	Bill, 1997[124] (PHT)	0.755 (95% CI: 0.375 to 1.515)
TGB	–	No data	
TPM	Placebo	Barrett, 1997[76]	0.250 (95% CI: 0.038 to 1.577)
VGB	–	No data	

Somnolence

Drug	Comparator	Study	RR (95% CI)
GBP	LTG	**Crawford, 2001[131] (LTG)**	**21.375 (95% CI: 2.291 to 211.135)**
	Placebo	**UK Gabapentin Study Group, 1990[73]**	**3.246 (95% CI: 1.003 to 10.744)**
	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	0.616 (95% CI: 0.216 to 1.697)
	Placebo	**US Gabapentin Study Group, 1993[138] (1200 mg)**	**2.911 (95% CI: 1.644 to 5.266)**
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.664 (95% CI: 0.794 to 3.439)
	Placebo	Anhut, 1994[156] (900 mg)	1.813 (95% CI: 0.989 to 3.361)
	Placebo	Anhut, 1994[156] (1200 mg)	1.129 (95% CI: 0.484 to 2.558)
LTG	TGB	Chmielewska, 2001[133] (TGB)	0.675 (95% CI: 0.232 to 1.879)
	GBP	Crawford, 2001[131] (GBP)	0.047 (95% CI: 0.005 to 0.437)
	Placebo	Schapel, 1993[161]	0.500 (95% CI: 0.144 to 1.701)
	Placebo	**Messenheimer, 1994[158]**	**3.750 (95% CI: 1.367 to 10.496)**
	Placebo	**Beran, 1998[134]**	**15.000 (95% CI: 1.647 to 148.967)**
	Placebo	Smith, 1993[55]	1.625 (95% CI: 0.731 to 3.649)
	Placebo	Binnie, 1989[159]	0.667 (95% CI: 0.216 to 2.018)
	Placebo	**Jawad, 1989[160]**	**6.000 (95% CI: 1.060 to 36.68)**
	Placebo	Schachter, 1995[56]	1.970 (95% CI: 0.990 to 4.023)
	Placebo	Matsuo, 1993[142] (500 mg)	1.419 (95% CI: 0.497 to 4.078)
	Placebo	**Matsuo, 1993[142] (300 mg)**	**3.085 (95% CI: 1.241 to 7.854)**
	CBZ	**GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)**	**0.616 (95% CI: 0.384 to 0.990)**
	VPA	**GlaxoSmithKline, 2001 (Kerr)[122] (VPA)**	**0.607 (95% CI: 0.382 to 0.963)**
	CBZ	**Nieto Barrera, 2001[119]**	**0.347 (95% CI: 0.162 to 0.748)**
	PHT	**Steiner, 1999[75]**	**0.245 (95% CI: 0.108 to 0.544)**
	VPA	Gilliam, 1998[112]	0.567 (95% CI: 0.243 to 1.302)
	CBZ	**Reunanen, 1996[120] (100 mg)**	**0.356 (95% CI: 0.159 to 0.786)**

continued

Drug	Comparator	Study	RR (95% CI)
	CBZ	**Reunanen, 1996[120] (200 mg)**	**0.369 (95% CI: 0.165 to 0.813)**
	VPA	**Biton, 2001[116]**	**0.392 (95% CI: 0.166 to 0.904)**
	CBZ	**Brodie, 1995[121]**	**0.543 (95% CI: 0.311 to 0.940)**
	Conv.	**GlaxoSmithKline, 2000[118]**	**0.451 (95% CI: 0.336 to 0.602)**
	CBZ	**Brodie, 1999[117]**	**0.403 (95% CI: 0.205 to 0.800)**
	VPA	**GlaxoSmithKline, 2001[62] (Tamhe)**	**0.372 (95% CI: 0.172 to 0.806)**
	Conv.	**Martinez, 2002[114]**	**0.204 (95% CI: 0.051 to 0.778)**
LEV	Placebo	Cereghino, 2000[143] (1000 mg)	1.491 (95% CI: 0.799 to 2.810)
	Placebo	Cereghino, 2000[143] (3000 mg)	1.375 (95% CI: 0.730 to 2.611)
	Placebo	Shorvon, 2000[145] (1000 mg)	2.113 (95% CI: 0.783 to 5.758)
	Placebo	Shorvon, 2000[145] (2000 mg)	2.536 (95% CI: 0.967 to 6.726)
	Placebo	Betts, 2000[139] (2000 mg)	1.021 (95% CI: 0.496 to 2.118)
	Placebo	Betts, 2000[139] (4000 mg)	1.745 (95% CI: 0.939 to 3.339)
	Placebo	Ben-Menachem, 2000[144] (3000 mg)	1.600 (95% CI: 0.550 to 4.670)
OXC	Placebo	**Barcs, 2000[70] (600 mg)**	**1.689 (95% CI: 1.019 to 2.815)**
	Placebo	**Barcs, 2000[70] (1200 mg)**	**2.333 (95% CI: 1.461 to 3.763)**
	Placebo	**Barcs, 2000[70] (2400 mg)**	**2.784 (95% CI: 1.767 to 4.439)**
	PHT	Bill, 1997[124] (PHT)	1.007 (95% CI: 0.699 to 1.450)
	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Sachdeo, 1998[111]	0.547 (95% CI: 0.122 to 2.385)
	Placebo	**Schachter, 1999[78]**	**17.000 (95% CI: 1.791 to 169.141)**
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Sachdeo, 1997[140] (16 mg b.d.)	1.442 (95% CI: 0.779 to 2.686)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s.)	1.456 (95% CI: 0.787 to 2.711)
	Placebo	Uthman, 1998[163] (16 mg)	1.026 (95% CI: 0.513 to 2.014)
	Placebo	Uthman, 1998[163] (32 mg)	1.163 (95% CI: 0.640 to 2.119)
	Placebo	Uthman, 1998[163] (56 mg)	1.297 (95% CI: 0.677 to 2.451)
	Placebo	Kälviäinen, 1998[164]	0.917 (95% CI: 0.437 to 1.918)
	LTG	Chmielewska, 2001[133]	1.481 (95% CI: 0.532 to 4.306)
TPM	Placebo	Barrett, 1997[76]	1.286 (95% CI: 0.546 to 3.061)
	Placebo	Biton, 1999[79]	1.752 (95% CI: 0.730 to 4.291)
	Placebo	Guberman, 2002[150]	1.749 (95% CI: 0.851 to 3.681)
	Placebo	**Rosenfeld, 1996[41]**	**4.192 (95% CI: 1.529 to 12.427**)
	Placebo	**Faught, 1996[67] (200 mg)**	**3.250 (95% CI: 1.225 to 8.979)**
	Placebo	**Faught, 1996[67] (400 mg)**	**3.000 (95% CI: 1.117 to 8.369)**
	Placebo	**Faught, 1996[67] (600 mg)**	**3.424 (95% CI: 1.304 to 9.389)**
	Placebo	**Korean Topiramate Study Group, 1999[149]**	**2.126 (95% CI: 1.003 to 4.586)**
	Placebo	Tassinari, 1996[42]	1.750 (95% CI: 0.609 to 5.175)
	Placebo	Sharief, 1996[148]	2.087 (95% CI: 0.774 to 5.888)
	Placebo	Yen, 2000[165]	2.000 (95% CI: 0.472 to 8.781)
	Placebo	Privitera, 1996[68] (600 mg)	0.979 (95% CI: 0.355 to 2.705)
	Placebo	**Privitera, 1996[68] (800 mg)**	**2.448 (95% CI: 1.084 to 5.722)**
	Placebo	**Privitera, 1996[68] (1000 mg)**	**2.667 (95% CI: 1.194 to 6.178)**
VGB	–	No data	

Tremor (slight)

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	Sivenius, 1991[157] (1200mg)	2.000 (95% CI: 0.219 to 17.635)
	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	0.822 (95% CI: 0.277 to 2.373)
	Placebo	US Gabapentin Study Group, 1993[138] (1200 mg)	1.617 (95% CI: 0.760 to 3.475)
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.412 (95% CI: 0.569 to 3.443)
LTG	Placebo	Binnie, 1989[159]	0.333 (95% CI: 0.049 to 2.207)
	Placebo	Jawad, 1989[160]	5.000 (95% CI: 0.478 to 54.669)
	Placebo	Matsuo, 1996[328]	1.667 (95% CI: 0.167 to 19.244)
	CBZ	**GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)**	**2.249 (95% CI: 1.019 to 5.030)**
	VPA	**GlaxoSmithKline, 2001 (Kerr)[122] (VPA)**	**0.344 (95% CI: 0.193 to 0.611)**
	VPA	Gilliam, 1998[112]	0.648 (95% CI: 0.289 to 1.436)
	VPA	**Biton, 2001[116]**	**0.105 (95% CI: 0.028 to 0.378)**
	Conv.	Martinez, 2002[114]	0.370 (95% CI: 0.130 to 1.028)
LEV	–	No data	
OXC	Placebo	Barcs, 2000[70] (600 mg)	0.877 (95% CI: 0.315, 2.442)
	Placebo	Barcs, 2000[70] (1200 mg)	1.944 (95% CI: 0.828, 4.591)
	Placebo	**Barcs, 2000[70] (2400 mg)**	**3.551 (95% CI: 1.622, 7.866)**
	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Uthman, 1998[163] (16mg)	2.486 (95% CI: 0.678 to 9.142)
	Placebo	**Uthman, 1998[163] (32 mg)**	**4.481 (95% CI: 1.432 to 14.337)**
	Placebo	**Uthman, 1998[163] (56 mg)**	**6.386 (95% CI: 2.034 to 20.417)**
TPM	–	No data	
VGB	Placebo	Dean, 1999[154] (1 g)	0.699 (95% CI: 0.249 to 1.942)
	Placebo	Dean, 1999[154] (3 g)	1.023 (95% CI: 0.403 to 2.593)
	Placebo	Dean, 1999[154] (6 g)	1.023 (95% CI: 0.403 to 2.593)
	Placebo	Grunewald, 1994[38]	0.697 (95% CI: 0.148 to 3.209)
	Placebo	**French, 1996[155]**	**2.935 (95% CI: 1.043 to 8.409)**

Vomiting

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	Placebo	Schapel, 1993[161]	2.000 (95% CI: 0.588 to 6.961)
	Placebo	Boas, 1996[136]	1.733 (95% CI: 0.403 to 7.708)
	Placebo	**Smith, 1993[55]**	**7.000 (95% CI: 1.862 to 27.105)**
	Placebo	**Matsuo, 1993[142] (500 mg)**	**4.394 (95% CI: 1.419 to 13.987)**
	Placebo	Matsuo, 1993[142] (300 mg)	2.742 (95% CI: 0.826 to 9.269)
	VPA	Gilliam, 1998[112]	1.805 (95% CI: 0.774 to 4.253)
	VPA	Biton, 2001[116]	0.418 (95% CI: 0.144 to 1.191)
LEV	–	No data	
OXC	Placebo	**Barcs, 2000[70] (600 mg)**	**2.815 (95% CI: 1.321 to 6.059)**
	Placebo	**Barcs, 2000[70] (1200 mg)**	**5.346 (95% CI: 2.657 to 10.924)**
	Placebo	**Barcs, 2000[70] (2400 mg)**	**7.208 (95% CI: 3.638 to 14.530)**
	Placebo	Sachdeo, 1998[111]	0.365 (95% CI: 0.053 to 2.407)
	Placebo	Schachter, 1999[78]	2.500 (95% CI: 0.588 to 10.857)
TGB	CBZ	**Sommerville, 1998[129] (CBZ)**	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Uthman, 1998[163] (16 mg)	0.995 (95% CI: 0.383 to 2.539)
	Placebo	Uthman, 1998[163] (32 mg)	0.804 (95% CI: 0.322 to 1.997)
	Placebo	Uthman, 1998[163] (56 mg)	0.532 (95% CI: 0.160 to 1.721)
TPM	–	No data	
VGB		No data	

Weight decrease

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	Placebo	Schmidt, 1993[91]	5.000 (95% CI: 0.479 to 54.629)
LEV	–	No data	
OXC	–	No data	
TGB	–	No data	
TPM	Placebo	Barrett, 1997[76]	2.500 (95% CI: 0.596 to 10.775)
	Placebo	**Biton, 1999[79]**	**6.308 (95% CI: 1.064 to 39.068)**
	Placebo	Tassinari, 1996[42]	2.500 (95% CI: 0.609 to 10.649)
	Placebo	Sharief, 1996[148]	3.130 (95% CI: 0.813 to 12.754)
	Placebo	Ben-Menachem, 1996[151]	5.000 (95% CI: 0.844 to 31.351)
VGB	–	No data	

Weight increase

Drug	Comparator	Study	RR (95% CI)
GBP	–	No data	
LTG	VPA	Biton, 2001[116]	0.299 (95% CI: 0.072 to 1.210)
	VPA	**GlaxoSmithKline, 2001[62] (Tamhe)**	**0.149 (95% CI: 0.052 to 0.423)**
	GBP	**Brodie, 2002[93]**	**0.476 (95% CI: 0.235 to 0.952)**
LEV	–	No data	
OXC	–	No data	
TGB	–	No data	
TPM	–	No data	
VGB	Placebo	**Beran, 1996[87] (2 g) per protocol**	**6.000 (95% CI: 1.001 to 37.315)**
	Placebo	Dean, 1999[154] (1 g)	1.467 (95% CI: 0.306 to 7.117)
	Placebo	Dean, 1999[154] (3 g)	1.534 (95% CI: 0.320 to 7.432)
	Placebo	Dean, 1999[154] (6 g)	2.557 (95% CI: 0.606 to 11.056)
	Placebo	Grunewald, 1994[38]	2.091 (95% CI: 0.494 to 9.160)
	Placebo	**Bruni, 2000[153]**	**6.397 (95% CI: 1.082 to 39.284)**
	VPA	Brodie, 1999[66]	0.762 (95% CI: 0.355 to 1.629)

Withdrawals

Limiting adverse events

Drug	Comparator	Study	RR (95% CI)
GBP	Placebo	**Crawford, 2001[131] (LTG)**	**10.125 (95% CI: 1.019 to 104.554)**
	Placebo	US Gabapentin Study Group, 1993[138] (600 mg)	1.009 (95% CI: 0.403 to 2.461)
	Placebo	**US Gabapentin Study Group, 1993[138] (1200 mg)**	**2.293 (95% CI: 1.224 to 4.371)**
	Placebo	US Gabapentin Study Group, 1993[138] (1800 mg)	1.650 (95% CI: 0.757 to 3.545)
	Placebo	**Anhut, 1994[156] (900 mg)**	**3.928 (95% CI: 1.234 to 12.726)**
	Placebo		
LTG	GBP	**Crawford, 2001[131] (GBP)**	**0.099 (95% CI: 0.010 to 0.981)**
	Placebo	Sander, 1990[135]	3.000 (95% CI: 0.259 to 35.757)
	Placebo	Messenheimer, 1994[158]	5.000 (95% CI: 0.794 to 32.006)
	Placebo	Boas, 1996[136]	1.156 (95% CI: 0.315 to 4.321)
	Placebo	Beran, 1998[134]	5.000 (95% CI: 0.476 to 54.740)
	Placebo	Stolarek, 1994[162]	0.333 (95% CI: 0.028 to 3.704)
	Placebo	Smith, 1993[55]	1.707 (95% CI: 0.578 to 5.153)
	Placebo	Binnie, 1989[159]	3.353 (95% CI: 0.292 to 39.739)
	Placebo	Jawad, 1989[160]	3.000 (95% CI: 0.268 to 35.269)
	Placebo	Schachter, 1995[56]	1.043 (95% CI: 0.522 to 2.131)
	Placebo	Matsuo, 1996[328]	1.667 (95% CI: 0.167 to 19.244)
	Placebo	Veendrick-Meekes, 2000[137]	0.545 (95% CI: 0.102 to 2.981)
	Placebo	**Matsuo, 1993[142] (500 mg)**	**10.139 (95% CI: 1.748 to 60.755)**
		Matsuo, 1993[142] (300 mg)	3.085 (95% CI: 0.453 to 21.281)
	Placebo	GlaxoSmithKline, 2001 (Kerr)[122] (CBZ)	0.827 (95% CI: 0.505 to 1.361)
	CBZ	GlaxoSmithKline, 2001 (Kerr)[122] (VPA)	0.820 (95% CI: 0.556 to 1.211)
	VPA	Nieto Barrera, 2001[119]	0.625 (95% CI: 0.372 to 1.060)
	CBZ	Steiner, 1999[75]	0.798 (95% CI: 0.418 to 1.508)
	PHT	**Gilliam, 1998[112]**	**2.632 (95% CI: 1.118 to 6.308)**
	VPA	Reunanen, 1996[120] (100 mg)	0.424 (95% CI: 0.160 to 1.113)

continued

Drug	Comparator	Study	RR (95% CI)
	CBZ	Reunanen, 1996[120] (200 mg)	0.439 (95% CI: 0.165 to 1.152)
	CBZ	Biton, 2001[116]	0.697 (95% CI: 0.271 to 1.778)
	VPA	**Brodie, 1995[121]**	**0.535 (95% CI: 0.323 to 0.875)**
	CBZ	GlaxoSmithKline, 2000[118]	0.981 (95% CI: 0.653 to 1.474)
	Conv.	**Brodie, 1999[117]**	**0.424 (95% CI: 0.250 to 0.725)**
	CBZ	GlaxoSmithKline, 2001[62] (Tamhe)	1.289 (95% CI: 0.541 to 3.131)
	VPA	Martinez, 2002[114]	0.611 (95% CI: 0.293 to 1.252)
	Conv.	Brodie, 2002[93]	1.416 (95% CI: 0.795 to 2.528)
	GBP		
LEV	Placebo	Cereghino, 2000[143] (1000 mg)	1.163 (95% CI: 0.389 to 3.491)
	Placebo	Cereghino, 2000[143] (3000mg)	1.317 (95% CI: 0.456 to 3.822)
	Placebo	Shorvon, 2000[145] (1000 mg)	1.409 (95% CI: 0.527 to 3.778)
	Placebo	**Shorvon, 2000[145] (2000 mg)**	**2.642 (95% CI: 1.103 to 6.405)**
	Placebo	Betts, 2000[139] (2000 mg)	1.702 (95% CI: 0.725 to 4.114)
	Placebo	Betts, 2000[139] (4000 mg)	0.855 (95% CI: 0.297 to 2.442)
OXC	Placebo	Barcs, 2000[70] (600 mg)	1.365 (95% CI: 0.732 to 2.554)
	Placebo	**Barcs, 2000[70] mg)**	**4.147 (95% CI: 2.497 to 6.993)**
	Placebo	**Barcs, 2000[70] (2400 mg)**	**7.689 (95% CI: 4.766 to 12.65)**
	PHT	**Bill, 1997[124] (PHT)**	**0.319 (95% CI: 0.124 to 0.812)**
	CBZ	Loiseau, 1998[72] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Sachdeo, 1998[111]	1.641 (95% CI: 0.346 to 7.859)
	Placebo	Schachter, 1999[78]	3.000 (95% CI: 0.252 to 36.174)
TGB	CBZ	Sommerville, 1998[129] (CBZ)	[Data have been designated commercial-in-confidence and have been removed]
	PHT	Sommerville, 1998[129] (PHT)	[Data have been designated commercial-in-confidence and have been removed]
	Placebo	Richens, 1995[146]	3.360 (95% CI: 0.558 to 21.617)
	Placebo	Crawford, 2001[147]	2.000 (95% CI: 0.272 to 14.923)
	Placebo	Sachdeo, 1997[140] (16 mg b.d.)	2.019 (95% CI: 0.875 to 4.708)
	Placebo	Sachdeo, 1997[140] (8 mg q.d.s.)	1.456 (95% CI: 0.595 to 3.581)
	Placebo	Uthman, 1998[163] (16 mg)	0.852 (95% CI: 0.274 to 2.600)
	Placebo	Uthman, 1998[163] (32 mg)	1.920 (95% CI: 0.829 to 4.498)
	Placebo	Uthman, 1998[163] (56 mg)	2.053 (95% CI: 0.832 to 5.047)
	Placebo	**Kälviäinen, 1998[164]**	**8.500 (95% CI: 2.304 to 32.450)**
TPM	Placebo	Barrett, 1997[76]	0.714 (95% CI: 0.256 to 1.965)
	Placebo	Biton, 1999[79]	1.051 (95% CI: 0.112 to 9.865)
	Placebo	Guberman, 2002[150]	3.497 (95% CI: 0.915 to 13.726)
	Placebo	**Rosenfeld, 1996[41]**	**3.186 (95% CI: 1.148 to 9.530)**
	Placebo	Faught, 1996[67] (200 mg)	0.667 (95% CI: 0.138 to 3.200)
	Placebo	Faught, 1996[67] (400 mg)	1.333 (95% CI: 0.351 to 5.102)
	Placebo	Faught, 1996[67] (600 mg)	1.957 (95% CI: 0.571 to 6.843)
	Placebo	Korean Topiramate Study Group, 1999[149]	2.205 (95% CI: 0.644 to 7.657)
	Placebo	Tassinari, 1996[42]	4.000 (95% CI: 0.646 to 25.895)
	Placebo	**Sharief, 1996[148]**	**6.261 (95% CI: 1.107 to 38.227)**
	Placebo	**Ben-Menachem, 1996[151]**	**13.000 (95% CI: 1.398 to 130.270)**
	Placebo	Yen, 2000[165]	1.000 (95% CI: 0.187 to 5.334)
	Placebo	**Privitera, 1996[68] (600 mg)**	**9.792 (95% CI: 1.730 to 58.339**)
	Placebo	Privitera, 1996[68] (800 mg)	4.896 (95% CI: 0.798, 31.068)
	Placebo	**Privitera, 1996[68] (1000 mg)**	**8.000 (95% CI: 1.383, 48.426)**
VGB	GBP	Lindberger, 2000[132]	0.962 (95% CI: 0.376 to 2.463)
	Placebo	Bruni, 2000[153]	1.371 (95% CI: 0.439 to 4.338)
	Placebo	French, 1996[155]	3.424 (95% CI: 0.836 to 14.270)
	VPA	Brodie, 1999[66]	1.156 (95% CI: 0.570 to 2.352)

Appendix 25

Extraction tables for studies of serious, rare and long-term adverse events

TABLE 99 *Gabapentin Prescription Event Monitoring Study*

Study ID	Aim	Study design	Participants	Treatment duration	Methods	Results	Conclusion
Wilton, 2002[170] UK	To monitor safety of adjunctive GBP prescribed by GPs in England	Non-interventional observational cohort study conducted by PEM Prescriptions issued from August 1993 to April 1995	3100 patients out of 5285 identified Median age 35.2 years (range 1–89) males, 35.6 years (range 1–86) females Indication: all forms of epilepsy 85.4%; not specified 15%	Known for 3008 patients >6 months in 76.2% (n = 2291); Median 8.1 months (IQ range 6.7, 9.3) Total months exposure 24,081	Calculation of incidence densities; follow-up of selected events (including visual events), pregnancies and deaths	130 suspected adverse reactions (ADR) reported in 77 patients; most frequent were drowsiness (12), headache (11), lassitude (9) 32.5% (1006 patients) discontinued GBP; 746 reasons were reported for 568 patients, the most frequent ADR reasons (i.e. excluding lack of efficacy) were drowsiness, lassitude, headache for which ID_1 was significantly greater than ID_2. Hallucinations was the event with the highest proportion of total cases (7/10) in which GBP was stopped A possible association of GBP with 2 cases of hyponatraemia could not be excluded No cases of visual field defect or serious skin reactions reported 17 patients took overdoses 3 cases of hair loss reported ≥ 6 months after starting treatment No congenital anomalies in 11 babies born to women who used GBP during first trimester In 12/45 patients who died, epilepsy was the cause of death, 1 recorded as sudden unexpected; 3 patients were still being treated with GBP. Overall crude mortality rate = 1.5/1000 patient months of observation; SMR all-cause mortality 5.58 (95% CI: 4.29 to 7.25)	Neurological AEs were the most frequently reported events, and the most frequent events reported as ADRs, and the commonest reason for discontinuation No previously unrecognised AEs were detected The standardised mortality rate (SMR) is comparable to published studies in patients with severe epilepsy

TABLE 100 *Gabapentin primary studies*

Study	Design	Participants	Intervention	Results	Comments
Fisher, 2001[173] Multicentre study USA	RCT of dose initiation (slow = 300 mg on day 1, 600 mg on day 2, then 900 mg/day; rapid = 900 mg/day from day 1)	781 patients with partial epilepsy. Median age 36 years (range 12–82). Tolerability evaluated per protocol (n = 574) against 4 AEs (somnolence, dizziness, ataxia and fatigue) identified from previous trials	GBP adjunctive Dose: 900 mg/day Duration: 5 days Concomitant drugs: PHT, CBZ, VPA	9 withdrawals due to AEs. Safety: 2/781 patients hospitalised with serious AEs, generalised oedema on day 6 in a 13 year old, reason and time unclear for an 85 year old man. Commonly reported events similar to RCTs	Exclusion criteria: severe liver or kidney insufficiency, progressive structural CNS lesion or encephalopathy, GBP in last 30 days or any experimental drug in last 2 months, those not expected to complete the trial, serious or unstable medical or psychological conditions AEs recorded on patient diary cards and reported 1 day after completing all doses of GBP
Mauri, 2001;[178] Laini,1999 [450] Italy	Uncontrolled trial	21 patients with bipolar disorder. Mean age 52 years (SD 11.5)	GBP adjunctive Dose: mean 1010.8 mg/day (range 300–2400) Duration: 12 months Concomitant drugs: benzodiazepines	Commonly reported events similar to RCTs. 1 patient required antidepressive treatment at 6 months	AEs assessed using a checklist on days 15 and 30 then monthly to 12 months. Drop-out n = 4
Schaffer, 1999[179] USA	Uncontrolled trial	18 patients with BPD I or II or cyclothymic disorder. Mean age 43 years (range 21–59) Inclusion criteria: positive clinical response in acute phase as judged by patient and psychiatrist	GBP adjunctive Dose: 100–2700 mg/day in the 7 patients continuing with GBP at end of follow-up Duration: 2–36 months Concomitant drugs: 14 psychotropic drugs listed	3 withdrawals due to AEs: excessive activation (n = 2), sedation (n = 1) at 5, 6 and 11 months 7 patients were continuing on GBP after mean 33 months (range 28–36)	Measurement tools and time of assessment of AEs not stated GBP dose not stated for patients who withdrew because of AEs Loss to follow-up n = 2, at 2 and 5 months

continued

TABLE 100 *Gabapentin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
McLean, 1999;[174] Morrell, 2000[449] Multicentre study USA	Uncontrolled trial	2216 patients with partial epilepsy. Mean age 39 years (safety), 37 years (tolerability) Safety evaluated in all patients who received at least one dose and provided any follow-up information (n = 2216) Tolerability: patients served as their own control to compare ≤ 1800 mg/day with >1800 mg/day (n = 281)	GBP adjunctive Dose: ≤ 1800 vs >1800 mg/day Duration: 16 months (16-weeks plus 1 year follow-up). Concomitant drugs: CBZ, PHT, VPA (most common)	234 withdrawals due to AEs Safety: serious AEs reported by 73/2216 patients; 17/2216 reported an associated serious AE; convulsion was the most common serious AE (20/2216) Tolerability: serious AEs, infection, overdose, sudden death, grand mal convulsion and hostility, reported by 2/278 patients while taking <1800 mg/day and in 4/278 patients taking >1800 mg/day Commonly reported events similar to RCTs At 1 year follow-up (n = 1095): 819 patients were taking GBP 1 year after study completion, mean dose 2048 mg/day (range 300–6400). Safety and tolerability physician rated as excellent or good in 773/819	Exclusion criteria: pregnant, nursing, GBP in last 30 days, any other experimental drugs in last 2 months, CNS lesion or progressive encephalopathy, hepatic or renal insufficiency, haematological disease Patients questioned about AEs at each of 6 visits over 16 weeks. Physician assessed safety and tolerability. Questionnaire 1 year after completion of 16-week study
Mayer, 1999[175] Multicentre study Europe	Uncontrolled trial	110 patients with partial or partial and secondarily generalised epilepsy. Mean age 37 years (range 16–72)	GBP adjunctive Dose: 1200–2400 mg/day Duration: 26 weeks Concomitant drugs: CBZ, PHT, PB, VPA, PRM, LTG, VGB	4 withdrawals due to overdose (n = 1), somnolence (n = 2), dizziness and amblyopia (n = 1). Mean duration of GBP 91 days in those who withdrew. Overall 8/110 patients experienced serious AEs, possibly related to GBP in 2 patients (headache, accommodation difficulty). Common AEs similar to RCTs	Data on AEs collected during scheduled visits at 6, 12, 18 and 26 weeks, measurement tools not stated

continued

TABLE 100 *Gabapentin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Wilson, 1998[176] UK	Uncontrolled trial	50 patients with partial or partial and secondarily generalised epilepsy. Age 16–75 years	Gabapentin Adjunctive. Dose: 1200 to at least 6000 mg/day Duration: at least 6 months. Concomitant drugs: CBZ, PHT, PB, VPA.	AEs at ≤ 2400 mg/day similar to RCTs; >3600 mg/day diarrhoea (n = 3), new onset myoclonic jerking (n = 2), aggression (n = 2)	Exclusion criteria: progressive neurological illness, brain lesion, serious medical or psychiatric disorder, seizures related to alcohol or drug abuse or acute medical condition Patients invited to report new symptoms at review visits every 4 weeks 24 patients completed the study
Knoll, 1998[451] USA	Uncontrolled trial, consecutive sample	12 patients with mania or hypomania, all had chronic psychiatric illness BPD I (n = 10), BPD II (n = 1), schizoaffective BPD (n = 1). Mean age 42 years (range 30–52) Inclusion criteria: persistent disabling symptoms, intolerance and/or resistance to standard mood stabilisers	GBP adjunctive Dose: Median 2400 mg/day (range 900–3300) Duration: 30–60 weeks Concomitant drugs: various psychotropic drugs listed	6 withdrawals due to AEs, 5 due to sedation or fatigue (2 within 4 weeks, 1 at 30 weeks and 1 at 36 weeks), 1 with mild alopecia (8 weeks) Commonly reported events similar to RCTs	AEs recorded every 3–4 weeks, measurement tools not stated
Baulac, 1998[177] Multicentre study France	Uncontrolled trial	610 patients with partial epilepsy. Mean age 37 years (range 18–76)	GBP adjunctive Dose: 900–2400 mg/day Duration: 6 months Concomitant drugs: CBZ, VGB, PB, benzodiazepines, VPA, PHT and others	57 withdrawals due to somnolence, asthenia, nausea/vomiting, ataxia, vertigo. Serious AEs in 45/610 included falls and fractures, surgery, personality disorders, somnolence and miscellaneous disturbances. Commonly reported events similar to RCTs, occurred in first few weeks and duration was limited. Dose did not influence occurrence of AEs After 6 months 368 patients continued on GBP, mean dose 1739 mg/day	Exclusion criteria: pregnant, nursing, progressive CNS lesion, severe liver or kidney insufficiency, low WBC count, other investigational drugs in last month, chronic drug or alcohol abuse Measurement tools and time of assessment of AEs not stated

continued

TABLE 100 *Gabapentin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
McElroy, 1997[181] Pilot study USA	Uncontrolled trial	9 patients with BPD I and II. Age 20–49 years	GBP adjunctive Dose: 1600–4800 mg/day Duration: 1–10 months Concomitant drugs: CBZ, VPA and various psychotropic and other drugs listed	1 withdrawal at 10 months due to exacerbation of migraine. Commonly reported AEs similar to RCTs	Exclusion criteria: neurological or unstable medical conditions Patients seen monthly or more frequently to assess side-effects (measurement tools not stated)
Beydoun, 1998[182] USA	Open-label extension of a double-blind trial, only patients who achieved monotherapy (GBP maintained at least 8 weeks) were evaluated	23 patients with partial epilepsy. Mean age 41 years	GBP monotherapy dose: mean maximum 3900 mg/day (range 3000–4800) Duration: mean 36 weeks (range 8–106) Concomitant drugs: CBZ (most common)	1 withdrawal due to weight gain and aching legs, at day 77, max. dose 4200 mg/day for 56 days. Author-defined rare AEs in 1 patient each: nervousness, confusion, acne, panic attacks, numbness, aching legs, insomnia, myoclonic jerks, paraesthesia, bruising, increased lacrimation Commonly reported AEs similar to RCTs	Open-ended questions used to collect information about AEs at clinic visits at week 0, 4 and 8, then every 12 weeks. Intensity and relationship to GBP assessed by the investigator. 'Rare' used to define events that occurred in only 1 patient in this study
Anhut, 1995[183] International	Open-label extension in patients who experienced a therapeutic response to GBP in 4 short-term studies, demonstrated compliance and could maintain a seizure diary	203 patients with partial epilepsy. Mean age 35 years (range 16–67)	Gabapentin Adjunctive. Dose: mean range 1283–2200 mg/day Duration: mean 385 days, maximum 1894 days Concomitant drugs: CBZ, PHT, VPA	7 withdrawals due to AEs. Clinically important severe AEs that led to withdrawal: non-Hodgkin's lymphoma ($n = 1$), seizure prolongation ($n = 1$), status epilepticus ($n = 1$), pneumonia and increased platelets ($n = 1$ with pleural disorder). Commonly reported AEs similar to RCTs	AEs monitored every 4 weeks and 4 weeks after the final dose of GBP
Sivenius, 1994[184] Finland	Open-label extension in patients who completed and had initially received GBP in a placebo-controlled double-blind study of 3 months duration	25 patients with partial or partial and secondarily generalised epilepsy. Mean age 41 years (range 23–59)	GBP adjunctive Dose: mean last dose 1385 mg/day non-responders, 1710 mg/day responders Duration: median 54.3 months (range 48–62). Concomitant drugs: CBZ, CZP, VPA, PHT	Reported AEs similar to RCTs. 7 patients received GBP for more than 4 years	Follow-up visits at 3-month intervals; measurement tools for AEs not stated

continued

TABLE 100 *Gabapentin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
US Gabapentin Study Group, 1994[185] Interim data USA	Open-label extension in patients with improved seizure management and who did not experience intolerable side-effects during 12 or 24 weeks of GBP treatment in a randomised double-blind study	240 patients with partial or partial and secondarily generalised epilepsy. Mean age 35 years (range 16–70)	GBP adjunctive Dose: mean 2096–2229 mg/day Duration: 342 days (range 10–784) Concomitant drugs: CBZ, PHT, VPA, clorazepate, PRM, PB	10 withdrawals due to AEs: brain tumour with and without haemorrhage (n = 3; 2/3 were recurrences of previously diagnosed tumours), depression with and without impotence and amnesia (n = 2), dysarthria, headache, insomnia, tremor (n = 1), nervousness, fatigue (n = 1), somnolence (n = 1), amnesia (n = 1), nausea and vomiting (n = 1). Commonly reported AEs similar to RCTs. 148 patients were continuing on GBP at time of data cutoff	Open-ended questions used to collect AEs information at clinic visits at 0, 4, 8 and 16 weeks and every 8 weeks thereafter in first year and every 12 weeks in second year
Putzke, 2002[186] USA	Cohort (uncontrolled) of patients with a diagnosis of spinal cord injury who had received analgesic therapy with GBP at one centre	27 patients with spinal cord injury, age not stated	GBP adjunctive Dose: 300–3600 mg/day Duration: 36 months Concomitant drugs: various other analgesics listed for the 14 patients who reported favourable analgesic effects of GBP and completed the second follow-up (36 months)	6 patients discontinued owing to side-effects including oedema, dizziness, muscle twitching, drowsiness, rash, nausea, hallucinations, blurred vision, slurred speech, clumsiness In those who continued treatment (n = 21), commonly reported AEs similar to RCTs	Side-effects assessed by questionnaire during a structured interview at 6 months (first follow-up) and 36 months (second follow-up)

TABLE 101 *Lamotrigine prescription event monitoring and postmarketing surveillance studies*

Study ID	Aim	Study design	Participants	Treatment duration	Methods	Results	Conclusion
Mackay, 1997[188] UK	To examine the safety of LTG used in general practice to treat epilepsy	Non-interventional observational cohort study conducted by PEM Prescriptions issued from December 1991 to February 1995 Plus a follow-up study of patients who took LTG for ≥ 6 months, to identify serious events	11,316 patients in the PEM study Mean age 29±17.4 years males, 30±17.0 years females Indication: epilepsy 78.1%; not specified 20.5% 3994 patients in the follow-up study	PEM study observation period 6 months Follow-up study: after 6 months 9171/10,930 patients for whom the date of stopping medication was known were still using LTG. Observation period 18 months	Calculation of incidence densities; follow-up of selected events, pregnancies and deaths	Excluding epileptiform events (convulsion, epilepsy, grand mal epilepsy, petit mal epilepsy, status epilepticus), rash had the highest ID_1 (19.7/1000 patient months). There were 510/11,316 first reports of rash during the total treatment period (4.5% of the cohort); median time to onset 41 days (95% CI: 33 to 50). Stevens–Johnson syndrome was reported in 7 adults (age15–60 years), 4 taking concomitant VPA. Rash was the most frequent reason for stopping LTG and led to withdrawal in 210/11,316 (1.9%) patients Other rare serious AEs possibly associated with LTG were neutropenia (4 cases), thrombocytopenia (3 cases), disseminated intravascular coagulation (2 cases) and 1 case each of leucopenia, a meningitic reaction, acute renal failure, hepatotoxicity and a lupus-like reaction. Age not specified 3/46 live births had serious congenital abnormalities, none specifically attributable to LTG In 37/124 patients who died, epilepsy was the cause of death; no death was specifically attributable to LTG In the follow-up study, rash and depression were most frequent events reported (both 8 cases/3994) 12 pregnancies resulted in 9 normal babies, 2 terminations for spina bifida (mothers had taken concomitant VPA in first trimester) and 1 spontaneous abortion None of 69 deaths was attributed to LTG	Patients had severe epilepsy, inadequately controlled by other AEDs. Rash was the most frequently reported non-pileptiform event. AEs including rash, depression, ataxia and visual disturbance were reported several months after starting therapy Serious AEs were reported rarely. No previously unrecognised AEs were detected. LTG is acceptably safe for the treatment of refractory epilepsy

continued

TABLE 101 *Lamotrigine prescription event monitoring and postmarketing surveillance studies (cont'd)*

Study ID	Aim	Study design	Participants	Treatment duration	Methods	Results	Conclusion
Wong, 2001;[189] 1999[463] UK	To determine the incidence of LTG-related rash and its risk factors	PMS through a retrospective case record survey Data collected from five tertiary referral centres in the UK from December 1993 to September 1996	1050 patients exposed to LTG and 361 patients exposed to GBP and 713 to VGB as comparators Mean age LTG group 31 years (range 7–77), GBP 35 years (range 11–78), VGB 33 years (range 7–80) Focal, generalised or unclassified epilepsy	Mean maximum dose LTG 303 mg/day (range 12.5–900), GBP 1575 mg/day (range 200–4800), VGB 2444 mg/day (range 250–5000)	Event rate on LTG in months 1–4 compared with months 5–8 ($p < 0.05$) Event rates in first 6 months LTG compared with GBP and VGB ($p < 0.01$) Crude mortality rate for each drug; SMR used to compare LTG with GBP and VGB Low-frequency serious AEs assessed for causality	Skin rash was the most common AE among LTG patients (10%); incidence in months 1–4 =0.0175 per patient-month vs 0.0038 in months 5–8 ($p < 0.05$) Hospitalisation for ADR: incidence in months 1–4 = 0.0022 per patient-month vs 0.0005 in months 5–8 ($p < 0.05$) LTG was strongly associated with rash compared with GBP and VGB ($p < 0.001$) Mortality rate LTG 1.7 per 100 patient-years, GBP 2.1, VGB 1.3. LTG SMR 10.4 not significantly different from GBP or VGB Four serious and unexpected ADRs ($n = 1$ each): acute exacerbation of ulcerative colitis (day 7), life-threatening hepatic failure (3 weeks), renal failure (3 weeks), disseminated intravascular coagulation (1 month) No death could be directly attributed to LTG Other AEs ($p < 0.05$) not already recognised or listed on manufacturers' data sheets included pruritus, nightmares and hallucinations	1326 patients exposed to LTG or comparators excluded from event rate and mortality analyses as treatment had commenced outside study centres. Funded by GlaxoSmithKline

continued

TABLE 101 *Lamotrigine prescription event monitoring and postmarketing surveillance studies*

Study ID	Aim	Study design	Participants	Treatment duration	Methods	Results	Conclusion
Tennis, 1999[190] UK	To assess the risk of birth defects in pregnancies exposed to LTG	PMS using a prospective LTG pregnancy registry	123 infants, 8 with birth defect (BD) and 115 without BD Data to September 1998 represent 6 years interim results	Exposure to LTG in 1st trimester; monotherapy $n = 40$, polytherapy $n = 123$	Risk of BD = no. BD/(no. BD + live births without BD)	Monotherapy risk of BD = 0/40 (95% CI: 0 to 11%). Polytherapy risk of BD is reported as 8/123 (6.5%, 95% CI: 3 to 13%); however; it is unclear why the denominator used was not 83 (i.e. 123–40, the number of 1st trimester exposures to polytherapy; 8/83 = 9.6%)	Abstract only. Registry maintained by GlaxoSmithKline
Faught, 1999[191] USA	To determine the rate of rash and other AEs in patients treated with VPA + LTG	PMS using prospective data from consecutive patients in the USA	418 patients started on LTG between November 1994 and May 1996 Adults and children Partial, generalised and unspecified epilepsy; Lennox–Gastaut syndrome	Median follow-up 6 months (range 3–27)	Rash rate = no. with rash/no. without. Univariate analyses using age, enzyme-inducing concomitant AEDs, initial LTG dose, titration rate as possible factors contributing to rash	Rash rate among patients who had LTG added to VPA = 14/108 (13%). LTG discontinued in 22/108 (rash $n = 7$, other AEDs $n = 7$). Rash rate among patients who had LTG added to AEDs other than VPA = 44/310 (14.2%). Time of rash 1 day to 10 weeks Univariate analyses not reported Serious AEs: hallucinations ($n = 2$), hepatic enzyme elevations ($n = 1$), low WBC count ($n = 1$). Time not stated	Postmarketing Antiepileptic Drug Survey (PADS) group No pharmaceutical company support

TABLE 102 *Lamotrigine primary studies*

Study	Design	Participants	Intervention	Results	Comments
Rzany, 1999[192] Multicentre study Europe	Case–control study	136 cases of SJS, 216 cases of TEN and 1579 controls Age of cases: 67 aged 0–24 years, 133 aged 25–49 years, 152 aged ≥ 50 years	LTG adjunctive Dose not stated Duration: ≤ 8 weeks LTG Concomitant drugs: 13/73 AED use cases reported intake of more than 1 drug vs 6/28 controls	73 cases (30 SJS, 43 TEN) and 28 controls reported use of AEDs 3 cases reported intake of LTG and comedication (CBZ, VPA). Confounding factors present in 1/3 cases. No controls reported intake of LTG Univariate analysis identified short-term (≤ 8 weeks) LTG as a risk factor for SJS/TEN, RR 25 (95% CI: 5.6 to infinity). Multivariate risk estimate not possible owing to small numbers	Skin reaction validated and classified as SJS and TEN by an expert committee Cases (n = 86) who developed SJS/TEN while in hospital for another reason (4 reported use of LTG) not included in this analysis
Pimentel, 1999[193] Multicentre study Portugal	Uncontrolled trial	61 patients with partial or generalised epilepsy. Mean age 31 years (range 8–62)	LTG adjunctive Dose: 100–700 mg/day. Final dose 100–500 mg/day (mean 205 mg/day) in patients also taking VPA, other patients 200–700 mg/day (mean 368 mg/day) Duration: 24 months Concomitant drugs: benzodiazepines, VPA, VGB, other AEDs (not specified)	4 withdrawals due to AEs. Withdrawals due to serious AEs: behavioural disturbance, unsteadiness/nystagmus, aggression, kidney pain/haematuria. Commonly reported AEs similar to RCTs	Exclusion criteria: status epilepticus in last 6 months or more than once in last 2 years, severe organic or psychiatric disease, progressive neurological disease, pregnant, lactating, at risk of pregnancy AEs recorded at clinic visits at months 1, 2, 3, 6, 9, 12, 18 and 24. Investigator assessed likelihood of LTG as cause

continued

TABLE 102 *Lamotrigine primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Calabrese, 1999[194] Multicentre study USA	Uncontrolled trial	75 patients with BPD I and II. Mean age 44 years (range 23–70)	LTG adjunctive (n = 60) or monotherapy (n = 15) Dose: max. 200 mg/day for monotherapy or concomitant with drugs other than VPA or CBZ; max. 500 mg/day concomitant with VPA; max. 700 mg/day concomitant with CBZ Duration: 48 weeks Concomitant drugs: Li, CBZ, VPA, benzodiazepines, antidepressants, antipsychotics, thyroxine	14 withdrawals due to AEs, rash (n = 7, 6 within 8 weeks), nausea (n = 1), somnolence (n = 1), tremor (n = 1). LTG related rash in 11 patients (4 mild, 5 moderate, 2 severe). 1 patient on LTG monotherapy developed serious rash and needed hospitalisation and steroid therapy. 4 patients hospitalised for exacerbation of mania (14, 15, 24, 190 days), 1 withdrawn. 4 patients hospitalised for switches in to mania (14, 35, 66, 90 days), 1 withdrawn Serious AEs experienced by 29% (22/75) patients, numbers on adjunctive or monotherapy not specified. Reasons for withdrawal of 2/14 patients unclear	Exclusion criteria: epilepsy, significant medical illness, prior LTG, active suicidality, alcohol or drug dependence in past year Verbal probe to elicit AEs at each visit at week 0, 1, 2, 4, 6, 8, 12, 16, 20, 24, 32, 40 and 48
Cocito, 1994[195] Italy	Uncontrolled trial	10 patients with partial or partial and secondarily generalised epilepsy. Mean age 30 years (range 14–61)	LTG adjunctive Dose: 200 mg/day for patients on combination enzyme-inducing drug and VPA (n = 5), 400 mg/day for patients on enzyme-inducing drugs only (n = 11) Duration: 15–38 months Concomitant drugs: CBZ, VPA, PHT, PB, ethosuximide, CLB	2 withdrawals due to SJS (n = 1 at 2 weeks) and macrocytic anaemia (n = 1 at 23 months). Plus 1 temporary discontinuation at 16 months due to leg purpura (dose reduced from 200 to 100 mg/day). Other AEs mild and similar to RCTs	Clinic visits at week 2 and 4, then every 4–6 weeks in first year, quarterly thereafter; measurement tools for AEs not stated

continued

TABLE 102 *Lamotrigine primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Mikati, 1989[196] USA	Uncontrolled trial	4 patients with partial epilepsy. Age 28–48 years	LTG adjunctive Dose: 100 or 400 mg/day Duration: 9.5–24 months Concomitant drugs: CBZ, PHT	Commonly reported AEs similar to RCTs	Exclusion criteria: neoplastic, metabolic or infectious aetiology, drugs other than CBZ and PHT, drug or alcohol abuse, progressive neurological disease, status epilepticus, significant medical or psychological disorder, gastrointestinal or clinical laboratory abnormalities, cancer Patients used diaries to record AEs. Outpatient visits weekly, biweekly or monthly; patients hospitalised for each dose increment
Sander, 1990[197] UK	Uncontrolled trial	125 patients with partial or generalised epilepsy. Mean age 32 years (17–63)	LTG adjunctive Dose: mean 367 mg/day; max. 250 mg/day with VPA, 900 mg/day without VPA Duration: 1–27 months Concomitant drugs: CBZ, PHT, PB, PRM, VPA, various other AEDs	19 withdrawals due to skin rash (n = 7), insomnia (n = 2), headache (n = 1), diplopia (n = 1), deterioration of seizure control (n = 8). 15/19 definitely associated with LTG. Treatment withdrawn before week 12 in 16/19 patients. 45 patients reported 81 AEs similar to RCTs 1 death in bed at 14 weeks, 1 overdose of concomitant AEDs at 5 weeks	Exclusion criteria: patients with pseudoseizures, at risk of pregnancy, systemic, psychiatric or progressive neurological conditions Measurement tools and time of assessment of AEs not stated
Huber, 1998[198] Germany	Cohort (uncontrolled) of residential patients in one centre. First 125 consecutive patients reported	125 patients with partial and generalised epilepsy. Mean age 41 years (19–66). All with intellectual and/or neurological deficits	LTG adjunctive Dose: not reported; physician choice Duration: unclear Concomitant drugs: CBZ, CBZ epoxide, PHT, PB	11withdrawals due to AEs: exanthema (n = 3), negative psychotrophic effects (n = 5), other AEs (n = 3). Time not specified (mean for all withdrawals 10.5 months). Common AEs similar to RCTs 71% patients still on LTG after mean duration 21.9 months	Inclusion/exclusion according to physician choice Undesirable effects and patients' complaints recorded before and during the 3 months prior to analysis

continued

TABLE 102 *Lamotrigine primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Leestma, 1997[199] USA	Cohort (uncontrolled) of patients included in open-label studies and patients given compassionate use of LTG	4700 patients with partial or generalised epilepsy. 2988 patients enrolled in open-label controlled trials and 1712 compassionate use patients. Mean age 34 years (range 16–65) in open-label studies, age not stated for compassionate use patients but did include children	LTG, unclear whether adjunctive, monotherapy or both Dose/duration: 5747 patient-years exposure Concomitant drugs: 57% were receiving 2 or more concomitant AEDs in the open-label studies, not stated for compassionate use patients	18/45 deaths classified as definite or highly probable SUDEP, 2 were not taking LTG at death. 6/45 deaths classified as possible SUDEP. The rate of SUDEP (definite, probable and possible) was 3.5/1000 patient-years exposure 16 definite or probable SUDEP cases comprised 11 patients from controlled trials (2/1323 patients from double-blind placebo-controlled trials, both deaths were placebo patients) and 5 compassionate use patients. 3 SUDEP/possible SUDEP cases were children (age 3.5–13 years). 2 adult cases of possible SUDEP were not included in rate calculations because LTG was discontinued before their deaths LTG-treated patients only: SUDEP/possible SUDEP $n = 20$, mean exposure 426 days (range 35–1463), mean last dose 309 mg/day (range 50–900) Non-SUDEP $n = 19$, mean exposure 467 days (range 8–1416), mean last dose 344 mg/day (range 15–700)	Open-label studies excluded alcohol or drug abuse, significant psychiatric or medical illness; compassionate use patients not stated All deaths evaluated by 6 experts and classified as SUDEP (definite or highly probable), possible SUDEP, non-SUDEP or insufficient data

continued

TABLE 102 *Lamotrigine primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Buchanan, 1996[200] Australia	Cohort (uncontrolled)	200 patients with partial and generalised epilepsy. Mean age 22 years (range 1–65)	LTG adjunctive (largely) Dose: only reported for patients who continued on LTG Duration: 0.01–4.1 years Concomitant drugs: only reported for patients who continued on LTG	13 withdrawals attributed to AEs alone, plus 4 due to lack of effect and AEs, plus 4 in which AEs supervened some effect. Events not specified. Overall 62 patients reported 83 AEs including rash ($n = 6$), profound agitation ($n = 1$) and LTG intoxication ($n = 17$). Other AEs similar to RCTs	Measurement tools and time of assessment of AEs not stated. Unclear reporting of AEs
Martin, 1994[201] UK	Cohort (uncontrolled). Prospective data collection from patients prescribed LTG at one outpatient clinic	45 patients with partial or partial and secondarily generalised epilepsy. Median age 34 years (range 17–60 years). Many patients had failed VGB treatment (*n* not stated)	LTG adjunctive Dose: median 150 mg/day (range 50–400) Duration: median 7 months (range 12–21) Concomitant drugs: PHT, CBZ, VPA, VGB, PRM, CLB, PB, methsuximide	9 withdrawals due to rash ($n = 5$), nausea ($n = 3$), headaches ($n = 3$), fatigue ($n = 2$). Withdrawal after 12 days to 10 months (median 3 months) 6/9 early withdrawals were taking 2 other AERs but a relationship between AERs and escalation of LTG dose was not found	Measurement tools and time of assessment of AEs not stated

TABLE 103 *Oxcarbazepine primary studies*

Study	Design	Participants	Intervention	Results	Comments
Schachter, 2001[203] USA	Open-label extension in patients who completed a 10-day double-blind phase of an RCT of monotherapy vs placebo, or who exited because of inadequate seizure control	97 patients with partial or partial + secondarily generalised epilepsy. Mean age 33 years (range 11–62)	OXC monotherapy (n = 27) or adjunctive (n = 70) Dose: not stated for extension phase; 2400 mg/day in RCT titrated to most effective dose in extension phase Duration: 52 weeks Concomitant drugs: PHT, CBZ, LTG, GBP, VPA, TPM	12 withdrawals due to AEs; nature and timing of events not stated. Common AEs similar to RCTs 56/97 patients remained on OXC throughout the 52 weeks extension phase	Clinic visits every 2 weeks for 8 weeks then every 12 weeks. Measurement tools for AEs not stated
Beydoun, 2001[204] USA	Open-label extension in patients who completed 126-day double-blind phase of RCT or who met exit criteria could participate in the extension phase	76 patients with partial onset epilepsy. Median age 35 years (range 11–66)	OXC monotherapy (n = 42) or adjunctive (n = 34) Dose: max. 3000 mg/day Duration: 48 weeks Concomitant drugs: TPM, CBZ, LTG, PHT, GBP, VPA	10 withdrawals due to AEs. Severe adverse events in 9 patients probably or definitely related to OXC. Monotherapy events: diarrhoea, dizziness, nausea, rash (n = 1 each). Polytherapy events: vomiting, abnormal dreams, flatulence, headache, insomnia (n = 1 each). Most mild to moderate events were dizziness, headache, diplopia, fatigue, nausea, rash. Most occurred early. Time not reported 55/76 patients completed the 48 weeks 1 woman who became pregnant had a healthy baby	Clinic visits at 4 weeks intervals for first 12 weeks then every 12 weeks. Patients were asked about AEs and their severity; relationships to the study drug were noted

TABLE 104 *Tiagabine primary studies*

Study	Design	Participants	Intervention	Results	Comments
Biraben, 2001[206] Multicentre study France	RCT of b.d. vs t.d.s.	347 patients with partial or partial and secondarily generalised epilepsy. Mean age 32 years (range 11–75)	TGB adjunctive Dose: 15–70 mg/day (protocol amended during study to allow patients who experienced limiting AEs at 30 mg/day to continue on doses as low as 15 mg/day) Duration: 24 weeks Concomitant drugs: 1–14 AEDs (not specified)	49/175 b.d. and 38/172 t.d.s. withdrawals due to AEs. 6 withdrawals due to one or more serious AEs. Serious AEs thought to be due to TGB in 5 b.d. and 2 t.d.s. patients included confusion; psychosis, depression and dysarthria; amblyopia and paranoid reaction; CNS neoplasia. Abnormal vision in 2 patients in weeks 12–24. 1 sudden death was not attributed to TGB. Commonly reported events similar to other RCTs Events of a severe nature in 44 patients in weeks 1–12; non-specific visual disturbances in 2–4% patients in weeks 1–12	Exclusion criteria: pregnancy AEs monitored at clinic visits in week 1, 4, 8, 12, 24
Nousiainen, 2000[208] Finland	Cohort (controlled). Patients converted to TGB monotherapy at one centre, not discontinued because of lack of efficacy, AEs or non-compliance (n = 16/40) Controls were healthy people with normal levels of general intelligence	15 patients with partial epilepsy treated with TGB. Mean age 52 years (range 31–71) Control group (n = 18) for visual fields, mean age 42 years (range 23–74) Control group (n = 35) for perimetry, mean age 51 years (range 23–72)	TGB monotherapy. Dose: mean 21 mg/day (range 5–60) Duration: mean 38 months (range 23–55) Concomitant drugs: CBZ, VPA, PHT, CLB, CZP	No TGB patient had concentric visual field loss. 7/14 examined had colour vision defects. Contrast sensitivity normal. No abnormalities among controls	Visual fields, colour vision and contrast sensitivity measured 1/16 TGB patient excluded because of bilateral cataracts

continued

TABLE 104 *Tiagabine primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Striano, 2002[207] Italy	Uncontrolled trial. Glial tumour patients and other aetiology patients treated with TGB in the same period of time with comparable protocol	11 patients with glial tumour partial epilepsy. Mean age 32 years (range 10–52). Also 12 matched patients with other lesional epilepsy aetiologies. Mean age 35 years (23–60)	TGB adjunctive Dose: 20–60 mg/day Duration: at least 1 year Concomitant drugs: glial tumour group, CBZ, PB, PHT, LTG, VGB; other aetiology group, CBZ, OXC, LTG, CLB, PB, PHT, VPA, felbamate	4 withdrawals due to epigastric aura (n = 1, glial tumour group), worsening seizures or myoclonus (n = 3, other aeteology group). Reported AEs similar to RCTs	Measurement tools and time of assessment of AEs not stated
Kälviäinen, 1999[209] Finland	Open-label extension in patients who achieved monotherapy in an RCT of slow vs fast titration	34 patients with less severe partial epilepsy. Adults	TGB monotherapy Dose: 5–60 mg/day Duration: 96 weeks	No cognitive AEs and no signs of concentric VFDs during open-label period. 19/34 patients completed 48 weeks, 18 patients completed 96 weeks follow-up. Reasons for drop-out not stated	Opthalmological examination included perimetry Abstract only

TABLE 105 *Topiramate primary studies*

Study	Design	Participants	Intervention	Results	Comments
Montouris, 2000[210, 217] USA	Open-label extension of double-blind placebo-controlled RCT. Patients treated with placebo were titrated to target dose TPM	131 patients with generalised epilepsy. Mean age 27 years (range 3–59)	TPM adjunctive Dose: mean 7 mg/kg/day (range 1–16) at last study visit Duration: mean 387 days (range 14–909) Concomitant drugs: not stated	11 withdrawals due to AEs, nature and time not reported. Commonly reported AEs similar to RCTs At last study visit TPM was continuing (up to 2.5 years) in 107/131 patients	Patients used diaries to record AEs, study visits monthly RCT YTC-E Study Group 1997
Singh, 2002[211] USA	Uncontrolled trial	19 patients with partial or generalised epilepsy and mental retardation, profound ($n = 5$), severe ($n = 3$), moderate ($n = 2$), mild ($n = 8$), borderline ($n = 2$). Age 21 to 57 years	TPM adjunctive Dose: 50–350 mg/day Duration: mean 42 weeks (range 20–54) Concomitant drugs: PHT, CBZ, PB, PRM, LTG, VPA	1 withdrawal due to disorientation, unsteadiness and pneumonia. One other discontinuation due to patient choice, reason not stated. One patient had low platelets and another had low WBC count. Commonly reported AEs similar to RCTs	AEs recorded on data forms by patients and/or care givers. AEs determined by physician's evaluations during clinic visits and information from care givers. Frequency of clinic visits unclear.
Mecarelli, 2001[212] Italy	Uncontrolled trial	31 patients with partial or partial and secondarily generalised epilepsy. Mean age 36 ± 14.7 years	TPM adjunctive Dose: mean 302 ± 99.4 mg/day Duration: mean 21.4 months (range 8–49) Concomitant drugs: CBZ, PB, VPA, GBP, CBL	7 withdrawals due to AEs including somnolence, ideomotor slowing, psychic disturbances, paraesthesias, ataxia, problems with calculating and language. Withdrawals occurred at 1–8 months (mean 5.8 months) of TPM; all were taking TPM in polytherapy. Overall, AEs were moderately severe in 3 patients, mild and short term in 7	Patients questioned about AEs at 3-monthly visits

continued

TABLE 105 *Topiramate primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Abou-Khalil, 2000[213] USA	Uncontrolled trial	277 patients with partial or generalised epilepsy. Mean age of 241 patients treated for ≥ 3 months was 33 years (range 13–74)	TPM, unclear whether adjunctive or monotherapy Dose: 100–1600 mg/day Duration: mean 413 days (range 84–804) Concomitant drugs: not stated	2 deaths reported as SUDEP. 90 withdrawals due to AEs, nature and time not reported. Two patients developed renal stones. Commonly reported AEs similar to RCTs	Exclusion criteria: significant medical disease in last 2 years, history of AED non-compliance, nephrolithiasis, alcohol or drug abuse, psychiatric or mood disorders requiring treatment (≤ 75 mg/day tricyclic antidepressants allowed), status epilepticus, taking carbonic anhydrase inhibitors, treated with experimental drug or device in last 2 months, unable to maintain seizure diary Patients reported AEs recorded at each study visit, monthly for first 6 months and every 3 months thereafter
Pellock, 2000[214] USA	Uncontrolled trial	808 patients with partial onset epilepsy. Adults	TPM adjunctive Dose: not stated Duration: 20 weeks Concomitant drugs: not stated	153 withdrawals due to AEs, most frequent somnolence, nausea, confusion, anorexia and fatigue. Numbers and time not reported. Commonly reported AEs similar to RCTs	Exclusion criteria: as cited in prescribing information Investigators recorded treatment-emergent AEs spontaneously reported by patients or in response to non-directed questioning
Canger, 1997[215] Multicentre study Italy Interim analysis	Uncontrolled trial	67 patients with partial epilepsy, Lennox–Gastaut syndrome or unclassified seizures. Mean age 33 years (range 15–63)	TPM adjunctive Dose: mean 291 mg/day (range 79–686) Duration: mean 11.9 months (range 0.4–43.4) Concomitant drugs: CBZ, PHT, PRM, PB, VPA, VGB, others	14 withdrawals due to AEs including irritability, somnolence, ataxia, speech disturbance, weight loss, increased seizure frequency. Time of withdrawal not stated. Commonly reported AEs similar to RCTs Events during study included 6 cases of metabolic acidosis and 5 of depression	AEs assessed at clinic visits, monthly for first 6 months then quarterly

continued

TABLE 105 *Topiramate primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Tartara, 1996[216] Italy Possibly single-centre data from multicentre trial (above)[215]	Uncontrolled trial	15 patients with partial epilepsy or Lennox–Gastaut syndrome. Mean age 37 years (range 19–48)	TPM adjunctive Dose: 400–800 mg/day Duration: 14–21 months Concomitant drugs: CBZ, PHT, VPA, VGB, PB, benzodiazepines	6 withdrawals due to AEs: ataxia (n = 2), somnolence (n = 1), metabolic acidosis (n = 1), irritability (n = 1) and psychotic symptoms (n = 1). Time not reported. One other patient showed biochemical evidence of uncompensated metabolic acidosis. Laboratory tests revealed mild abnormalities consistent with TPM-induced inhibition of carbonic anhydrase in 11 patients. Commonly reported AEs similar to RCTs	Exclusion criteria: progressive neurological disorder, significant systemic pathology, drug or alcohol abuse, nephrolithiasis, risk of pregnancy Questions about AEs and safety tests at clinic every 4 weeks during first 6 months then at intervals of no more than 3 months

TABLE 106 *Vigabatrin prescription event monitoring study*

Study ID	Aim	Study design	Participants	Treatment duration	Methods	Results	Conclusion
Wilton, 1999[219] UK	To determine the incidence of (VFDs) in patients treated with VGB for ≥ 6 months	Long-term follow-up study of patients still being treated with VGB at the end of a PEM non-interventional observational cohort study Prescriptions issued from 1991 to 1994 Patients referred for eye tests, or unspecified changes in vision recorded or VFC/VFD reported, were followed up	PEM cohort, n = 10,178 Follow-up study, n = 7228 6793/7228 questionnaires returned; 5090 contained clinical data; 328 deceased; 4762 surviving	PEM study observation period 6 months Follow-up study: 7228/10,178 patients were still taking VGB at end of PEM study (≥ 6 months)	Calculation of incidence of VFDs	PEM study: 4 cases with objective evidence of bilateral persistent VFDs were reported during the 6 month observation period; incidence = 0.4/1000 patients Follow-up study: 77 cases identified among the 4762 surviving patients are being followed-up. Interim data: 12 cases of VFDs have been confirmed by formal perimetry tests; 10/12 probably or possibly related to VGB use; incidence = 2.0/1000 patients BMJ 2000.[220] Wilton *et al* replied: <2% of the 4741 patients in follow-up study were referred for visual field (VF) testing. Of these 89 cases, 36 had objective evidence of VFDs and 30 were considered to be probably or possibly associated with VGB	Interim results show a substantial increase in incidence of VFDs associated with long-term use of VGB Publicity bias may have influenced the number of patients referred for visual tests since the original study. This does not detract from the clinical importance of VFDs in the long-term use of VGB Study not designed to address the question of incidence of asymptomatic VFDs[222]

TABLE 107 *Vigabatrin primary studies*

Study	Design	Participants	Intervention	Results	Comments
Cocito, 1989[221] Italy	Non-randomised controlled trial. All patients given 2 months placebo, then 2 months VGB, then 2–4 months dose modification, then long-term VGB. Patients entered long-term phase only if tolerance was good and >50% seizure reduction or improvement in QoL (n = 16, 14 completed)	19 patients with partial or partial and secondarily generalised epilepsy. Mean age 30 years (range 16–57) Co-morbidities: abnormal neurological examination (n = 1), EEG (n = 19), CT (n = 11) at baseline	VGB adjunctive Dose: 1–4 g/day Duration: 13–15 months Concomitant drugs: CBZ, PHT, PB, PHT, PRM, VPA	Reported events similar to RCTs. Included 2 cases of diplopia. No withdrawals due to AEs	Exclusion criteria: severe medical, psychiatric or progressive neurological disease, brain tumour, risk of pregnancy, intestinal malabsorption, alcohol or drug abuse, inability to comply Visits at month 1, 2, 4, 6 and 9 of the long-term phase; measurement tools for AEs not stated
Comaish, 2002[222] UK	Cohort (controlled). Patients and controls able to agree to testing protocol recruited from one hospital's neurology department	24 patients with epilepsy and 10 control patients treated with other AEDs. Mean age 44 years (SD 9.53) VGB group, 40 years (SD 12.2) control group	VGB adjunctive or monotherapy Dose: not stated Duration: mean 55 months (range 9–108) Concomitant drugs: most patients were taking or had taken other AEDs; 2 patients stopped VGB in previous 12 weeks (took VGB for 24 and 72 months). Control group all on CBZ, some also taking other AEDs (not specified)	8/14 VGB patients had constricted VFs. All 10 controls had full VFs. No correlation found between duration of VGB treatment and VF areas	Exclusion criteria: occular pathology, other possible causes of VFDs, unable to cooperate with testing Visual acuity, ocular examination, ERG, EOG, Goldmann perimetry

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Jensen, 2002[223] Denmark	Cohort (controlled). Consecutive selection from referred patients who had epilepsy for at least 3 years. Those never exposed to VGB comprised the control group	10 patients with localisation-related epilepsy exposed to VGB and 10 control patients not exposed to VGB. Age 13–47 years in VGB group, 19–43 years in control group	VGB adjunctive Dose: mean 3.2 g/day (range 1–6) Duration: mean 6.6 years (range 2–11) Concomitant drugs: PHT, OCBZ, CBZ, phenemal, CLB VPA, GBP, LTG, TPM, TGB in VGB group. Control group as VGB group plus PRM	All 20 patients had normal visual acuity. 3/10 VGB patients had VFC compared with none of the controls. ERG abnormalities in 9/10 VGB patients; the 4 most severe cases had received 4–6 g/day VGB. ERG abnormalities in 5/10 controls	Exclusion criteria: disease other than epilepsy Ophthalmological examination including VF by Goldmann perimetry or campimetry (2 patients)
Nousiainen, 2001[224] Finland	Cohort (controlled) of patients treated with VGB and a control group of healthy volunteers	60 patients with epilepsy and 18 healthy controls Mean age: 40 years (range 17–62) adjunctive VGB; 41 years (range 20–74) monotherapy; 42 years (range 23–74) control group	VGB adjunctive or monotherapy Dose: adjunctive 2.6 g/day (range 1–5); monotherapy 2.7 g/day (range 2–4). Cumulative dose: adjunctive 3.8 kg (range 0.42–18); monotherapy 6 kg (range 1.8–18.7) Duration: adjunctive mean 49 months (range 7–168); monotherapy mean 70 months (range 29–120) Concomitant drugs (adjunctive group): CBZ, benzodiazepines, GBP, TPM	Adjunctive group: VF normal in 15/25, mildly constricted in 6/25, severely constricted in 4/25 Monotherapy group: VF normal in 21/35, mildly constricted in 10/35, severely constricted in 4/35 Cumulative dose did not correlate with VF extent or change in VF during follow-up. No significant recovery observed during follow-up of 4–38 months among patients who stopped VBG, or in progression among patients who continued on VGB Control group: not clearly reported but apparently no VF abnormalities found	Goldmann perimetry at 6 and 12 months Study design unclear, cohort-like

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Toggweiler, 2001[225] Switzerland	Cohort (controlled) of patients taking or who had previous exposure to VGB attending a clinic at one hospital. Controls matched for age, concomitant medication, history of seizures and relevant operations	15 patients with partial or partial and secondarily generalised epilepsy. Age 13–52 years 12 controls. Age 12–52 years History of selective amygdalo-hippocampectomy in 10 VGB patients and 8 control patients	VGB monotherapy (n = 4) or adjunctive (n = 11) Dose: 2 or 2.5 g/day Duration: mean 47.2 months (range 13–94) Concomitant drugs: 11/15 VGB patients taking other AEDs including CBZ, PHT, VPA. Controls, CBZ, VPA, PHT (most common)	9/15 VGB patients showed moderate to severe VFC. The degree of restriction depended on the duration of VGB treatment. 1/12 control patients showed slightly restricted VF Only 5/15 patients taking VGB at time of evaluation	Perimetry. 2/17 patients excluded from VGB group owing to homonymous hemianopsia
Manuchehri, 2000[226] Pilot study UK	Cohort (controlled) of consecutive patients who had taken VGB at some time, and 11 control patients matched for history of epilepsy, previous and current other AEDs, selected from one epilepsy clinic	20 patients with partial or generalised epilepsy. 15 still taking VGB and 5 patients who had stopped VGB 1–7 years earlier. Age 24–77 years 11 controls. Age 21–63 years Co-morbidities: moderate diffuse nuclear sclerotic cataracts (1 VGB), peripheral cortical cataracts (1 control), controlled hypertension (6 VGB, 1 control)	VGB monotherapy (n = 4), adjunctive (n = 16) Dose: total 2–8395 g Duration: 1–9 years Concomitant drugs: CBZ, GBP, PHT, VPA, PB, TPM, CLB, LTG	9/20 VGB patients complained of blurring of vision. 4/20 complained of flickering lights. In patients still taking VGB, 11/15 had >10% VFDs. Correlation between severity of VFD and total dose of VGB was significant for all 20 patients exposed to VGB. 2/11 complained of blurring of vision. 1/11 complained of flickering lights. 1/11 had >10% VFDs In patients still taking VGB, 3/30 eyes had distant visual acuity of 6/12 or worse vs 3/22 control eyes, and 5 eyes had near visual acuity worse than N6 vs 1 control eye. Other tests also reported	1 VGB patient excluded because of unreliable VF results VF assessment and ophthalmic examination 1 VGB patient had myopia and 1 control patient had emmetropia, but neither had visible posterior vitreous detachment

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Midelfart, 2000[227] Norway	Cohort (controlled) of consecutive patients taking VGB for >6 months referred to one centre for ophthalmological examination regardless of visual symptoms. Source of controls not exposed to VGB not stated	18 patients with partial epilepsy. Mean age 44 years (±12) 5 Controls: mean age 41 years (±15)	VGB monotherapy and adjunctive Dose: 0.375–3 g/day at examination Duration: 0.5–9.5 years Concomitant drugs, VGB: 13/18 patients taking concomitant AEDs, not specified Controls: VPA, LTG, TPM, GBP, CBZ	1 VGB patient had normal VF in both eyes. VFD in right eye $n = 15$ patients (9 severe, 6 mild), left eye $n = 16$ patients (8 severe, 8 mild). 11/18 did not complain of visual problems. All controls had normal VFs	Exclusion criteria: known eye disease or systemic disease that could affect the VF Ophthalmological examination and perimetry 2 VGB patients did not turn up for ophthamological examination
Lawden, 1999[228] UK	Cohort (controlled) of 25/33 unselected patients identified as taking VGB at 2 hospital neurology and epilepsy clinics. Control group of patients not exposed to VGB	25 patients with partial or generalised epilepsy. Age 12–67 years (only 1 patient <17 years) 16 controls. Age 17–58 years	VGB monotherapy ($n = 2$), adjunctive ($n = 23$) Dose: 1.5–5 g/day Duration: 0.8–8.2 years Various previous and concomitant drugs listed including CBZ, VPA, PRM, PHT, TPM, LTG, GBP	12/25 patients had a definite bilateral field defect with no other plausible causal ophthalmic or neurological pathology. Cumulative VGB dose 0.6–10.3 kg ($n = 25$). 12/16 controls had normal VFs, 4 inconclusive. None had definitely abnormal fields	Ophthalmic and VF examinations and other tests Excluded 2 VGB patients who failed to attend, 2 unable to cooperate with testing and 4 where a plausible cause of their VFD was identified
van der Torren, 2002[229,453] The Netherlands	Cohort (uncontrolled) of patients referred to ophthalmic departments at two hospitals between 1998 and 1999	29 patients with epilepsy. Age 15–69 years Co-morbidities: 2 patients had pre-existing VFDs caused by brain tumours	VGB adjunctive Dose: mean 1.7 g/day (range 0.5–3). Mean cumulative dose 3 kg (range 0.9–8.8) Duration: mean 4.6 years (range 2–8) Concomitant drugs: most common VPA, CBZ	VFD in 19/29, 90% of these patients had EOG and/or ERG changes. Correlation between VFD and daily dose but not cumulative dose. No significant relation between severity of VFD and duration of VGB Re-examination up to 1 year later of 9 patients who stopped VGB showed no change in VFs, but did show recovery of EOG and ERG components	Exclusion criteria: 4/33 patients excluded as unable to cooperate Ophthalmological investigations, contrast sensitivity, VF, colour vision, ERG and EOG. 9 patients who stopped VGB during the study had repeated examinations every 3–6 months

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Malmgren, 2001[230] Sweden	Cohort (uncontrolled) of patients who had undergone a full neuro-ophthalmological workup between 1988 and 1998 at one centre. The same investigator who made the initial neuro-ophthalmological measurements re-evaluated the perimetry data blinded to medication	155 patients with epilepsy. Mean age 35 years (range 17–58)	VGB adjunctive Dose: cumulative dose ranged from 0.3 to >7 kg Duration: 1–152 months Concomitant drugs: median number of other AEDs (not specified) was 4 (range 1–11)	25/155 initial perimetry examinations showed abnormalities; 19 of the 25 had been treated with VGB before the first VF examination (99/155 in total) Prevalence of VFD increased significantly with increasing cumulative dose. Difference in duration was significant 16/19 VGB patients with VFD at first examination were re-examined after a mean interval of 62 months (range 31–124); 12 were evaluable. 5 had worsened; in 2 cases VGB had been discontinued before the first VF examination (31 and 37 months earlier). 7/12 were unchanged; in 5 cases VGB had been discontinued before the first VF examination	Patients treated with VGB before the first examination were re-examined for possible progression
Ponjavic, 2001[231] Sweden	Cohort (uncontrolled) of consecutive referrals from treating neurologists	12 patients with complex epilepsy. Age 23–66 years	VGB, whether add-on or monotherapy not stated Dose: not stated Duration: 2–10 years Concomitant drugs not stated	7/12 patients had concentric defect in VF and reduced retinal cone function on full-field ERG. Treatment ranged from 3 to 10 years in patients ($n = 7$) with VF defect and from 3 to 7 years in patients ($n = 5$) with normal VF	VF examination, multifocal and full-field ERG
Arndt, 1999[232] France	Cohort (uncontrolled) of 20/22 consecutive patients presenting with a history of partial seizures currently treated with VGB	19 patients, seizure type not stated. Age 8–65 years (only 1 patient was <17 years old)	VGB monotherapy ($n = 3$), adjunctive ($n = 17$) Dose: 1.5–4 g/day Duration: mean 12 months (range 10–60). Follow-up 12–312 months Concomitant drugs: CBZ, VPA	12/19 patients tested had VFC (mild in 6, severe in 6), 5 complained of symptoms (blurring in 3 mild VFC cases, constriction in 2 severe VFC cases) Additional results: marked impairment in EOG findings in 14/20 patients. ERG normal	Clinical ophthalmological and neurological examination, including perimetry, EOG and ERG 2 patients excluded: ocular hypertension and glaucomatous VFDs ($n = 1$) diabetic retinopathy ($n = 1$). VFs of 1/20 patients not analysed

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
de Feo, 1994[233]; 1998[452] Multicentre pilot study Italy	Uncontrolled trial	40 patients with partial or partial and secondarily generalised epilepsy. Mean age 33 years (range 14–73)	VGB (first line) monotherapy Dose: ~20–44 mg/kg/day Duration: 1 year	3 withdrawals due to AEs, nature and time not reported. Commonly reported AEs in evaluable patients at 1 year (n = 40) similar to RCTs	Assessments every 3 months. Measurement tools for AEs not stated
Arzimanoglou, 1997[234] Multicentre study France	Uncontrolled trial	397 patients with partial or partial and secondarily generalised epilepsy. Mean age 37 years (range 12–74)	VGB adjunctive Dose: mean final dose 2.21 g/day (±0.64) Duration: mean 112.4 days (±35.3) Concomitant drugs: CBZ, VPA, PB, CLB, PHT	32 withdrawals due to intolerability. 10 patients withdrawn because of AEs (not specified) at <30 days. Reasons for discontinuation given were drowsiness, insomnia and/or irritability, difficulties in concentrating; 1 patient reported depression. Commonly reported AEs similar to RCTs	Patients instructed to report all adverse reactions. Follow-up visits at 0, 2, 6 and 17 weeks Tolerability ITT (n = 397). Reporting of numbers of patients discontinued because AEs/intolerability is unclear (possibly 10, 32 or 14)
Russ, 1995[235] Multicentre study Switzerland	Uncontrolled trial	127 patients with partial or partial and secondarily generalised epilepsy. Mean age 29 years (range 0.5–72). 61 patients were resident in tertiary care, most had behavioural disturbance or mental retardation	VGB adjunctive Dose: mean 2.3 g/day Duration: mean 10 months (range 0.1–49) Concomitant drugs: other AEDs, not specified	6 patients withdrawn owing to AEs at ≤ 3 months; 1 patient at 9.5 months (depression/aggression), 1 patient at 12 months (irritability/aggression), 1 patient at 14 months (somnolence/fatigue) and 1 patient at 24 months (irritability). All 10 withdrawals were patients from tertiary care. Other AEs similar to RCTs	Exclusion criteria: pregnancy, breastfeeding Information on AEs obtained from patients at every follow-up, apparently monthly. Physician rated as mild, moderate, severe and assessed causality in relation to VGB
Buchanan, 1994[236] Australia	Uncontrolled trial (possibly not a prospective trial but pseudo-cohort)	72 patients with partial or generalised epilepsy. Age not stated for all patients, adults and children were included	VGB adjunctive Dose: ≥ 2 g/day Duration: ~3 to >18 months Concomitant drugs: PHT, CBZ, VPA, barbiturates, CLB, CZP	Withdrawals due to behavioural change/psychosis (n = 5 at 5 days to 2 months), increased seizure frequency (n = 3), profound oedema (n = 1, time not stated). Patients withdrawn because of behavioural change/psychosis had history of either previous psychiatric or behavioural disturbance	Patients seen every month then 2- or 3-monthly. AEs assessed by patient and physician; measurement tools not stated

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Dam, 1989[237] Denmark	Uncontrolled trial	62 patients with partial or partial and secondarily generalised epilepsy. Mean age 31 years	VGB adjunctive Dose not stated Duration: 36 months Concomitant drugs: CBZ, VPA, benzodiazepines, other AEDs	41 patients continued beyond 19 months, reasons for discontinuation not reported. Around 39% experienced psychiatric symptoms (including depression) and a similar % sedative effects. Visual disturbance and dermatological events occurred but numbers not reported	Measurement tools and time of assessment of AEs not stated Possibly includes patients reported in Pedersen, 1985[238]
Pedersen, 1985[238] Denmark	Uncontrolled trial	36 patients with partial or generalised epilepsy. Mean age 28 years (range 4–69)	VGB adjunctive Dose: mean 2.6 g/day (range 1–6) Duration: mean 9.3 months (range 2–32) Concomitant drugs: CBZ, VPA, CZP, OXC, ethosuximide, PB	2 withdrawals owing to unacceptable nausea ($n = 1$) and vomiting ($n = 1$), time not reported. Commonly reported AEs similar to RCTs	Measurement tools and time of assessment of AEs not stated These patients are possibly included in Dam, 1989[237]
Guberman, 2000[239] Multicentre study Canada	Open-label extension of 97/100 patients who completed a double-blind study (≥ 50% reduction in seizures)	97 patients with intractable long-standing partial epilepsy. Adults	VGB adjunctive Dose: 3–4 g/day Duration: 1 year Concomitant drugs: not listed but included PHT and PB	12 withdrawals due to neurological/psychiatric AEs (not specified). 12 patients hospitalised including 15 events classified as serious, 4 possibly (status epilepticus, $n = 1$ at 60 weeks), probably (delerium, suicidal ideation, $n = 1$ each at 2–6 weeks) or definitely (psychosis, $n = 1$ at 11 weeks) related to VGB. Ophthamological examination did not show any clinically important effects of VGB. Commonly reported AEs similar to RCTs	Exclusion criteria: progressive neurological disorder, previous cranial radiotherapy, frequent status epilepticus, psychiatric illness, drug or alcohol abuse, known allergy to VGB, poor compliance AEs recorded during study visits at week 2, 4, 6, 10, 14, 18, 22, 26, 38 and 52. Visual evoked potential measured at week 6 and end of study

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Michelucci, 1994[240] Italy	Open-label extension study of patients with >50% reduction in seizure frequency or clinically important improvement in QoL in response to VGB in two previous trials	30 patients with partial or partial and secondarily generalised epilepsy. Mean age 28 years (range 16–52)	VGB adjunctive Dose: 1.5–4 g/day Duration: median 60 months (range 26–70) Concomitant drugs: PB, PHT, CBZ, CLB, other benzodiazepines, VPA, AZM	Commonly reported AEs similar to RCTs. All transient except weight gain (n = 7). None of 10 withdrawals due to AEs	AEs noted in patient diaries, clinic visits at 2–3-month intervals The 11 patients enrolled from one of the previous studies had VGB discontinued for 1–16 months between the first and follow-up study owing to shortage of drug supply
Sivenius, 1991[243] Finland	Open-label extension study of patients who showed benefit from 3 months treatment with VGB and then completed a 3 month dose-reduction study	54 patients with partial epilepsy. Mean age 29 years (range 15–52)	VGB adjunctive Dose: mean 3 g/day (range 1.5–5) Duration: median 59 months (range 54–65) Concomitant drugs: other AEDs, not specified	Withdrawals due to drowsiness (n = 1 at 6 months), psychosis (n = 1 at 1 year), visual disturbance, later diagnosed as optic neuritis (n = 2 at <2 years), depression (n = 1 at <2 years). Other AEs dose-related (psychotic symptoms, n = 2) or resolved with time 1 patient withdrawn because of pregnancy at 3 years follow-up; baby showed normal development at 1 year 28 patients remained in study for 5 years	Clinic visits every 3 months; measurement tools for AEs not stated
Reynolds, 1991[242] UK	Open-label extension study of responders (>50% reduction in seizure frequency) who completed 8-week open phase and 8-week double-blind placebo-controlled phase of a previous study	17/33 patients with partial or generalised epilepsy. Mean age 29 years (range 16–61) Co-morbidities: 10 patients had neurological or mental handicap	VGB adjunctive Dose: 2–3 g/day Duration: 16 weeks plus 1 year Concomitant drugs: CBZ, PHT, VPA, PB, CLB, others	7 withdrawals due to unacceptable AEs in open phase (3 patients developed depression). AEs continued to emerge during long-term phase (12–18 months). All reported AEs similar to RCTs	Exclusion criteria: risk of pregnancy, unable to keep seizure diary, serious renal, hepatic, cardiovascular, gastrointestinal or other medical or psychiatric disease, drug or alcohol abusers AEs recorded from spontaneous patient reports, responses to questions, physical, haematological/metabolic examination at each clinic visit (times not specified)

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Browne, 1991[241] USA	Open-label extension study of patients who had a favourable response to VGB in a 16-week single-blind study 89 patients entered single-blind phase, 84 completed. 66 entered long-term phase. 26 patients followed for >5 years	66 patients with partial epilepsy. Age not stated	VGB adjunctive Dose: median 3 g/day (range 1–4) Duration: median 43 months (range 5–72) Concomitant drugs: not stated	6/37 withdrawals due to AEs, another 5 due to AEs and seizure breakthrough. Events and time not stated. Median treatment duration across all withdrawals 13 months (range 5–65). No clinical abnormalities detected by visual evoked response testing, details not reported. Commonly reported AEs similar to RCTs	Follow-up every 3 months during long-term phase. Visual evoked potential studies every 3 months. Measurement tools for other AEs not stated
Schmitz, 2002[244] Germany	Follow-up of patients with epilepsy who completed a previous short-term study	29 VGB patients compared with 31 patients who received another AED. Seizure types not stated. Median age at follow-up 32–51 years (range 20–68)	VGB monotherapy ($n = 6$), adjunctive ($n = 23$) Dose: adjunctive median ~3 g/day (range 1.5–4); monotherapy not stated Duration: median 3 months (range 3–7) VGB monotherapy, 23 months (range 8–37) VGB adjunctive, 5 months (range 2–8) control group Concomitant drugs: not reported in full for all patients. Common AEDs included CBZ and VPA	Observation period median 46 months (range 40–53) VGB monotherapy, 56 months (range 34–72) adjunctive, 65.5 months (range 38–102) control group Development of clinically relevant VFC was significantly more common in patients who received VGB (2/6 monotherapy + 11/23 adjunctive vs 3/31 controls). VFC severe in 2 monotherapy patients, 8 adjunctive patients and 1 control; mild in 3 adjunctive patients and 2 controls In adjunctive VGB patients with VFC, median duration of treatment was 41 months (range 9–71) vs 20 months (range 6–54) in patients without VFC, $p = 0.04$. No significant difference shown in maximum dose between adjunctive patients with and without VFC. VFC was not related to type and severity of epilepsy, type and number of concomitant AEDs or length of follow-up At the time of follow-up, 6 adjunctive patients and 2 monotherapy patients were still taking VGB	Ophthalmological assessment of perimetry and VFs at baseline and follow-up

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Paul, 2001[245] USA	Follow-up of patients who continued to take VGB following a prior study and completed visual testing every 3 months for 1 year	15 patients with partial or generalised epilepsy. Age 27–71 years	VGB adjunctive Dose: 1.5–6 g/day Duration: 27–75 months Concomitant drugs: CBZ, PHT, VPA, GBP, LTG, PRM	15 patients who completed 1-year serial testing showed no worsening of VFC, visual acuity or colour vision (6 had constricted VFs on initial testing). Similar results in 7 patients who completed 3–9 months of testing (3 had constricted VFs on initial testing)	Ophthalmologic examinations every 3 months while taking VGB
Kälviäinen, 1999[246] Finland	Follow-up study of patients from an RCT of VGB vs CBZ monotherapy (n = 135) still using that treatment and still attending the clinic. Controls: 10 healthy adults	VGB: 32 patients with partial epilepsy. Age 40 years (range 19–73) CBZ: 18 patients. Age 43 years (range 20–70) Controls: age 42 years (range 23–74)	VGB monotherapy Dose: not stated Duration: mean 68.7 months (range 29–119) 5/32 VGB patients discontinued CBZ as primary monotherapy in the RCT and 1 CBZ patient switched from VGB as primary monotherapy (1.5 months VGB 8 years earlier)	13/32 VGB patients had concentrically restricted VFs (3 severe, 10 mild). Correlation between extent of VF and duration, dose or cumulative amount of VGB consumed was not statistically significant. 1 VGB patient complained of visual problems. No CBZ patients or controls had VFDs	Ophthalmologic examination, perimetry, other visual tests. Related paper Nousiainen (2000)[476] reports colour vision in same VGB and CBZ patients and 45 age-matched controls. Abnormal colour perception found in 10/31 (32%) VGB patients and 5/18 (28%) CBZ patients
Tartara, 1997;[247] 1994;[457] 1992[464] Italy	Follow-up study, initially of responders from a short placebo-controlled trial of adjunctive VGB; source of further recruited patients unclear	162 patients with partial or partial and secondarily generalised epilepsy. Adults	VGB adjunctive Dose: 2.8 g/day (range 1–4) Duration: mean 34.3 months (range 6–161) Concomitant drugs: not stated	Withdrawals due to ataxia (n = 3 within 1 month), depression (n = 2 at 2 and 7 months), psychotic reactions (n = 3 at 2, 12 and 22 months) and exacerbation of seizures (n = 3 within first 6 months) 8/11 withdrawals because of AEs within first 6 months, no new events reported beyond 22 months	Measurement tools and time of assessment of AEs not stated. First 6 years of follow-up (25 patients) reported clinic visits every 3–6 months
Pitkänen, 1993;[248] Matilainan, 1988[454] Finland	Follow-up of patients who were responders (>50% reduction in seizure frequency) to adjunctive VGB in a short-term (3 months) study (n = 36)	15 patients with partial or generalised epilepsy. Mean age 28 years (SD 9) Co-morbidities: mental handicap	VGB adjunctive Dose: 2.5 g/day (±0.5) Duration: 5 years Concomitant drugs: other AEDs, not specified	5 withdrawals due to AEs, psychosis in 3 patients and reason unclear in 2 patients. Psychic side-effects often appeared during the second year At 5 years follow-up 10/15 responders still taking VGB	Clinic visits every 3 months for 2 years then every 6 months; measurement tools for AEs not stated, other than psychological tests at 1, 2 and 4 years Very similar report is a study in 21 probably not independent patients[477]

continued

TABLE 107 *Vigabatrin primary studies (cont'd)*

Study	Design	Participants	Intervention	Results	Comments
Remy, 1989;[249] Cosi, 1988;[455] 1989[456] Multicentre study Europe	Follow-up of responders from various primary studies who continued on VGB	254 patients with partial or generalised epilepsy. Mean age 28 years (range 1–69). 217 patients >16 years	VGB adjunctive Dose: mean 3.1 g/day (range 0.5–9.0) Duration: mean 22.7 months (range from at least 12 to>24) Concomitant drugs: CBZ, PB (most common)	4 withdrawals due to severe psychotic reaction, mild visual disturbance, constipation. AEs (severe schizophrenic symptoms, mild acne, mild vertigo) contributory to withdrawal of 3 additional patients. 25% of patients reported AEs, 68% of events attributed to VGB; severe in 10.5% of reports. Commonly reported AEs similar to RCTs Evoked potentials, including visual, in 17 patients measured before and after 7 weeks of treatment showed no significant influence of VGB	At clinic visits every 3 months investigator recorded details of patient reported AEs including relationship to VGB. Ophthalmological examination every 6 months

TABLE 108 *Prescription event monitoring study of more than one AED*

Study ID	Aim	Study design	Participants	Treatment duration	Methods	Results	Conclusion
Wilton, 1998[171] UK	To determine the proportion and nature of congenital anomalies in babies born to women exposed, in general practice in England, to newly marketed drugs (including GBP, LTG and VGB) in the 1st trimester	Non-interventional observational cohort studies conducted by PEM	GBP 17 women LTG 68 women VGB 81 women 1 woman exposed to LTG and VGB was included in the VGB cohort	Exposure in the first trimester	Outcomes of pregnancy, and proportion and nature of congenital anomalies among babies born, were recorded	**GBP**: 17 pregnancies exposed in 1st trimester; 11 births (1 premature). Congenital anomaly absent **LTG**: 59 pregnancies exposed in 1st trimester; 39 births. Congenital anomaly in 1 premature and 3 full-term babies: 1 ventricular septal defect; concomitant medication aminophylline, steroids, salbutamol, PB, VPA 1 congenital respiratory stridor; concomitant medication PHT, folic acid, simple linctus 1 palatal cleft, hypospadiasis, undescended testes; concomitant medication CBZ, VPA and PHT increased in dose 1 possible congenital intestinal obstruction; concomitant medication Labetolol in last 4 months **VGB**: 76 pregnancies exposed in 1st trimester; 47 births. Congenital anomaly in 2 full-term babies: 1 bowed tibiae, increased muscle tone; concomitant medication VPA, CBZ 1 occipital plagiocephaly, premature fusion of lamboid suture, clicky hips; concomitant medication PHT, folic acid An additional full-term baby in the VGB cohort had clicky hips, classed as a minor congenital anomaly	Of 831 pregnancies among women who had taken a newly marketed drug during the 1st trimester, 6/16 cases of congenital anomaly were in women who had epilepsy and were receiving multiple AEDs. In 6 of these women treatment included one of the newer AEDs. Established AEDs may be associated with adverse pregnancy outcomes, and the role of epilepsy itself should be considered when evaluating birth defects

TABLE 109 *Primary studies of more than one AED*

Study	Design	Participants	Intervention	Results	Comments
Samren, 1999[205] The Netherlands	Cohort (controlled) of 1411 children born from 1972 to 1994 to 921 mothers using antiepileptic drugs during the 1st trimester and non-epileptic matched controls (1955 mothers, 2000 children)	6 women treated with new AEDs. Age <20 to 35+ years were included in the study	OXC monotherapy (n = 2) or polytherapy (n = 3); VGB polytherapy (n = 1)	1/3 babies exposed to OXC polytherapy (OXC 3000 mg/day, VPA 1800 mg/day, CLB 22 mg/day) had a major congenital abnormality (spina bifida cystica and clubfoot). RR = 34.0 (95% CI: 3 to 386). Mother had partial epilepsy	Data collected from medical records
Kwan, 2001[202] UK	Cohort (uncontrolled) of 470 patients treated with a first-line AED at one centre between 1984 and 1997	78 patients treated with LTG. Mean age 35 years (SD 19.4); 90% >15 years	78 patients received LTG Dose: 50–400 mg/day Duration: duration of treatment not stated; mean follow-up (all 470 patients) 5.6 years (SD 3.4)	LTG withdrawals 8/78, time not reported. Proportion who changed treatment due to AEs: idiopathic epilepsy CBZ 8/29 vs LTG 0/20, p = 0.01; symptomatic/cryptogenic epilepsy CBZ 49/183 vs LTG 8/58, p = 0.04. Dose in patients with intolerable side-effects 300 mg/day (range 150–375) Rash was the most common AE reason for withdrawal of LTG (3/8), no significant difference compared with CBZ or to VPA. Other AEs similar to RCTs	Patients who did not comply with treatment excluded from analysis Patients reviewed at clinic every 4–6 weeks in first 6 months then at least every 4 months
Lhatoo, 2000[187] UK	Cohort (uncontrolled) of all patients with chronic refractory epilepsy ever treated with GBP (n = 158), LTG (n = 424), TPM (n = 393) at given centres identified through clinic notes and GPs	975 patients with partial and/or generalised epilepsy. Mean age 32–35 years (range 13–78). 196 with learning disability	GBP, LTG or TPM monotherapy or adjunctive Dose: max. GBP 1440 mg/day (range 180–3600); LTG 297 mg/day (range 12–900); TPM 308 mg/day (range 24–1800) Previous new AED exposure LTG, GBP, TPM and VGB	At 3 years 30% continued on TPM, 29% on LTG and 10% on GBP. AEs (not specified) led to withdrawal of 40% on TPM, 22% on LTG and 37% on GBP Cox regression estimated one-quarter of patients are likely to continue with a new AED beyond 5 years	Exclusion criteria: patients treated at other centres and patients on the drug before referral, or in clinical trials AEs patient reported. Retrospective sources of information were records and interviews with patients and GPs Possibly same patient pool as Wong (2001)[189] PMS study

Selected abbreviations throughout Appendix 25:
ADR, adverse drug reaction; AED, antiepileptic drug; IQ, interquartile range; ID_1, incidence density for each event during first month of treatment; ID_2, incidence density for each event during treatment months 2–6; PEM, prescription event monitoring; PMS, postmarketing surveillance; QoL, quality of life; SD, standard deviation; SMR, standardised mortality ratio with drug compared with the population of England.

Appendix 26

Extraction tables for studies included in the assessment of cost-effectiveness

Published cost-effectiveness evaluations

Studies of monotherapy (*n* = 4)

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Bryant, 1998[252] Adult patients with epilepsy Review/synthesis of previous studies Literature Expert opinion	Cost-effectiveness analysis £Sterling Not stated Health service	CBZ, monotherapy, 600 mg/day LTG, monotherapy, 100 mg/day LTG, monotherapy, 200 mg/day PHT, monotherapy, 300 mg/day	Proportion of patients seizure free after 24 weeks of maintenance therapy	Simple decision tree To compare costs associated with LTG and CBZ for 3 alternative treatment pathways Costs and benefits were combined for a 24-week maintenance regimen Proportion of patients seizure free at 24 weeks; titration rates; drug costs; cost of consultations (primary, secondary and follow-up); cost of safety monitoring; cost of plasma level tests. The model assumes patients who withdrew early from the studies incur the same costs as those who completed the trial Drug cost per patient seizure free after 24 weeks of maintenance	Sensitivity analyses: no sensitivity analysis was undertaken. Authors' conclusions: drug cost per patient seizure free after 24 weeks of maintenance on LTG could be 5–10 times greater than on CBZ Even when comparing the minimum management scenario for LTG (200 mg/day) with the maximum management scenario for CBZ, LTG is still 1.5 times more expensive. Comments: the authors also briefly assessed the use of LTG as adjunctive therapy. The drug cost of achieving one patient with 50% reduction in seizure frequency at 24 weeks was estimated to be £2871

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Heaney, 1998[253] Patients aged >12 years, with newly diagnosed epilepsy (partial and generalised onsets) Review/synthesis of previous studies Literature Review/synthesis of previous studies + expert opinion	Cost minimisation analysis £Sterling 1996 Health service	CBZ, monotherapy, 600 mg/day LTG, monotherapy, 150 mg/day PHT, monotherapy, 300 mg/day VAP, monotherapy, 1000 mg/day	Health outcomes were not included in the economic evaluation	Simple decision tree To compare the expected costs of treatment associated with each of the 4 AEDs Direct healthcare costs were modelled over a 2-year period; the model assumed therapeutic equivalence between the AEDs and no difference in their respective rates of AEs or hospitalisations. Patients who fail first monotherapy can switch to second monotherapy or to polytherapy Drug costs (AED); withdrawal rate; prevalence of side-effects; cost of polytherapy; cost of specialist follow-up; costs of consultations (primary, secondary and emergency care); laboratory tests; costs associated with AED withdrawal; cost of treating AEs Total per patient cost of (2 years') treatment	Sensitivity analyses: a series of one-way sensitivity analyses were undertaken, using best and worst case values. The sensitivity analysis was conservative: worst and best case values for any AED (for withdrawal rate and prevalence of side-effects) were applied to all AEDs Parameters tested included: AED dose; withdrawal rate; prevalence of side-effects; proportion of patients requiring polytherapy; costs associated Analyses on both an ITT and on a 'maintained on monotherapy' basis were performed Even when the best case scenario for LTG was compared with the worst case scenario for the other AEDs, LTG was still more costly Authors' conclusions: LTG for newly diagnosed patients is significantly more expensive than CBZ, PHT or VPA, even when differences in side-effect profiles and tolerability are taken into account. However, this precludes any QoL assessment. Comments: none

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Heaney, 2000[254] Adults with newly diagnosed epilepsy (partial and generalised onsets) Review/synthesis of previous studies Literature Review/synthesis of previous studies + expert opinion	Cost minimisation analysis $US Not stated Health service	CBZ, monotherapy, 600 mg/day LTG, monotherapy, 150 mg/day PHT, monotherapy, 300 mg/day VAP, monotherapy, 1000 mg/day	Health outcomes were not included in the economic evaluation	Simple decision tree To compare the expected costs of 4 AEDs in 12 European countries Direct healthcare costs were modelled over a 1-year period; the model assumed therapeutic equivalence between the AEDs and no difference in their respective rates of AEs or hospitalisations. Patients who fail first monotherapy can switch to second monotherapy or to polytherapy AED cost; proportion of patients treated with polytherapy; cost of consultations (primary, secondary and follow-up); emergency admissions; laboratory tests; plasma level tests; inpatient days Total per patient cost of treatment	Sensitivity analyses: assumptions made by the expert panel were tested using a series of one-way sensitivity analyses. In addition, the AED dose derived from clinical trial data was tested using the range judged by the consensus panel to be appropriate for each of the 12 countries Parameters tested included: frequency of hospitalisation; AED dose; frequency of follow-up visits; proportion of patients treated with polytherapy Although costs were sensitive to the parameters tested, the overall conclusion of the economic evaluation was robust. Authors' conclusions: in each country considered, LTG was 2–3 times more expensive over the first year of treatment than the other drugs considered Comments: the authors report that a societal perspective was taken, but include only direct healthcare costs in the analysis The authors used one-way sensitivity analyses rather than best and worst case scenarios to investigate uncertainty around the findings The research was supported by Sanofi-Synthelabo

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Shakespeare, 1998[255] Patients aged ≥ 13 years, with newly diagnosed tonic–clonic seizures (partial and generalised onsets) Single study Literature Review/synthesis of previous studies, experts	Cost minimisation analysis £Sterling 1994 Health service	CBZ, monotherapy, 600 mg/day LTG, monotherapy, 150 mg/day	Health outcomes were not included in the economic evaluation	Simple decision tree To compare the expected annual average cost per patient of treatment for AEs associated with LTG and CBZ Direct healthcare costs were modelled over a 1-year period. Therapeutic equivalence between the AEDs was assumed. Patients who fail first monotherapy switch to second monotherapy Rate of AEs; withdrawal rate; mean time to withdrawal; drug costs (AED and others); switching cost; cost of consultations (primary and secondary), inpatient admissions and laboratory tests Total per patient cost of treatment	Sensitivity analyses: changes in the rate of AEs were not explored. One-way sensitivity analyses were conducted as follows. Using UK recommended AED doses (CBZ, 800 mg; LTG, 250 mg) increased the cost difference between the two AEDs by almost 80% When the withdrawal rate (proportion of patients switching therapy) was lowered to levels reported by a different trial, the cost difference rose by 15% As mean time to withdrawal increased, the cost difference increased (by 8% maximum) When the 'switched to' drug for CBZ was changed from VPA to LTG, the cost difference fell by 25% Authors' conclusions: even when the cost of treating AEs and the cost of switching AEDs are taken into account, CBZ is cost saving relative to LTG for the monotherapy treatment of patients with newly diagnosed epilepsy Comments: in the absence of published data, treatment pathways for AEs were based on expert opinion The rate of AEs was taken from a single study, where titration rates may not reflect clinical practice

continued

Studies of adjunctive therapy (*n* = 7)

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Hughes, 1996[256] Patients aged >12 years, with intractable partial epilepsy Review/synthesis of previous studies Literature Review/synthesis of previous studies and opinion	Cost minimisation analysis £Sterling 1995 Health service	GBT, adjunctive, 1200 mg/day LTG, adjunctive, 200 mg/day VGB, adjunctive, 2000 mg/day	Health outcomes were not included in the economic evaluation	Simple decision tree To compare the expected direct healthcare costs associated with three AEDs over a 1-year period Direct healthcare costs were modelled over a 1-year period. Therapeutic equivalence between the AEDs was assumed, but differences in tolerability were modelled. Change in adjunctive AED therapy following treatment intolerance was not specified Incidence rates of side-effects (minor and major); dosage rates; consultations (primary and secondary care); scanning; plasma levels Total per patient cost of treatment	Sensitivity analyses: the authors used high and low estimates from the literature to deal with uncertainty around the cost estimates. These were applied to the incidence of side-effects and to assumption of dosage levels Authors' conclusions: treatment with GBP has similar initial direct costs but fewer side-effects, resulting in savings of £18.52 per patient in the first year compared with LTG and £47.18 compared with VGB. If all NHS patients with intractable epilepsy who are suitable for the new drugs were treated with GBP, rather than LTG, this would result in cost savings to the NHS of £166,680 in the first year. The corresponding figure for GBP compared with VGB is £424,620 Comments: the authors' findings are highly dependent on the estimated incidence rates of side-effects and treatment pathways. However, these findings should be treated with caution, because it is unclear how the review was conducted. Specifically, neither the search strategy for the literature review nor the criteria for inclusion of studies were reported. In addition, findings do not appear to have been adjusted for any between-trial differences (such as sample size) and no statistical analysis of estimates was undertaken. This study is therefore unable to offer reliable guidance for clinical practice

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Markowitz, 1998[258] Patients with refractory epilepsy (uncontrolled by any single older AED or by any combination of the older AEDs) Review/synthesis of previous studies Literature Review/synthesis of previous studies + expert opinion	Cost-effectiveness analysis US$ Not stated Health service	LTG, adjunctive, 400 mg/day No adjunctive therapy (monotherapy with older AEDs)	Seizure-free days gained	Simple decision tree To estimate the expected cost per seizure-free day gained from adjunctive LTG therapy The model compared costs and benefits over a 10-year period. Patients who withdraw owing to AEs do so in the first year. Only patients with a reduction in seizure frequency of at least 25% are treated for a second year with LTG. Otherwise, trial outcomes are assumed to persist over the time horizon of the model. Treatment responders are assumed to be less likely to undergo evaluation for surgery (34%) compared with those not on LTG (50%) Seizure days; cost of hospitalisations; surgery-related costs; consultations (outpatient and emergency); plasma levels; cost of scans; drug costs; AEs; reduction in seizure days; LTG dose; withdrawal rate; discount rate Cost per seizure-free day gained	Sensitivity analyses: a series of one-way sensitivity analyses were used to explore the impact on the estimate of cost-effectiveness of changes in the following parameters. Increasing the percentage of LTG patients evaluated for surgery increased the cost per seizure-free day gained Increasing the number of seizure days per year by 1 SE above the mean was cost saving; decreasing the parameter by the same amount increased the cost-effectiveness ratio by a factor of 9 Changes in the rate of hospitalisation and in LTG dose resulted in same-direction changes in the cost-effectiveness estimate. The impact of changes in withdrawal rate and the discount rate was not considered Authors' conclusions: the expected cost per seizure-free day was $6.90. Although treatment of refractory patients with LTG adds to overall healthcare costs in most years, the extra drug costs are partially offset by savings because of decreases in other healthcare use Comments: the most important variable tested in the sensitivity analysis was 'seizure days'. Using SEs around the mean of this parameter, the cost-effectiveness of LTG ranged from –$5.61 to $63.60 The parameter was estimated from data in two short-term clinical trials used to model the number of seizure-free days, with data extrapolated to a 10-year time horizon. As the modelling methods were not fully reported, it is unclear if these were appropriate

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
					The impact of surgery rates and rate of evaluation for surgery were also important in determining cost-effectiveness. Estimates were based on expert opinion, in the absence of clinical trial data. Although the impact of increasing the rate of surgical evaluation was explored, the effect of postponing, rather than averting, surgical costs was not considered The work was supported by Burroughs Wellcome/Glaxo Wellcome
Messori, 1998[261] Patients aged 18–65 years, with refractory partial seizures Single study Literature Single study + expert opinion	Cost–utility analysis US$ Not stated Health service	LTG, adjunctive, 500 mg/day No adjunctive therapy (monotherapy with older AEDs)	Short-term clinical outcomes were assumed to remain stable over subsequent years. These outcomes were converted into QALYs years: trial data were extrapolated to produce survival curves, which were adjusted using utility data taken from a separate prospective study	Simple decision tree To determine the expected lifetime cost per QALY gained of using adjunctive LTG vs no adjunctive therapy Short-term (6-month) clinical outcomes were assumed to remain stable over the patient's lifetime QoL scores; proportion of patients in each outcome/event category; drug costs; consultations (primary, secondary and emergency care); scans; plasma level tests; costs associated with surgery; cost of treating AEs Cost per QALY gained	Sensitivity analyses: a one-way sensitivity analysis was used to examine the effect of varying the QoL score associated with level 3 (patients experiencing a partial response to the intervention). The resulting range of cost per QALY gained ($25,000–83,000) was reported to be undramatic Authors' conclusions: the ICER of adjunctive LTG was $41,300 per QALY gained Comments: the authors reported the study perspective taken to be societal. However, indirect and non-medical costs were excluded from the analysis

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
O'Neill, 1995[262] Patients with intractable epilepsy (patient age range not reported) Review/synthesis of previous studies + expert opinion Literature Expert opinion	Cost-effectiveness analysis £Sterling 1993 Health service	CLB, adjunctive, 20 mg/day LTG, adjunctive, 150 mg, b.d. VGB, adjunctive, 2000 mg/day	Treatment success was defined as the achievement of both the following conditions: 1. Long-term seizure control (at 12-month follow-up) 2. Duration of seizure control of at least 9 months of the 12-month period	Simple decision tree To compare the expected cost of the AEDs for 12 treatment pathways Costs and benefits were modelled over a 1-year period. The cost of treating AEs was not included. It was assumed that, after 3 months of therapy with either VGB or LTG, there would be no withdrawal due to drug tolerance Proportion of treatment successes at follow-up visits; AED doses; sequencing of adjunctive therapy following treatment failure; duration of seizure control; drug costs; cost of additional clinic visits for the treatment of uncontrolled seizures Cost per successfully treated patient	Sensitivity analyses: five one-way sensitivity analyses were performed. The parameters explored included number of clinic visits; efficacy of CLB; efficacy of LTG and VGB; the dose of CLB; the doses of LTG and VGB. None of these changed the cost-effectiveness advantage for CLB. In addition, best and worst case scenarios (for CLB) using all five parameters were reported. The worst case scenario gave the newer drugs a small (10%) cost-effectiveness advantage Authors' conclusions: there appears to be a clear cost-effectiveness advantage for CLB over LTG and VGB Comments: the costs of plasma monitoring and of treating side-effects were excluded from the model

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Reinharz, 1995[259] Adult patients with epilepsy Not applicable Literature Other	Other Can$ 1993 Health service	VGB, adjunctive (2000, 3000 or 4000 mg/day) No adjunctive therapy (monotherapy with older AEDs)	Health outcomes were not included in the economic evaluation	Simple decision tree To evaluate the effects of VGB on the cost of treating patients with epilepsy Direct healthcare costs were modelled over a 1-year period. Proportion of patients treated with VGB; rates of hospital admissions; rate of emergency services; surgery theatre time; cost and dose of VGB; cost of hospital and emergency services Total per patient cost	Sensitivity analyses: two scenarios were explored: 1. Dose adjustment for the purpose of seizure control is not a major reason for use of hospital services A series of multi-way sensitivity analyses were conducted, in which the following parameters were varied: use of ('responsive') hospital and emergency services; surgery theatre time; VGB usage rate; VGB dose A threshold analysis was also performed, in which VGB usage rate was varied to find the level of hospital utilisation that would make the introduction of VGB cost neutral, relative to current care. VGB was found to be cost saving at doses of 2 and 3 g/day, but cost generating at 4 g/day if the reduction in the rate of hospital/emergency services used was not high and vigabatrin usage rates were not low (approx.) 2. Dose adjustment for the purpose of seizure control is a major reason for use of hospital services A series of multi-way sensitivity analyses were conducted, in which the following parameters were varied: use of ('responsive') hospital and emergency services; surgery theatre time; VGB usage rate; VGB dose A threshold analysis was also performed, in which VGB usage rate and the utilisation of emergency services were varied to find the level of hospital utilisation that would make the introduction of VGB cost neutral, relative to current care. VGB was found to be cost saving at doses of 2 g/day, but cost generating at 3 and 4 g/day

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of economic evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
					Authors' conclusions: the effect of introducing VGB on treatment costs for patients with epilepsy depends on the VGB dose, the impact on hospital admissions and the proportion of patients who take VGB Comments: the paper was published before the serious side-effects associated with VGB were known In the UK, the use of VGB is currently restricted to patients in whom all other combinations of AEDs are inadequate or not tolerated. The work was partially funded by a grant from Marion Merrell Dow Canada
Schachter, 1999[260] Patients with at least 4 complex partial seizures per month, refractory to monotherapy with older AEDs Single study Not stated Single study	Cost-effectiveness analysis US$ Not stated Health service	PHT + CBZ, adjunctive, doses not stated Phenytoin + TGB, adjunctive, doses not stated CBZ + PHT, adjunctive, doses not stated CBZ + TGB, adjunctive, doses not stated	A reduction in complex partial seizure rate of at least 50%.	Simple decision tree To compare the mean management costs associated with four treatment regimens Direct treatment costs measured as part of a 16-week trial Incidence of AEs; cost of treatment failure; drug costs; cost of AEs The direct healthcare costs associated with four treatment regimens	Sensitivity analyses: no sensitivity analysis was undertaken Authors' conclusions: newer AEDs may have potential cost savings due to improved tolerance of long-term therapy Comments: only summary details of this economic evaluation are available The research was supported by Abbott Laboratories

continued

Author, Year Study population Source of effectiveness data; source of unit cost data; source of resource use data	Type of Economic Evaluation Currency Cost year Perspective	Interventions	Economic outcomes reported	Type of model Purpose of model Key components Key input parameters Model outputs	Sensitivity analysis Authors' conclusions Comments
Selai, 1999[257] Adult patients with refractory epilepsy (partial) (uncontrolled by monotherapy with older AEDs) Single study Literature Single study	Cost-effectiveness analysis £Sterling Not stated Health service	LTG, adjunctive, dosage not stated TPM, adjunctive, dosage not stated	Patients were deemed to be 'satisfied' if they met all 4 of the following conditions: 1. still on drug at 6-month follow-up 2. experiencing no side-effects 3. had no AEs 4. had a >50% reduction in seizure frequency QoL was assessed, but findings not reported	No modelling was undertaken The economic evaluation was a prospective randomised study to estimate the costs and effects over a 6-month follow-up period Patient-level resource use data were collected for drug therapy, incidence of AEs and inpatient episodes. Cost-effectiveness was expressed as the cost per successfully treated patient	Sensitivity analyses: no sensitivity analysis was performed Authors' conclusions: 7/47 (15%) patients receiving TPM and 3/26 (11%) patients receiving LTG were satisfied with treatment. The cost per patient with topiramate (without telemetry costs) was £472 compared with £587 for LTG Comments: the cost of AEs for patients lost to follow-up (8/81) were not included in the cost estimates The authors acknowledge the limitations of a prospective, short-term clinical audit in providing evidence on which treatment decisions may be based

Unpublished economic models submitted by companies

Evaluation of industry evidence of cost-effectiveness of monotherapy lamotrigine compared with older AEDs[264]

Health technology
LTG 150 mg/day as monotherapy. Comparator CBZ 1000 or VPA 1500 mg/day.

Study question
To assess the incremental cost-effectiveness of LTG as first-line monotherapy over CBZ and VPA relating to seizure control, likelihood of discontinuation of treatment and treatment-related side-effects.

Economic study type
CUA.

Study population
Newly diagnosed patients with partial or generalised onset tonic–clonic seizures.

Dates to which the data relate
The effectiveness data are based on studies published between 1995 and 2001.
Resource use is based on studies published in 1998.
Unit costs are based on references published in 2001 and 2002.
Utilities are taken from a study completed in 2002.
The price year is not stated in the study.

Modelling
The model aims to estimate the incremental cost and utility of LTG compared with VPA or CBZ. The model is a decision tree. All patients start treatment with monotherapy. Patients who fail owing to unacceptable side-effects are assumed to switch to a non-drug-specific second-line therapy after 10 weeks. The remaining patients who are not completely seizure free are assumed to remain on therapy until the end of the trial and then switch to a non-drug-specific second-line therapy. Patients who are seizure free at the end of the trial are assumed to remain seizure free until the end of the modelling period (52 weeks).

Effectiveness inputs to the model
The inputs to the model are the proportion of patients seizure free at the end of the trial, the proportion that discontinued the therapy, the proportion seizure free and discontinued in their second-line therapy and the utilities for each state.

Study designs and other criteria for inclusion in the review
Effectiveness evidence for the first-line monotherapy is taken from pivotal RCTs. Effectiveness of second-line therapy is taken from a non-drug-specific prospective audit. Utility evidence is taken from a bespoke unpublished, non-peer-reviewed study.

Sources searched to identify primary studies
Not specified.

Criteria used to ensure the validity of primary studies
Not specified.

Methods used to judge relevance and validity and for extracting data
Not specified.

Number of primary studies included
Five studies are used for effectiveness of first-line monotherapy. One study is used for effectiveness of second-line therapies. One study is used for utilities.

Method of combination of primary studies
The model was run for each study individually.

Investigation of differences between primary studies
Not stated.

Results of the review
RCTs lasted between 18 and 40 weeks. Seizure control varied between 22 and 52% for LTG, between 29 and 55% for CBZ and between 16 and 26% for VPA. Discontinuation rates varied between 9 and 15% for LTG and between 13 and 27% for the older AEDs.

The result of the observational study was that seizure control on second-line therapy was less likely if the patient failed first therapy owing to inadequate seizure control than if they failed owing to unacceptable side-effects.

Economic analysis
Measure of health benefits used in the economic analysis
The measure of health benefit is the QALY. Utility weights were estimated from a questionnaire administered to the UK general public, using standard gamble to derive preferences. The questionnaire included scenarios describing likelihood of side-effects experienced by patients on each of the three medications in combination

with levels of seizure freedom. Only scenarios given to women aged 18–45 years included side-effects relating to contraception and foetal health.

Costs
Unit costs and resource use were described separately. The direct costs used were the costs of medications, GP consultations and neurology outpatient attendances. Resource use was taken from two UK studies. Discounting was not used since the model extrapolated over 1 year.

Sensitivity analysis
One-way sensitivity analysis was carried out on utility weights, time of discontinuation and rates of discontinuation.

Results
The base case employs utility weights derived from all respondents. The expected incremental QALY gain for LTG varied between 0.012 and 0.027 for the 1-year duration of the model for data from different studies. The expected incremental cost of LTG per patient per year varied between £152 and £307. The ICER varied between £10,600 and £17,100. The authors report the mean ICER across the five studies to be £13,000.

Sensitivity analysis was performed using the utility weights for men only, for women only and for women aged 18–45 years only. Men gave a lower utility preference to the stated side-effects of LTG (rash) than the side-effects of older AEDs (weight gain, hair loss and loss of concentration) when seizure control was similar. When utility weights for men only were applied, the ICER increased or LTG was dominated by the comparator therapy.

The authors varied the time in the model that patients who experience severe AEs withdraw from the treatment from 6 to 12 weeks. They increase the probability of withdrawal for LTG by up to 50%. They state that these changes do not affect the conclusions.

Authors' conclusions
The authors conclude that LTG provides a cost-effective alternative, particularly in women of child-bearing age, and that the ICER is comparable to that of other funded interventions used in the NHS.

Commentary
The model assumes that patients withdraw early only owing to unacceptable side-effects. Patients who withdraw owing to lack of control are assumed to remain on therapy until the end of the trial. LTG tends to perform better than older AEDs when comparing rates of withdrawal during the trial period for AEs. However, there is less difference between AEDs when comparing rates of withdrawal for all reasons. Therefore this assumption tends to benefit LTG.

The model assumes that the percentage of patients seizure free at the end of the trial period will remain constant for the remainder of the modelling period (52 weeks). This assumption benefits LTG, which has slightly superior seizure freedom at the end of the trial period. This superiority may not be statistically significant. There is certainly no evidence this can be sustained over the long term.

The authors combine their results as a mean of the ICER for each trial. This approach is not recommended in the literature.[267] The authors state that they cannot use meta-analysis to estimate the effectiveness parameters from the trials since each trial has a different end-point. However, some of the trials reported survival curves of withdrawal rates and time to first seizure. This information could be used to interpolate effectiveness measures over a common end-point. Sensitivity analysis could then be used to handle second-order uncertainty about these parameters. Many of the primary studies do not find a significant difference in seizure control between the treatments. This uncertainty has not been addressed by the analysis.

Other studies have shown that results can also be sensitive to the dose assumed in the model, and this should be addressed in sensitivity analysis.

Evaluation of industry evidence of cost-effectiveness of lamotrigine compared with monotherapy alone[264]

Health technology
LTG as combination therapy compared with placebo (standard therapy alone). The dose is not stated explicitly but appears to be 150 mg/day when concomitant with VPR and 300 mg/day when taken concomitant with enzyme-inducing drugs.

Study question
To compare the cost-effectiveness of LMT used as adjunctive therapy compared with placebo. An NHS perspective is stated, but the only costs considered are those of LTG therapy.

Economic study type
CUA.

Study population
Adult patients with refractory epilepsy experiencing partial and generalised onset seizures.

Dates to which the data relate
Effectiveness data are taken from a Cochrane review published in 2001, plus an additional RCT published in 1998. Unit costs are taken from sources published in March 2002. Utility data were published in 1998.

Modelling
The model aims to estimate costs and utilities of LTG add-on therapy compared with placebo. It is a simple decision tree. Patients either succeed in seizure control in therapy or fail. Patients who fail receive the same utility as the placebo group. No patients withdraw from the treatment group over the year of the model.

Effectiveness inputs to the model
The inputs are the absolute risk difference in achieving a 50% reduction in seizure frequency compared with placebo, the utility of achieving 50% response and the utility of patients who withdraw from the study drug.

Study designs and other criteria for inclusion in the review
Effectiveness data are taken from a systematic review of RCTs. The authors include a further RCT in the analysis

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity and for extracting data
Not stated.

Number of primary studies included
Ten.

Method of combination of primary studies
The authors computed a measure of 50% response from the data in the review, but it is not clear how they arrived at this estimate. They weight each efficacy measure using a simple factor based on the study sample size.

Investigation of differences between primary studies
Not stated.

Results of the review
The authors state that a mean efficacy (>50% reduction in seizure frequency) of 22% was calculated across the studies. The utility of 50% response was 0.83. The utility of lack of response or from placebo was 0.66.

Economic analysis
Measure of health benefits used in the economic analysis
QALY.

Costs
The only costs considered were those of LTG therapy.

Sensitivity analysis
Variation of estimate of QALY gain.

Results
The additional costs of LTG concomitant with VPA were £609 per patient per year and £1348 when concomitant with enzyme-inducing drugs. No additional benefit was claimed when using the latter. The expected QALY for the treatment group was 0.6974 and for the placebo group was 0.6600. The incremental QALY gain was 0.0374. The cost per QALY was £16,300 for add-on with VPA and £36,035 for add-on with enzyme-inducing drugs.

Authors' conclusions
LTG is cost-effective as an add-on therapy when compared with other treatments currently recommended for use within the NHS.

Commentary
The authors acknowledge that the analysis is rudimentary. A major weakness is that it assumes that results achieved at the end of the trial period will be carried forward for at least 1 year. No withdrawal or change of therapy is considered. The conclusions are sensitive to changes in utility estimates. It is not clear from the paper how the estimates of effectiveness were calculated from the source data. No costs other than drugs and no consequences of AEs were considered.

Evaluation of industry evidence of cost-effectiveness of adjunctive levetiracetam compared with monotherapy alone[266]

Health technology
LEV 1, 2 and 3 g used as combination therapy, compared with a standard monotherapy.

Study question
The cost-effectiveness of LEV over a 1 year period. The perspective is the UK health service.

Economic study type
CEA.

Study population
Refractory adult patients with partial epilepsy.

Dates to which the data relate
Effectiveness trials published in 2000. Data on resource use collected prospectively during the trials. [Text relating to commercial-in-confidence data removed.]

Modelling
A decision tree is used to estimate the costs and incidence of seizure freedom. [Text relating to commercial-in-confidence data removed.]

Effectiveness inputs to the model
[Text relating to commercial-in-confidence data removed.]

Study designs and other criteria for inclusion in the review
RCT parallel studies. [Text relating to commercial-in-confidence data removed.]

Sources searched to identify primary studies
[Text relating to commercial-in-confidence data removed.]

Criteria used to ensure the validity of primary studies
[Text relating to commercial-in-confidence data removed.]

Methods used to judge relevance and validity and for extracting data
[Text relating to commercial-in-confidence data removed.]

Number of primary studies included
Three RCTs.

Method of combination of primary studies
[Text relating to commercial-in-confidence data removed.]

Investigation of differences between primary studies
[Text relating to commercial-in-confidence data removed.]

Results of the review
[Text relating to commercial-in-confidence data removed.]

Economic analysis
Measure of health benefits used in the economic analysis
Seizure freedom.

Costs
The costs considered are days in hospital, Accident and Emergency visits, GP visits and specialist visits and the resource use employed to treat AEs.

Sensitivity analysis
[Text relating to commercial-in-confidence data removed.]

Results
Cost per patient per year on standard therapy is £900 (excluding cost of drugs), cost on LEV + standard monotherapy is £1595. [Text relating to commercial-in-confidence data removed.]

The ICER is £5301 per seizure-free patient per year in a hypothetical cohort of 100 patients. [Text relating to commercial-in-confidence data removed.]

Authors' conclusions
The authors conclude that the additional cost of LVT is low compared with the benefit gained.

Commentary
The choice of comparator is against no adjunctive therapy. No attempt has been made to undertake a head-to-head comparison against other adjunctive AEDs. This would be necessary in order to decide whether LEV was preferred to other adjunctive therapies. [Text relating to commercial-in-confidence data removed.]

The primary measure of health benefit was seizure freedom. This measure is not sensitive to reduction in seizure frequency for patients who are not in complete remission. Many trials do not report this measure for refractory patients and this makes comparison between AEDs difficult. [Text relating to commercial-in-confidence data removed.]

Evaluation of industry evidence of cost-effectiveness of adjunctive oxcarbazepine compared with monotherapy carbamazepine[263]

Health technology
OXC 1040 mg/day used as monotherapy. The comparator is CBZ 684 mg/day.

Study question
To evaluate the cost-effectiveness of OXC relative to an older AED. The perspective is that of the UK healthcare system.

Economic study type
CEA.

Study population
The target population is adult patients with newly diagnosed partial epilepsy.

Dates to which the data relate
The effectiveness analysis is from a study published in 1989.
Resource use is not based on any published study.
Unit costs are from data published in 2001.
The price year is not stated explicitly.

Modelling
The model aimed to estimate costs and AEs for treatment and comparator. The type of model is a decision tree. If patients fail first-line therapy they do so at 8 weeks. Patients who fail go on to LTG monotherapy for the maintenance period (48 weeks). Patients on LTG are assumed not to have any AEs. No patients withdraw from therapy during the maintenance period. No allowance is made in the models for patients who withdrew owing to lack of seizure control.

Effectiveness inputs to the model
The effectiveness input to the model is the percentage of patients withdrawing during the titration phase owing to lack of tolerability.

Study designs and other criteria for inclusion in the review
The study design for the effectiveness inputs was an RCT.

Sources searched to identify primary studies
The review of evidence found several studies using OXC as treatment. Only one study was chosen as an input to the model. No reasons were given for the exclusion of other studies.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity and for extracting data
Not stated.

Number of primary studies included
One.

Method of combination of primary studies
Not applicable.

Investigation of differences between primary studies
The authors state that another study was excluded because the results were inconsistent with the primary study chosen.

Results of the review
14% of patients did not tolerate OXC compared with 25% of patients taking CBZ.

Economic analysis
Measure of health benefits used in the economic analysis
The measure of health benefit is the number of AEs leading to withdrawal that were avoided.

Costs
Resource use and unit costs were reported separately. Costs included were the cost of the drugs, GP visits during titration, GP visits, neurologist outpatient attendances and medications used as a result of AEs.
Resource use was derived from 'expert opinion', but this is not defined.
No indirect costs were reported.

Sensitivity analysis
An alternative scenario of second-line VPA was employed. No other sensitivity analysis was performed.

Results
Eleven AEs (leading to withdrawal) were avoided in a hypothetical cohort of 100 patients over the 56-week analysis period. This does not extrapolate beyond the trial period that reports outcomes after 48 weeks.

The incremental cost of treating 100 patients is £180 per patient per year. This is mainly the cost of the drugs.

The incremental cost per AEs avoided is ~£1600.

The authors report that the dosage is of high importance but no sensitivity analysis is reported.

Authors' conclusions
The authors conclude that if only a small incremental utility (0.006) is placed on the benefits of OXC for tolerability and efficacy, then the ICER will be within the threshold of £30,000/QALY.

Commentary
The estimate of effectiveness is taken from a single study. This approach ignores the results of other

studies and therefore appears to have been chosen selectively. The measure of benefit is limited since it does not consider withdrawal owing to lack of seizure control or other reasons. The model does not consider the impact on utility of side-effects that do not lead to withdrawal. The model does not attempt to look beyond a one-year horizon nor does it consider the effects of failing second line therapy.

Estimates of resource use were not based on a study.

The authors state that only a small incremental utility is needed for OXC to demonstrate cost-effectiveness. This approach assumes greater patient preference for OXC over the comparator, but evidence is not provided to support this.

Evaluation of industry evidence of cost-effectiveness of oxcarbazepine as monotherapy compared with lamotrigine[263]

Health technology
Monotherapy OXC 1040 mg/day compared with monotherapy LTG 200 mg/day. Second-line treatment is VPA 500 mg/day for both arms.

Study question
To compare the costs of monotherapy OXC with an alternative new AED for the treatment of newly diagnosed patients.

Economic study type
CMA.

Study population
Newly diagnosed adult patients with POSs.

Dates to which the data relate
Efficacy data are taken from trials published 1989 and 1995.

Modelling
A decision-tree model is used for a cost-minimisation analysis.

Effectiveness inputs to the model
The effectiveness inputs are the proportions of patients completing the 'trial period'.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity and for extracting data
Not stated.

Number of primary studies included
The authors stated that no direct trials were found comparing LTG with OXC. Data from two trials comparing LTG with CBZ and OXC with CBZ were included in the model.

Method of combination of primary studies
Not required.

Investigation of differences between primary studies
The authors report that one trial was excluded from the model because the results are not consistent with those from other trials, and that this is due to heterogeneous baseline populations.

Results of the review
14% of patients did not tolerate OXC versus 25% of patients taking CBZ. The authors state that the LTG trial gave similar results, although further details are not provided.

Economic analysis
Measure of health benefits used in the economic analysis
None used.

Costs
Resource use and unit costs were reported separately. Costs included were the cost of the drugs and GP visits during titration.

Resource use was derived from 'expert opinion', but this is not defined.

Sensitivity analysis
None used.

Results
The cost per patient per year of OXC is £653 and of LMT is £1283.

Authors' conclusions
LTG is more costly with no evidence of clinical benefit.

Commentary
The authors do not present sufficient evidence to support their claim that the treatments are

equivalent. The OXC trial quoted by the authors has a number of weaknesses. First, the trial does not report the number of patients randomised to each arm, and therefore an unbiased estimate of withdrawal rates cannot be derived from the data. Second, the dosages used in the trial are lower than currently recommended for both OXC and CBZ. Third, the efficacy measure reported in the trial is a >50% reduction in seizure frequency. This is not comparable to the efficacy measure reported for the LTG trial (seizure freedom).

The authors do not appear to have used a systematic method to identify other trials using these treatments. This further undermines their claim that the treatments are equivalent.

Evaluation of industry evidence of cost-effectiveness of oxcarbazepine as adjunct therapy compared with lamotrigine[263]

Health technology
Adjunctive OXC 1800 mg/day versus LTG 200–400 mg/day.

Study question
To compare the costs of adjunctive therapy for OXC with those for LTG.

Economic study type
CMA.

Study population
Refractory adult patients with partial seizures.

Dates to which the data relate
The authors state equivalence of effectiveness based on a review of LTG published in 2002 and an OXC trial published in 2000.
Unit costs are taken from data published in 2001.

Modelling
The model aimed to compare costs for each treatment. It is a simple decision tree. No patients are assumed to withdraw from treatment during the model time span (1 year).

Effectiveness inputs to the model
Response to treatment (>50% reduction in seizure frequency).

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity and for extracting data
Not stated.

Number of primary studies included
One systematic review of data on LTG and one RCT for OXC.

Method of combination of primary studies
Simple measures of relative and absolute risk are calculated for each drug. These were compared without statistical tests.

Investigation of differences between primary studies
Not stated.

Results of the review
The absolute risk reduction of a >50% reduction in seizure frequency for OXC compared with placebo is 27%. The absolute risk reduction of LTG compared with placebo is 12%. The authors conclude that OXC is at least equivalent to LTG.

Economic analysis
Measure of health benefits used in the economic analysis
None.

Costs
The costs included were the cost of the medications only.

Sensitivity analysis
None.

Results
Yearly costs per patient would be £867 for OXC and between £1144 and 2289 for LTG on top of the costs of concomitant medication.

Authors' conclusions
The authors conclude there is a strong case for a preference of OXC over LTG.

Commentary
The authors concluded that the therapies are equivalent. This conclusion is not supported by the evidence presented. They did not compare withdrawal rates or AEs between the therapies. They did not undertake a systematic review of the evidence. They based their conclusions on indirect comparisons and did not adequately adjust for

baseline characteristics or consider how the length of the trials might affect their conclusions.

Evaluation of industry evidence of cost-effectiveness of tiagabine compared with other new AEDs[265]

Health technology

Add-on TGB 15–55 mg/day compared with LTG 300–500 mg/day, TPM 200–1000 mg/day, VGB 1000–6000 mg/day and GBP 600–1800 mg/day.

Study question

A CEA of TGB as a combination therapy compared with other new AEDs used as combination therapy.

Economic study type

CEA.

Study population

Adult patients with refractory epilepsy.

Dates to which the data relate

Effectiveness data are taken from a systematic review published in 1997. Unit costs are taken from data published in February 2002.

Modelling

A simple decision tree is used to estimate drug costs and success rate over a 12-week period. Results are estimated for each dose evaluated separately in the systematic review and for the average dose.

Effectiveness inputs to the model

The effectiveness measure is the proportion of patients with >50% reduction in seizure frequency between baseline and the end of the trial (50% responders).

Study designs and other criteria for inclusion in the review

The effectiveness measures are taken from a systematic review of parallel and crossover RCTs.

Sources searched to identify primary studies

Not stated.

Criteria used to ensure the validity of primary studies

Not stated.

Methods used to judge relevance and validity and for extracting data

Not stated.

Number of primary studies included

One systematic review containing data from about 30 trials was used.

Method of combination of primary studies

Percentage responders as a simple ratio of number of responders divided by number of subjects. Calculation of 'success rate' as the absolute difference between the percentage responders in the AED group and the placebo groups.

Investigation of differences between primary studies

Not stated.

Results of the review

The success rates for TGB was 15%, for LTG 11%, for TPM 32%, for VGB 27% and for GBP 11%.

Economic analysis

Measure of health benefits used in the economic analysis

The measure of health benefit was the success rate.

Costs

Only the costs of the adjunctive AEDs were included.

Sensitivity analysis

The authors state that they varied the success rate (risk difference) based on the upper and lower bounds of its 95% CI. However, the outcome of the systematic review is an OR and CIs calculated by the Peto method. The authors do not state how they calculated CIs for the risk difference.

Results

The costs are calculated assuming a 12-week period and the assumed dose is 'recommended by MIMS February 2002'. The AED costs per patient are TGB 30 mg £229, LTG 450 mg £384, TPM 725 mg £651, VGB 3 g £227 and GBP 1.1 g £147. The authors calculate a ratio that is 'cost per successful outcome per 12-week period for a hypothetical cohort of 100 patients'. This is an average cost-effectiveness ratio. ICERs were not calculated.

Authors' conclusions

The authors conclude that add-on TGB had 'less than half' the cost per successful outcome than LTG and is comparable to other AEDs.

Commentary

The analysis concluded that TGB was cost-effective by reference to average cost-effectiveness

ratios. This method is not recommended in the literature. The authors did not calculate ICERs. The model is very limited; in particular, no allowance is made for differences in withdrawal rate between AEDs or for the different end-points of the trials. The model is very short term, which is not appropriate for this chronic disease with a high probability of seizures recurring after the trial period. No side-effects are considered by the analysis. The model takes its estimate of the success rate from trials based on both parallel design and crossover design. The crossover design can give a biased estimate of efficacy because it is possible that effects of earlier phases can contaminate the crossover phase.

Evaluation of industry evidence of cost-effectiveness of topiramate as monotherapy compared with other new and older AEDs[218]

Health technology

The base case is monotherapy TPM 100 mg/day as first-line therapy followed by LTG 150 mg/day versus monotherapy CBZ 600 mg/day as first-line followed by LTG 150 mg/day.

Study question

To compare the cost-effectiveness of monotherapy TPM for partial seizures and for generalised onset seizures with other AEDs. The perspective is the UK health service.

Economic study type

CUA.

Study population

Two models are presented: newly diagnosed adult patients with POSs and with generalised onset seizures.

Dates to which the data relate

Effectiveness data are taken from studies published in 1995 and 2002.
Resource use data are taken from a UK study published in 1998, relating to the financial year 1993–94. Drug unit costs are taken from data published in September 2001. Utilities are taken from a recently published study.

Modelling

The model is structured in a similar manner to the adjunctive therapy model. The model aims to estimate the cost and QALY of each treatment over a 15-year period. The model is a Markov chain. The cycle length is 3 months. In the initial period (cycle 0), patients are categorised as seizure free or not seizure-free according to trial data. In the first 3 months, patients who have no response switch to a new monotherapy (LTG 150 mg/day). Other patients are assumed to continue therapy or to have an AE (proportion estimated from the trial data) and switch therapy, or to die. The model assumes that the probability of withdrawal owing to AE is independent of seizure response. The patients enter a Markov chain model whose states are seizure freedom, <100% seizure freedom (leading to new treatment), AE (leading to new treatment) or death. Patients who fail second-line monotherapy progress to adjunctive therapy and incur AED costs as the average of TPM 200 mg, LTG 500 mg and LEV 2000 mg until the end of the model time horizon or death, and incur health service costs as though they had less than one seizure per month.

The model assumes that partial onset patients will receive CBZ and generalised onset patients will receive VPA as concomitant drug or comparator.

Effectiveness inputs to the model

The inputs to the models are the proportion seizure free, with AEs leading to withdrawal in the short term, the death rate due to epilepsy and the long-term transition probabilities.

Study designs and other criteria for inclusion in the review

Not stated.

Sources searched to identify primary studies

Not stated.

Criteria used to ensure the validity of primary studies

Not stated.

Methods used to judge relevance and validity and for extracting data

Not stated.

Number of primary studies included

For the base-case analysis, one trial was used for effectiveness of TPM versus CBZ or VPA and one trial for effectiveness of LTG. The LTG trial provided subgroup analysis enabling separate results to be used for partial and generalised onset patients. The TPM trial provided only aggregate data. Utilities are estimated separately for the first 6 months and for the maintenance period, based on the data obtained from refractory patients using adjunctive therapies. UK general population preferences are used to value the health states.

Method of combination of primary studies
No pooling of data was required.

Investigation of differences between primary studies
Not stated.

Results of the review
For TPM, 49% were seizure-free; 19% withdrew owing to AEs. The long-term utility weight for seizure freedom is 0.98 and for not controlled 0.86.

Economic analysis
Measure of health benefits used in the economic analysis
QALYs.

Costs
The costs are the costs of AEDs, medical visits, laboratory tests and hospitalisations.

Sensitivity analysis
The authors use a different set of utility weights in a secondary analysis. This was performed using a type of discrete choice experiment with 'months given up after 30 years of life' as an attribute in a bid to elicit utility values for avoiding the side-effects of AEDs.

The authors considered several alternative combinations of drugs as comparators and second-line therapies in order to model different treatment pathways.

The authors performed probabilistic sensitivity analysis by modelling key parameters as random variables using Monte Carlo simulation. The chosen distributions were log-normal for relative risks of mortality, triangular for probabilities of effectiveness or AEs, triangular for utilities and log-normal for costs.

Results: partial onset
The costs per patient for the base case for TPM followed by second-line LTG are £12,390, and for the comparator CBZ followed by LTG are £12,117. The QALY gain is 9.8 years for TPM and 9.6 years for CBZ. Both of these options are dominated by CBZ followed by TPM, which has costs of £11,094 and benefits of 9.8 QALYs. The authors state the ICER of the base case compared with no treatment (zero cost and zero QALYs) as £1127/QALY, but this is misleading since they did not calculate the cost and benefit of no treatment in the model. They calculate the ICER of TPM and CBZ compared with CBZ and TPM as £38,241/QALY. Sensitivity analysis shows that there is little to choose between treatment pathways.

Results: generalised onset
The cost of TPM and LTG is £12,016 and for VPA and LTG is £11,807. The QALY gain is 9.99 and 9.87 years, respectively. VPA and LTG is extendedly dominated by VPA and TPM and TPM and LTG. The authors consequently calculate the ICER of TPM and LTG as £6635/QALY compared with VPA and TPM, and present a CEAC showing the probability of cost-effectiveness to be >90% at a threshold willingness to pay >£20,000.

Authors' conclusions
The authors conclude that TPM followed by LTG second-line treatment is the most cost-effective option for generalised seizures, and TPM followed by CBZ or vice versa dominates other options for POS patients.

Commentary
The choice of the Markov model allows the authors to assign utility to each health state and model the progression of the disease over time. The model is also able to deal with many different treatment pathways and rank them according to costs and benefits. The Markov chain is not able to deal with variations in the rate of withdrawal from the therapy over time. The analysis implies that nearly all patients who start combination therapy will withdraw by the end of the modelling timeframe. The long-term observational data[270] that are available indicate that the hazard rate of withdrawal falls over time.

The model considers only a limited subset of the trials available in estimating the effectiveness of the therapies. The analysis assumes that effectiveness evidence from trials recruiting newly diagnosed patients can be used to estimate the effectiveness of therapies aimed at refractory patients.

The authors have used measures of utility in the analysis. The estimates used in the base case were originally derived from studies of refractory patients on new adjunctive AEDs. This may limit their applicability to this newly diagnosed patient group, but there are few available utility data for this patient group.

Evaluation of industry evidence of cost-effectiveness of topiramate as adjunctive therapy compared with other new AEDs[218]

Health technology
The base case is adjunctive TPM 200 mg/day as

first-line therapy followed by LEV 2 g/day versus adjunctive LTG 500 mg/day as first-line therapy followed by LEV 2 g/day.

Study question
To compare the cost-effectiveness of adjunctive TPM therapy for partial seizures with other new AEDs. The perspective is the UK health service.

Economic study type
CUA.

Study population
Adult refractory patients with partial seizures.

Dates to which the data relate
Effectiveness data are taken from studies published in 1996 and 2002.
Resource use data are taken from a UK study published in 1998, relating to the financial year 1993–94. Drug unit costs are taken from data published in September 2001. Utilities are taken from a recently published study.

Modelling
The model aims to estimate the cost and QALY of each treatment over a 15-year period. The model is a Markov chain. The cycle length is 3 months. In the initial period (cycle 0), patients are categorised as seizure free, partial response or no response according to trial data. In the first 3 months, patients who have no response switch to a new adjunctive therapy (LEV 2 g/day). Other patients are assumed to continue therapy or to have an AE (proportion estimated from the trial data) and switch therapy, or to die. The model assumes that the probability of withdrawal due to AEs is independent of seizure response. The patients enter a Markov chain model whose states are seizure freedom, >50% reduction in seizure frequency (>50% response), <50% response (leading to new treatment), AE (leading to new treatment) or death. Patients who fail second-line adjunctive therapy incur AED costs as the mean of TPM 200 mg, LMT 500 mg and LEV 2000 mg until the end of the model time horizon or death, and incur health service costs equivalent to patients who have less than one seizure per month.

Effectiveness inputs to the model
The inputs to the models are the proportion of responders, the proportion with AEs leading to withdrawal in the short term, the death rate due to epilepsy and the long-term transition probabilities of moving from one state to another. Utilities are estimated separately for the first 6 months and for the maintenance period, based on a long-term (5-year) prospective observational study of refractory epileptic patients on new AEDs who completed the EQ-5D questionnaire. UK general population preferences are used to value the health states.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity and for extracting data
Not stated.

Number of primary studies included
For the base-case analysis, two trials were used for effectiveness of TPM, one trial for effectiveness of LTG and three trials for effectiveness of LEV. Utilities and long-term follow-up transition probabilities are taken from one prospective observational study.

Method of combination of primary studies
Weighted averages were taken to combine trial results. No allowance was made for heterogeneity between trial populations and uncertainty arising from that.

Investigation of differences between primary studies
Not stated.

Results of the review
For TPM, 5% were seizure free, 36% with >50% response and 59% with <50% response. On average, 7% withdrew owing to AEs. For LTG, 7% were seizure free, 26% with >50% response and 67% with <50% response. On average 14% withdrew owing to AEs. The utility study classified patients with >50% response according to whether they had more or less than one seizure per month. The authors take a weighted average of these utilities to match the states in their model. The long-term utility weight for seizure freedom is 0.98, for partial freedom 0.89 and for not controlled 0.86.

Economic analysis
Measure of health benefits used in the economic analysis
QALYs.

Costs
The costs are the costs of adjunctive AEDs, medical visits, laboratory tests and hospitalisations.

Sensitivity analysis
Using alternative utility weights derived from a discrete choice model. Using alternative therapies as comparators and second-line therapies. Probabilistic sensitivity analysis over important variables. The chosen distributions were log-normal for relative risks of mortality, triangular for probability of effectiveness or AEs, triangular for utilities and log-normal for costs.

Results
The costs per patient for the base case for TPM followed by second-line LEV are £15,811 and for the comparator LTG followed by LEV £17,593. The QALY gain is 8.730 years for TPM and 8.726 years for LTG. The authors calculate the ICER of the base case (TPM followed by LEV) compared with no add-on as £1812/QALY. However, this is not a valid comparison since it compares with patients who are assumed to achieve no QALYs and zero costs. They calculate the ICER of LEV followed by TPM compared with the base case as £31,700/QALY. Sensitivity analysis shows that there is little to choose between LEV followed by TPM and the base case.

Authors' conclusions
The authors conclude that TPM followed by LEV second-line treatment dominates LTG followed by LEV and LEV followed by LTG. Other combinations incur greater cost for minimal QALY gain.

Commentary
The choice of the Markov model allows the authors to assign utilities to health states, and models the progression of the disease over time. The model also allows several combination therapies to be compared with one another, and allows probabilistic sensitivity analysis to be undertaken. It has a long-term perspective and incorporates QoL into the measure of health benefit.

The Markov chain is not able to deal with variations in the rate of withdrawal from the therapy over time. The analysis implies that nearly all patients who start combination therapy will withdraw by the end of the modelling time frame. The available observational studies[270] suggest that this overestimates the failure rate.

The model does not use a systematic search strategy to identify parameter inputs. It uses a simple weighted average to combine results of different studies, but no allowance is made for heterogeneity between trials.

Appendix 27

Review of cost, utility and mortality data to use as input parameters in the Centre for Health Economics (CHE) model

This Appendix is a review of utility, cost and mortality data available in published literature and in the company submissions, in order to estimate suitable parameters with which to populate the CHE model.

Utility data

Overview of available data

AEDs have an effect on seizure frequency and to induce side-effects, both of which are likely to affect the QoL of the patient. Researchers have used a wide range of methods to try to quantify patients' QoL on and off drug therapy.

GlaxoSmithKline utility weights for monotherapy

GlaxoSmithKline commissioned the School of Health and Related Research (ScHARR) to elicit the utility weights for monotherapy AEDs.[264] A questionnaire was administered to 65 members of the general population, none of whom had epilepsy. The health states on the questionnaire were intended to correspond to the side-effect profiles of CBZ, VPA and LTG. These were built up using the summary of product characteristics (SPC), published data and the opinion of an expert. The questionnaire administered to women aged 18–45 years included a different scenario with a probability of side-effects relating to foetal health and adverse interactions with the contraceptive pill. Participants evaluated expressed their preference between states by responding to the standard gamble (SG) techniques. *Table 110* shows the results as described in the submission.

GlaxoSmithKline utility weights for adjunctive therapy

The GlaxoSmithKline utility weights have been published in a peer-reviewed journal.[261] Refractory epileptic patients referred to an Italian outpatient clinic and who had been treated with adjunctive AEDs were interviewed by two neurologists. Patients were asked to value their current health state relative to 'full health' using the time trade-off technique. Patients were classified by the neurologist into one of five categories (*Table 111*).

Janssen-Cilag EQ-5D study[467]

A total of 125 UK patients with refractory epilepsy, who were already being prescribed newer AEDs as adjunctive therapy, were asked to classify their QoL using the descriptive system in the EQ-5D instrument. Utilities were assigned to these health states using published preference weights taken from the UK general population using the time trade-off method. The patients classified their health state at baseline, 6 months and 5 years. All 125 patients were followed up at baseline and 6 months. Results were classified according to the response to the therapy at 6 months (*Table 112*). A subsample of 73 patients was approached at 5 years, of whom 48 responded to the questionnaire.

TABLE 110 *Results of ScHARR study: all respondents (*n = 64*)*[264]

Seizure control	Side-effects (% risk)	AED	Mean	SD
SF	Add weight (30%) and lose hair (10%) and grow hair on body (F)	VPA	0.748	0.307
SF	Rash (10%)	LTG	0.751	0.300
SF	Concentration (10%) and BD (6% F)	CBZ	0.712	0.338
SR	Add weight (30%) and lose hair (10%) and grow hair on body (F)	VPA	0.706	0.322
SR	Rash (10%)	LTG	0.743	0.308
SR	Concentration (10%) and BD (6% F)	CBZ	0.689	0.340
NR	Uncontrolled epilepsy	–	0.571	0.380

F, affect females only; NR, non-responder; SF, seizure freedom; SR, responder.

TABLE 111 *Utility values from Messori study*[261]

Condition	*n*	Mean	SD	Range
SF[a]	15	0.96	0.04	0.88–1.00
SR ≤ 1/m[a]	15	0.91	0.09	0.74–1.00
SR > 1/m[a]	30	0.79	0.13	0.51–1.00
NR[a]	12	0.66	0.08	0.56–0.78
Not on study drug	9	0.40	0.07	0.32–0.50
All patients	81	0.78	0.19	0.32–1.00

NR, <50% reduction in seizure frequency (non-responder); SF, seizure free; SR ≤ 1/mg, >50% reduction in seizure frequency compared with baseline (responder) and not more than one seizure per month; SR > 1/m, responder and more than one seizure per month.
[a] Response conditional on patient still receiving study drug.

TABLE 112 *Changes in EQ-5D score according to response to newer AEDs*[218]

Response category	Mean[b]	SD	*n* 6 months	Mean 6 months	SD 6 months	*n* 5 years	Mean 5 years	SD 5 years
SF[a]	0.89	0.19	11	0.94	0.08	9	0.98	0.05
SR ≤ 1/m[a]	0.90	0.13	16	0.88	0.15	2	0.90	0.13
SR > 1/m[a]	0.96	0.07	9	0.93	0.09	6	0.89	0.15
NR[a]	0.85	0.15	42	0.83	0.20	3	0.86	0.13
Not on study drug	0.81	0.21	47	0.84	0.20	28	0.80	0.15
All patients	0.85		125	0.86		48		

NR, <50% reduction in seizure frequency (non-responder); SF, seizure free; SR, ≤ 1/m, >50% reduction in seizure frequency compared with baseline (responder) and not more than one seizure per month; SR > 1/m: responder and more than one seizure per month.
[a] Response conditional on patient still receiving study drug.
[b] Baseline values quoted are for all patients started on treatment.

Janssen-Cilag discrete choice study

Janssen-Cilag considered an alternative method of estimating utility.[467] The aim was to identify the relative importance of the individual attributes of such drugs. The paper is commercial-in-confidence. The method is a discrete choice experiment study conducted by E. McIntosh. Epilepsy patients subscribed to the 'Epilepsy Action' website were asked for their preferences for the side-effect profiles of various 'hypothetical' AEDs. The first survey used cost as an attribute to elicit willingness to pay values. A second survey used the discrete choice approach with 'months given up after 30 years of life' as an attribute to elicit utility values. Janssen-Cilag used the results of the second survey to weight the side effects profile of each AED (*Table 113*).

Norwegian study[465]

A community sample of people with epilepsy was asked to score classify their health state using the descriptive system in the EQ-5D. Utilities were

TABLE 113 *Absolute utility weights for identified epileptic health states*[218]

Health state	Absolute utility weight
Seizure free with no side-effects	1.000
SF with 13 lb weight gain	0.988
SF with weight loss	1.000
SF with hair loss	0.837
SF with rash	0.432
SF with sickness	0.906
SF with concentration reduced by 50%	N/A
50% reduction in seizures with no side-effects	0.924
SR with 13 lb weight gain	0.913
SR with hair loss	0.762
SR with rash	0.356
SR with sickness	0.830

NR, non-responder; SF, seizure free; SR, responder.

TABLE 114 *Utility scores from the Norwegian study*[465]

	Adjusted mean		Unadjusted mean (SD)	
	Yes (*n* = 272)	**No (*n* = 62)**	**Yes (*n* = 307)**	**No (*n* = 69)**
AED use	0.78	0.77	0.81 (0.23)	0.83 (0.24)
Seizures last year	0.67	0.84		

assigned to these health states using published preference weights taken from the UK general population using the time trade-off method. Results were adjusted for age, gender, education and co-morbidity. However, this weighting, together with missing data, produced results that were difficult to interpret. Both adjusted and unadjusted scores are reported in *Table 114*.

Review of quality of life and epilepsy literature

Berto[479] reviewed published work on the QoL of patients with epilepsy. The author found that studies using the SF-36 and other generic measures demonstrated the following:

- QoL is worse in patients with epilepsy than in the general population.
- QoL in patients with epilepsy is comparable to or even worse than that in patients with other chronic conditions.
- QoL is similar to that of healthy persons when epilepsy is well controlled.
- Frequencies of seizures seems to be one of the most relevant determinants of poor QoL scores.
- Not much is known about differences in QoL scores among subgroups of patients.

Discussion

The results for the Messori and the Selai studies should be comparable, since they were both elicited from a similar population. The results for Messori show a much greater range for utility weights than in the Selai study. Partial and ineffective seizure control and not being on the study drug are given a higher preference weight by Selai. The mean utility weight estimated by Messori for patients who are not on the study drug is 0.40. This is an unexpectedly low utility, and on the EQ-5D scale would be expected in someone with, for example, extreme depression. This may be partly a function of the valuation instrument, in that SG is expected to give higher utility values than time trade-off.[466] Another possibility is that the Italian study was administered by the same neurologists who were treating the patients, and who could have influenced the answers. At the 6 month follow-up there is an invalid preference direction in the Selai study where mean utility for patients experiencing 'more than one seizure per month' is greater than the utility of those with 'less than one seizure per month'.

Three studies used epileptic patients to classify their health state profiles [261,465,467] and two studies used expert judgements.[218,264] Two studies used epileptic patients to value these health states[218,261] and three used the preferences of the general population.[264,465,467]

The utility weights derived using the discrete choice method[218] imply that rash is a highly undesirable side-effect. This has the greatest effect on the cost-effectiveness of LTG. There is an obvious contrast to the model developed by GlaxoSmithKline that does not estimate a significant utility decrement due to rash.[261,264]

The Stavem model is not used by any of the submissions and is reported as the only other estimates of utility in this patient group found from a search of the literature.[465] The results show that there is a large (probably significant) utility gain for being seizure-free over 1 year. However, there is no difference in utility between those on AED and those not. This might be because AED use is not associated with seizure freedom. This could happen if patients who have been seizure free for long periods are withdrawn from the AED.

Values used for the CHE model

The CHE model classifies patients according to their frequency of seizure while receiving treatment. These states correspond closely to the Selai study,[467] hence these have been used in the model here. The model does not distinguish between patients with more or less than one seizure per month so these results have been pooled. After the data have been pooled there is a monotonic relationship between utility and degree of seizure control (*Table 88*). It is assumed in the model that if a patient experiences serious side-effects then he or she will withdraw from the therapy, and therefore will not sustain a prolonged

TABLE 115 *Percentage of patients reporting service use in last year*[468]

	Seizures in last year		
	0 ***n* = 350**	**<1/month** ***n* = 174**	**>1/month** ***n* = 168**
Hospital based			
Inpatient admission	1	16	16
A&E attendance	2	23	27
Outpatient attendance	18	42	49
EEG[a]	4	21	22
CT or MRI[a]	5	15	16
Blood test[a]	22	43	52
Community based			
Epilepsy-related GP consultation	18	58	61
District/practice nurse	4	6	10
Health visitor	0	1	2
Social worker	1	4	2
Psychologist/psychiatrist	2	2	8

A&E, Accident and Emergency.
[a] Diagnostic-related costs.

utility decrement. Furthermore, following Berto's conclusions that seizure frequency, rather than treatment-induced side-effects, is the main determinant of QoL,[479] it is also assumed that mild side-effects that do not lead to withdrawal have no measurable effect on utility.

Cost data

Review of estimates of resource use

Most studies classify the costs incurred as:

- treatment (AED) costs
- costs associated with seizures (GP visits, hospitalisations)
- costs associated with treatment of AEs
- costs associated with diagnosis of epilepsy (EEG, MRI, blood tests)
- other healthcare costs associated with starting and maintaining treatment (GP visits, neurology clinic outpatient attendances)

Treatment AED costs

The differences in the cost of AEDs are likely to be the main factor in determining differences in total costs between treatment options. This parameter is sensitive to the assumption of the dose used. Unit costs and the maximum and minimum doses in the economic analysis are taken from the BNF, March 2002. TPM monotherapy is not licensed at the time of writing, and the dosage range is taken from the draft SPC. Where a choice of pack size is available, the cheapest cost per milligram has been chosen. The cost of treatment in the maintenance phase of the model, where patients have failed all other therapies, is assumed to be equivalent to that of an older AED monotherapy such as VPA. This assumption is tested in sensitivity analysis.

Cost associated with seizures

The most common method of estimation of costs associated with seizures is use of 'Delphi panels' or 'expert opinion', and only to consider GP visits and neurology outpatient attendances. A few studies have evaluated resource use in more detail and these are described below.

Jacoby and colleagues[468] conducted a retrospective study in 1993 on a UK cohort of more than 1000 adults and children with active epilepsy. Patients were asked to describe the frequency of contacts with health services over the past year (*Table 115*).

Heaney and colleagues[253] assumed three GP visits and three outpatient attendances per year if seizure free and four GP visits and four outpatient attendances if not seizure free. Heaney and colleagues[254] asked a panel of experts to predict resource use for groups of patients following different treatment pathways (*Table 116*).

Begley and colleagues[469] estimated resource use in the USA based on 'expert opinion' in 1990 (*Table 117*). The results are not easily generalisable to the CHE model because of the differences from

TABLE 116 *Health service resource use per patient per year*[254]

Health service resource use per patient	Mono	Fail 1st mono, treat 2nd mono	Fail 1st-line mono, treat combination
GP visit (number of visits per year)	3	3	4
Neurologist outpatient (number of visits per year)	2	2	4
Laboratory tests (number of tests per year)	1	1	1
Hospital admittance (probability of admittance per year)	1%	1%	8%
A&E (number of attendances per year)	0	0	0.3

TABLE 117 *Probability of use of hospital services in initial evaluation following diagnosis*[469]

Service use	Probability of use (%)
A&E	50
Inpatient	25
Outpatient (generalist)	75
Outpatient (specialist)	40

TABLE 119 *Average length of stay in hospital*

	Days
Cockerell, 1994 (NGPSE) [471]	4.5
Jacoby, 1998[468]	2–6
NHS reference costs (2002), HRG A30 [276]	4
NHS reference costs (2002), HRG A29 [276]	7
Heaney, 2000[254]	10

A30, epilepsy in adult <70 years old or without complications; A29, epilepsy in adult >69 years old or with complications; HRG, healthcare resource group.

the UK pattern of care, the age of the study and the different classification of patients into groups.

[Text removed owing to reference to commercial-in-confidence data.]

Wong and colleagues[470] conducted a retrospective case-records survey examining long-term use of adjunctive GBP, LTG and VGB on refractory patients (*Table 118*).

Estimates of average length of stay in hospital for seizure-related treatment are shown in *Table 119* They show similar results apart from Heaney and colleagues.[254]

Values for costs of health-related services used in the CHE model

Jacoby and colleagues' study[468] has the advantages that it is based on the UK experience, it is an observational study rather than expert opinion and the groups of patients are compatible with the states of the CHE model. It has two main disadvantages. First, the survey asked patients whether or not they had any use of each service in the last year, and not the number of contacts or the length of stay. The second disadvantage is the age of the study and therefore questionable applicability to new AEDs and modern treatment pathways. It is noted that Jacoby and colleagues' study[468] predicts considerably less service use than Heaney and colleagues' model.[254] The probability of hospital admission estimated by Jacoby and colleagues[468] and Wong and colleagues[470] are similar.

The CHE model will use the probabilities of any service use provided by Jacoby and colleagues

TABLE 118 *Numbers of patients using adjunctive therapy with seizure-related event*[470]

	GBP (n = 361)	LTG (n = 1050)	VGB (n = 713)
Total follow-up time (patient-years)	432	2352	2391
Number of events			
Hospital admissions for seizures	35	110	117
Hospital admissions for seizure-related injury	9	29	18
Hospital admissions for seizure assessment	53	167	178
Seizure-related injury without hospital admission	13	73	65
Number of patients with seizure-related event	96	296	301
Rate of affected patients per year	22%	13%	13%

TABLE 120 *Average cost of seizures*

Intervention	Expected no. of visits[a] given non-zero use	Unit cost[b]	Probability of use in 1 year[c]		Cost (£)	
			Seizure free	Not seizure free	Seizure free	Not seizure free
Inpatient	1	£1584	0.010	0.160	16	253
A&E	1	£75	0.020	0.230	2	17
Outpatient	3	£128	0.180	0.420	69	161
GP	3	£21	0.180	0.580	11	37
expected total cost per patient					98	469

[a] Source: Heaney and colleagues, 1998.[253]
[b] Source: NHS reference costs 2001–02[276] and PSSRU, 2002.[275]
[c] Source: Jacoby and colleagues, 1993.[468]

multiplied by the expected number of contacts estimated by Heaney and colleagues[253] (*Table 120*). The CHE model does not distinguish between states with more or less than one seizure per month. The difference in service use between these states in Jacoby and colleagues' study[468] is small, and the service use assuming more than one seizure per month will be used for all patients who are not seizure free.

Jacoby and colleagues' study[468] includes community health services such as district or practice nurse contacts. The costs of these staff are already included in the PSSRU unit costs of a GP attendance, and so will not be included in the CHE model. The use of other community health services (health visitors, social workers) is low and therefore will not be included in the CHE model.

Costs associated with adverse events or side-effects

The costs of AEs are difficult to estimate, because an accurate estimate requires both the incidence of AEs and the treatment consequences. Most AEs can be assumed to disappear once the treatment is discontinued with no further treatment necessary.

[Text removed owing to reference to commercial-in-confidence data.]

Janssen-Cilag[218] estimated incidence and treatment costs of serious rash and Stevens–Johnson syndrome (applied to LTG) and renal stones (applied to TPM). [Text removed owing to reference to commercial-in-confidence data.]

Other costs

Specific costs associated with diagnosis will not be included in the CHE model because the costs of EEG and other diagnostic tests are already fully absorbed in the unit cost of a neurology outpatient attendance.

Costs associated with starting and switching treatment can be estimated from the synthesis of literature results. Most authors estimate the use of one GP visit and possibly one outpatient visit per patient when starting a new treatment.

Costs of routine care and maintenance on therapy (GP visits, outpatient attendances) are assumed to be similar for all patients and are therefore excluded from the model.

Estimates of unit costs

The NHS reference cost schedule 2002[276] estimates the mean cost per finished consultant episode for elective adult epilepsy patients (HRG A30) to be £1584. It is noted that this mean is greater than the interquartile range (£597–1434), indicating that costs are highly skewed. This could be because the HRG may include both medical and surgical interventions of varying complexity. For comparison, the mean cost per bed-day for the speciality of neurology calculated by PSSRU[275] is £272, or £1088 per finished consultant episode assuming a mean length of stay of 4 days. Other unit costs used in *Table 120* are taken from PSSRU (2002).[275]

Mortality data

The model uses observed deaths in the NGPSE study[277] and expected deaths from Mortality Statistics (2000)[273] to calculate the SMR of people with epilepsy. The NGPSE study[277] calculates the HR for people with epilepsy without seizures, compared with patients with epilepsy with seizures

TABLE 121 *Mortality rate*

Age (years)	Death rate per 1000 in general population[a]	Obs $n = 792$[b]	SMR = Obs/Exp	Not SF	SF
0–49	0.9	20	28.6	32.0	22.4
50–59	5.0	25	6.3	40.0	28.0
60–69	14.0	32	2.9	51.1	35.8
70–79	39.1	48	1.5	76.7	53.7
80+	116.7	74	0.8	118.3	82.8

Exp, expected deaths; Obs, observed deaths; SF, seizure free; SMR, standardised mortality ratio.
[a]Mortality statistics (ONS, 2000).[273]
[b]Lhatoo and colleagues, NGPSE.[277]

to be 0.7. Assuming 70% of patients in the NGPSE study are seizure free, the estimates of death rates for patients with and without seizures are as shown in *Table 121*.

The death rates with and without seizure freedom (Death rate_{SF} and Death rate_{NSF}) are calculated using the following identities:

$$\text{SMR}_{\text{all patients}} \equiv \text{SMR}_{\text{Not SF}} \times [1 - \text{P(SF)}] + \text{SMR}_{SF} \times P(\text{SF})$$

$$\text{Hazard ratio} \equiv \text{SMR}_{SF}/\text{SMR}_{\text{not SF}}$$

$$\text{Death}_{\text{rateSF}} \equiv \text{Death rate}_{\text{general population}} \times \text{SMR}_{SF}$$

$$\text{Death rate}_{\text{Not SF}} \equiv \text{Death rate}_{\text{general population}} \times \text{SMR}_{NSF}$$

where P(SF) is the probability a patient is seizure free.

Appendix 28

S-plus code

```
#gamma random number terminal
gamma <- function(N,mean,sd)
      {
      shape <- (mean/sd)^2
      scale <- mean/sd^2
   return(rgamma(N,shape,scale))
      }


init <- function()
   {
   #utility variates are set globally so that they are
     common across simulations
   #set utility decrement parameters, mean and sd
     for each state
   u.mn.sf <<- 1-0.94
   u.sd.sf <<- 0.08 /sqrt(11)
   u.mn.pr <<- 1-0.90
   u.sd.pr <<- 0.10 / sqrt(25)
   u.mn.nr <<- 1-0.84
   u.sd.nr <<- 0.2 / sqrt(47)

   #generate utility random variates from a
     gamma distribution using method
   #of moments estimators.
   u.sf <<- 1-gamma(nSims,u.mn.sf,u.sd.sf)
   u.pr <<- 1-gamma(nSims,u.mn.pr,u.sd.pr)
   u.nr <<- 1-gamma(nSims,u.mn.nr,u.sd.nr)
   u.death <<- rep(0,nSims)
   }

testPath <- function(type=partial,drug1=1,
drug2=1,drug3=1,therapy=1,T=30)

   {
   print(date())

   #Set working directory
setwd("//ntcr1/checrd/common/crd/Epilepsy/econo
mic model/")

   #import meta-analysis parameters from
   WinBugs as vector of random variates
   #data files have no row numbers or column
   headings, tab delimited format

   #names of datafiles
   datafile <- c("mono1_rs.txt","mono1_wd.txt",
   "mono2_rs.txt","mono2_wd.txt","comb_rs.txt",
   "comb_wd.txt")

#read in response and withdrawal data for
  mono1 as data frames
r.mono1.data <- read.delim(datafile[1],
header=FALSE)[[2]]
ae.mono1.data <- read.delim(datafile[2],
header=FALSE)[[2]]

#read in data for mono2
r.mono2.data <- read.delim(datafile[3],
header=FALSE)[[2]]
ae.mono2.data <- read.delim(datafile[4],
header=FALSE)[[2]]

#read in data for combination therapy
r.comb.data <-read.delim(datafile[5],
header=FALSE)[[2]]
ae.comb.data <-read.delim(datafile[6],
header=FALSE)[[2]]

#set model parameters
#set cycle length in years
d=0.5

#set starting states
if (therapy == 1) start<-c(1,0,0,0,0,0,0,0)
if (therapy == 2) start<-c(0,0,1,0,0,0,0,0)
if (therapy == 3) start<-c(0,0,0,0,1,0,0,0)

#set qaly discount rate 1.5%, also 6% and 0%
q.disc = 0.000

#set cost discount rate
#base case 6%
c.disc <- 0.060

#mortality in seizure free state is
  28/thousand/year for 50 year old epileptic
mort.sf<- 0.028*d

#mortality in not seizure free state is
  40/thousand/year for 50 year old
mort.nsf <- 0.040*d

#set drug names, order is important
drugs.mono1 <- c("LMT","OXC","CBM","VAL",
"PHN","TOP")
drugs.mono2 <- c("LMT","CBM","VAL")
drugs.comb <- c("PLA","GBP","LEV","LMT",
"OXC","TGB","TOP")
```

```
#set study random variates for mono1 therapy

#set drug names for mono1 therapy
name.mono1 <- drugs.mono1 [drug1]

#probability of response
#redim data to obtain 1 column per drug
dim(r.mono1.data) <- c(length(r.mono1.data)/
length(drugs.mono1),length(drugs.mono1))

#select column representing current drug
p.r.mono1<-r.mono1.data[1:nSims,drug1]

#probability of an ae
#redim data to obtain 1 column per drug
dim(ae.mono1.data) <- c(length(ae.mono1.data)/
length(drugs.mono1),length(drugs.mono1))

#select column representing current drug
p.ae.mono1<-ae.mono1.data[1:nSims,drug1]

#set study random variates for mono2 therapy

#set drug names for mono2 therapy
name.mono2 <- drugs.mono2[drug2]

#probability of response
#redim data to obtain 1 column per drug
dim(r.mono2.data) <- c(length(r.mono2.data)/
length(drugs.mono2),length(drugs.mono2))

#select column representing current drug
p.r.mono2<-r.mono2.data[1:nSims,drug2]

#probability of an ae
#redim data to obtain 1 column per drug
dim(ae.mono2.data) <- c(length(ae.mono2.data)/
length(drugs.mono2),length(drugs.mono2))

#select column representing current drug
p.ae.mono2<-ae.mono2.data[1:nSims,drug2]

#set study random variates for comb therapy

#set drug names for comb therapy
name.comb <- drugs.comb[drug3]

#probability of response
#redim data to obtain 1 column per drug
dim(r.comb.data) <- c(length(r.comb.data)/
length(drugs.comb),length(drugs.comb))

#select column representing current drug
p.r.comb<-r.comb.data[1:nSims,drug3]

#probability of an ae
#redim data to obtain 1 column per drug
dim(ae.comb.data) <- c(length(ae.comb.data)/
length(drugs.comb),length(drugs.comb))

#select column representing current drug
p.ae.comb<-ae.comb.data[1:nSims,drug3]

#set treatment path name
if (therapy==1) name<-paste(name.mono1,
name.mono2,name.comb,sep="->")
if (therapy==2) name<-paste(name.mono2,
name.comb,sep="->")
if (therapy==3) name<-name.comb


#long term survival-on-drug parameters
#ft(t)dt from Tiagabine Study No. M91-604/
  M91-604C
a.tiag <-
b.tiag <-

# ft(t)dt from NGPSE study (time to discontinue
   first therapy)
a.ngpse <- c(NA,28,17,17,9,9,8,8,7,7)
b.ngpse <-
c(NA,508,491,474,465,456,448,440,433,426)

#Define time dependent failure rates - ft(t)dt
  for mono1, mono2 and comb therapies

#initialise array ft(t)dt for mono1 therapy
ft.mono1 <- array(numeric(),c(T,nSims))

#ft(1)dt for mono1 from Meta analysis of study
  data
ft.mono1[1,] <- 1-((1-p.ae.mono1)*(p.r.mono1))

#ft(2:T)dt for mono1 therapy from NGPSE data
for (t in 2:T)
   {
   ft.mono1[t,]<-rbeta(nSims,a.ngpse[min(t,10)],
   b.ngpse[min(t,10)])
   }

#Initialise array ft(t)dt for mono2 therapy
ft.mono2 <- array(numeric(),c(T,nSims))

#ft(1)dt for mono2 from Meta analysis of study
  data
ft.mono2[1,] <- 1-((1-p.ae.mono2)*
(p.r.mono2))

#ft(2:T)dt for mono2 therapy
for (t in 2:T)
   {
   ft.mono2[t,]<-rbeta(nSims,a.tiag[min(t,10)],
   b.tiag[min(t,10)])
   }
```

```
#Initialise array ft(t)dt for comb therapy
ft.comb <- array(numeric(),c(T,nSims))

#ft(1)dt for comb from Meta analysis of study
  data
ft.comb[1,] <- 1-((1-p.ae.comb)*(p.r.comb))

#ft(2:T)dt for comb therapy
for (t in 2:T)
   {
   ft.comb[t,]<-rbeta(nSims,a.tiag[min(t,10)],
   b.tiag[min(t,10)])
   }

#stochastic cost version, assume costs follow a
  gamma distribution
#lower and upper dosages and cost in mg,
  from BNF website
#drugs.mono1 <- c("LMT","OXC","CBM",
  "VAL","PHN","TOP")
#drugs.mono2 <- c("LMT","CBM","VAL")
#drugs.comb <- c("PLA","GBP","LEV","LMT",
  "OXC","TGB","TOP")
c.mono1.dose.low <-
c(100,600,800,1000,200,100)
c.mono1.dose.hi <-
c(200,2400,1200,2000,500,500)
c.mono1.mg <- c(0.0121,0.0013,0.0003,0.0003,
0.0013,0.0108)
c.mono2.dose.low <- c(100,800,1000)
c.mono2.dose.hi <-c(200,1200,2000)
c.mono2.mg <- c(0.0121,0.0003,0.0003)
c.comb.dose.low <-
c(0,900,1000,100,600,15,200)
c.comb.dose.hi <-
c(0,1200,3000,200,2400,30,400)
c.comb.mg <- c(0,0.0016,0.0016,0.0121,0.0013,
0.0907,0.0108)

#obtain estimates of mean and sd assuming
  dosage follows a gamma
#distribution with min, max rec
  dosage=2.5,97.5 percentiles
   c.mono1.dose.mn <-
   (c.mono1.dose.hi+c.mono1.dose.low)/2
   c.mono2.dose.mn <-
   (c.mono2.dose.hi+c.mono2.dose.low)/2
   c.comb.dose.mn <-
   (c.comb.dose.hi+c.comb.dose.low)/2
   c.mono1.dose.sd <-(c.mono1.dose.hi-
   c.mono1.dose.low)/(2*1.96)
   c.mono2.dose.sd <-(c.mono2.dose.hi-
   c.mono2.dose.low)/(2*1.96)
   c.comb.dose.sd <-(c.comb.dose.hi-
   c.comb.dose.low)/(2*1.96)
#generate random variates of costs per patient
  per year from gamma distribution
   c.mono1.drug<-
   gamma(nSims,c.mono1.dose.mn[drug1],c.mo
   no1.dose.sd[drug1])*c.mono1.mg[drug1]*365
   c.mono2.drug<-
   gamma(nSims,c.mono2.dose.mn[drug2],c.mo
   no2.dose.sd[drug2])*c.mono2.mg[drug2]*365
   #if drug3 is 1 (placebo) all drug costs are zero
   if (drug3==1)
      {
      c.comb.drug<-rep(0,nSims)
      }
      else c.comb.drug<-
      gamma(nSims,c.comb.dose.mn[drug3],
      c.comb.dose.sd[drug3])*c.comb.mg[drug3]
      *365

#healthcare costs
c.switch=149
c.hc.sf=98
c.hc.nsf=469

#maintenance drug assumed to be VAL
c.main.drug=153

#set costs for therapy states

cost <- array(numeric(),c(8,nSims))

#note all cost values per year, d used to correct
  for cycle length

#state 1 start monotherapy
cost[1,]<- (c.mono1.drug+c.switch+(1-
ft.mono1[1,])*c.hc.sf + ft.mono1[1,]*c.hc.nsf)*d

#state 2 continue monotherapy and seizure free
cost[2,]<- (c.mono1.drug + c.hc.sf)*d

#state 3 start 2nd mono
cost[3,]<- (c.switch + c.mono2.drug +
c.hc.nsf)*d

#state 4 continue 2nd mono
cost[4,] <- (c.mono2.drug + c.hc.nsf)*d

#state 5 start combination therapy
cost[5,] <- (c.switch + c.comb.drug +
c.main.drug + c.hc.nsf)*d

#state 6 continue combination therapy
cost[6,] <- (c.comb.drug + c.main.drug +
c.hc.nsf)*d

#state 7 maintenance therapy
cost[7,] <- (c.main.drug + c.hc.nsf)*d

#state 8 death
```

```
cost[8,] <- 0

#set qols for therapy states, d used to adjust for
  cycle length

qol <- array(numeric(),c(8,nSims))

#qol for mono1 1st cycle
qol[1,] <- (ft.mono1[1,]*u.nr +
(1-ft.mono1[1,])*u.sf)*d

#qol for mono1 subseq cycles
qol[2,] <- u.sf*d

#qol for mono2 1st cycle
qol[3,] <- (ft.mono2[1,]*u.nr +
(1-ft.mono2[1,])*u.pr)*d

#qol for mono2 subseq cycles
qol[4,] <- u.pr*d

#qol for comb 1st cycle
qol[5,] <- (ft.comb[1,]*u.nr +
(1-ft.comb[1,])*u.pr)*d

#qol for comb subseq cycles
qol[6,] <- u.pr*d

#qol for maintenance state
qol[7,] <- u.nr*d

#qol for death state
qol[8,] <- u.death

#create arrays containg total pop in each state,
  cost and qaly at each cycle

#initalise array
total.pop <- array(0,c(T,8,nSims))
total.cost <- numeric()
total.qalys <- numeric()

#Run nSims simulations
for (rep in 1:nSims)
   {
   #Set up transition matrix
   #initialise transition matrix
   trans <- array(0,c(8,8,T))

   #transitions following 1st cycle in current
   state

   #mono1.new to mono1.ongoing
   trans[1,2,1] <- (1-ft.mono1[1,rep])*(1-mort.sf)

   #mono1.new to mono2.new
   trans[1,3,1] <- (ft.mono1[1,rep])*(1-mort.nsf)

   #mono1.new to death
   trans[1,8,1] <-
   mort.sf+ft.mono1[1,rep]*(mort.nsf-mort.sf)

   #mono2.new to mono2.ongoing
   trans[3,4,1] <- (1-ft.mono2[1,rep])*
   (1-mort.nsf)

   #mono2.new to comb.new
   trans[3,5,1] <- ft.mono2[1,rep]*(1-mort.nsf)

   #mono2.new to death
   trans[3,8,1] <- mort.nsf

   #comb.new to comb.ongoing
   trans[5,6,1] <- (1-ft.comb[1,rep])*(1-mort.nsf)

   #comb.new to maint
   trans[5,7,1] <- ft.comb[1,rep]*(1-mort.nsf)

   #comb.new to death
   trans[5,8,1] <- mort.nsf

   #maint to maint
   trans[7,7,1] <- 1-mort.nsf

   #maint to death
   trans[7,8,1] <- mort.nsf

   #transitions during subsequent cycles in
   current state

   #cs = time in current state
   for (cs in 2:T)
      {
      #mono1.ongoing to mono1.ongoing
      trans[2,2,cs] <- (1-ft.mono1[cs,rep])*
      (1-mort.sf)

      #mono1.ongoing to mono2.new
      trans[2,3,cs] <- ft.mono1[cs,rep]*
      (1-mort.nsf)

      #mono1.ongoing to death
      trans[2,8,cs] <- mort.sf+ft.mono1[cs,rep]*
      (mort.nsf-mort.sf)

      #mono2.ongoing to mono2.ongoing
      trans[4,4,cs] <- (1-ft.mono2[cs,rep])*
      (1-mort.nsf)

      #mono2.ongoing to comb.new
      trans[4,5,cs] <- ft.mono2[cs,rep]*
      (1-mort.nsf)

      #mono2 ongoing to death
      trans[4,8,cs] <- mort.nsf
```

```
    #comb.ongoing to comb-ongoing
    trans[6,6,cs] <- (1-ft.comb[cs,rep])*
    (1-mort.nsf)

    #comb.ongoing to maint
    trans[6,7,cs] <- ft.comb[cs,rep]*
    (1-mort.nsf)

    #comb.ongoing to death
    trans[6,8,cs]<-mort.nsf
    }

#death to death
trans[8,8,] <- 1

#Initialise Population Matrix
pop <- array(0,c(T,8,T))

#Determine initial states
pop[1,,1] <- start

#Loop through total remaining cycles, 2 to T
#c = cycle
for (c in 2:T)
    {
    #cs = time in current state
    for (cs in 1:(c-1))
     {
     #determine destination states, note %*%
       =matrix multiplication
     dest <- pop[c-1,,cs] %*% trans[,,cs]

     #transitions to new states, set cs to 1, note
       time in current state note tracked for
       maintenance
     pop[c, c(1,3,5,7,8),1] <-
     dest[c(1,3,5,7,8)]+pop[c,c(1,3,5,7,8),1]

     #transitions remaining in current states,
       set cs to cs+1
     pop[c, c(2,4,6),cs+1] <- dest[c(2,4,6)]
     }
    }


#sum over all 'times in current state' for each
  cycle and state
for (c in 1:T)
    {
    for (s in 1:8)
     {
     total.pop[c,s,rep] <-sum(pop[c,s,])
     }
    }

#calculate total qalys
qalys = total.pop[,,rep] %*% qol[,rep]

    #discount qalys
    total.qalys[rep] <- sum(qalys *
    (1-q.disc)^(1:T-1))

    #calculate total cost
    costs = total.pop[,,rep] %*% cost[,rep]

    #discount costs
    total.cost[rep] <- sum(costs * (1-c.disc)^
    (1:T-1))
    }

    total.sum <- array(0,c(T,5))

    #Summarise population matrix for all
      simulation
    total.sum[,1]<-apply(total.pop[,1,]+
    total.pop[,2,],1,mean)
    total.sum[,2]<-apply(total.pop[,3,]+
    total.pop[,4,],1,mean)
    total.sum[,3]<-apply(total.pop[,5,]+
    total.pop[,6,],1,mean)
    total.sum[,4]<-apply(total.pop[,7,],1,mean)
    total.sum[,5]<-apply(total.pop[,8,],1,mean)

    #Summarise data for trial data as check for
      validity of inputs
    ther<-c("Mono1","Mono2","Comb")
    drug<-c(name.mono1,name.mono2,
    name.comb)
    cost<-c(mean(c.mono1.drug),
    mean(c.mono2.drug),mean(c.comb.drug))
    rsp<-c(mean(p.r.mono1),mean(p.r.mono2),
    mean(p.r.comb))
    wd<-c(mean(p.ae.mono1),mean(p.ae.mono2),
    mean(p.ae.comb))
    trial.data<-data.frame(ther,drug,cost,rsp,wd)


  print(date())

  return(summary=data.frame(cost=total.cost,
  qalys=total.qalys),name,total.sum=total.sum,tria
  l.data=trial.data)
  }
#WINBUGS CODE FOR META-ANALYSIS

Random Study Effects / Fixed Treatment Effects
model for Epilepsy

  model
    {
    #####Define Prior Distributions

    #prior distribution for beta[1], note beta[1] is
      a dummy parameter = 0
    beta[1] ~ dnorm(0.0,1.0E10)
```

```
    #prior distribution for beta[2:Ndrugs] drug
      effect relative to drug 1
    for (d in 2:Ndrugs)
        #prior distributions for fixed treatment
          effects
        {
        beta[d] ~ dnorm(0.0,1.0E-6)
        }

    #prior distributions for random study effect
      (alpha)
    alphamean ~ dnorm(0.0,1.0E-6)

    alphatau ~ dgamma(0.01,0.01)

    #use for mono2 only
    #alphatau ~ dgamma(3,1)

    #random baseline effect
    for (s in 1 : Nstudies)
        {
        alpha[s] ~ dnorm(alphamean,alphatau)
        }

    #model
    for(i in 1 : Nobs )
        {
        #logit link for probability of response
          control and
#alpha and beta parameters
        #logit(p[i]) <- alpha[study[i]] +
          beta[drug[i]]

        #binomial link between number of
          responses and
#probability of response from treatment arm
        r[i] ~ dbin(p[i],n[i])
        }

    #generate absolute probabilities for each
      drug
    for (d in 1:Ndrugs)
       {
       logit(Pd[d]) <- alphamean+beta[d]
       }

    }

#Data for Monotherapy for Newly Diagnosed
Patients

    #drug1=lmt
    #drug2=oxc
    #drug3=cbz
    #drug4=val
    #drug5=phe
    #drug6=top

    list(Nobs = 24,
        Ndrugs = 6,
        Nstudies = 11)

    #study data for WITHDRAWL
    study[ ]    drug[ ]    n[ ]    r[ ]

    END

    #Initial Values
    list(beta = c(0,0,0,0,0,0),alpha =
    c(0,0,0,0,0,0,0,0,0,0,0),
        alphamean=0,alphatau=1)

    #drug1=lmt
    #drug2=oxc
    #drug3=cbz
    #drug4=val
    #drug5=phe
    #drug6=top

    list(Nstudies=11,
        Nobs = 24,
        Ndrugs = 6)

    #study data for response
    study[ ]    drug[ ]    n[ ]    r[ ]

    END

    #Initial Values
    list(beta = c(0,0,0,0,0,0),alpha =
    c(0,0,0,0,0,0,0,0,0,0,0),
        alphamean=0,alphatau=1)

#'#Data for Mono2 Therapy

    #drug1=lmt
    #drug2=cbz
    #drug3=val

    list(Nstudies=3,
        Nobs = 6,
        Ndrugs = 3)

    #study data for Withdrawl
    study[ ]    drug[ ]    n[ ]    r[ ]

    END

    #Initial Values
    list(beta = c(0,0,0),alpha = c(0,0,0),
        alphamean=0,alphatau=1)

    #drug1=lmt
    #drug2=cbz
    #drug3=val
```

```
    list(Nstudies=2,
        Nobs = 4,
        Ndrugs = 3)

    #study data for response
    study[ ]    drug[ ]    n[ ]    r[ ]

    END

    #Initial Values
    list(beta = c(0,0,0),alpha = c(0,0),
        alphamean=0,alphatau=1)

##Data for combination therapy

    list(Nobs = 30,
        Ndrugs = 7,
        Nstudies = 15)

    #study data for withdrawl
    study[ ]    drug[ ]    n[ ]    r[ ]

    END

    #Initial Values
    list(beta = c(0,0,0,0,0,0,0),alpha =
c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0),
        alphamean=0,alphatau=1)

#drug1=placebo
#drug2=gbp
#drug3=lev
#drug4=lmt
#drug5=oxc
#drug6=tgb
#drug7=tpm

list(Nobs = 30,
    Ndrugs = 7,
    Nstudies = 15)

#study data for response
study[ ]    drug[ ]    n[ ]    r[ ]

END

#Initial Values
list(beta = c(0,0,0,0,0,0,0),alpha =
c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0),
    alphamean=0,alphatau=1)
```

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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