Appendix M
Health Economic Evidence Extractions

Which AEDs are clinically effective and cost-effective for people with focal epilepsy with or without secondary generalisation seizures?

Frew E, Sandercock J, Whitehouse WP, Bryan S. The cost-effectiveness of newer drugs as add-on therapy for children with focal epilepsies. *Seizure.* 2007; 16: 99-112.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model using individual sampling simulation **Perspective:** UK NHS **Time horizon:** up to 15 years **Discounting:** Costs and QALYs, 6% and 1.5% per annum, respectively	**Population:** Children between 3-18 years of age with a new diagnosis of focal epilepsy with or without secondary generalisation; personal characteristics for hypothetical individuals (gender, age, presence of learning difficulties) are assigned from sampling distributions for each characteristic. **Intervention 1:** drug sequences not including any newer AEDs **Intervention 2:** drug sequence with lamotrigine as first choice adjunctive therapy **Intervention 3:** drug sequence with gabapentin as first choice adjunctive therapy **Intervention 4:** drug sequence with topiramate as first choice adjunctive therapy **Intervention 5:** drug sequence with oxcarbazepine as first choice adjunctive therapy	**Health outcomes incorporated:** Intolerable adverse effects; lack of effect on seizure rate; partial efficacy with tolerable or no adverse effects; complete seizure freedom with tolerable or no adverse-effects; complete seizure freedom following withdrawal of drug therapy; no seizure free but prefers to remain untreated **Mean total QALYs (95% CI):** Cannot summarise results	**Cost components incorporated:** AED costs, GP consultations, outpatient consultations, emergency department visits, telephone calls to clinical departments from patients (and family) for advice, inpatient stays **Mean total costs (95% CI)** Cannot summarise results **Currency & cost year:** 2002/03 UK pounds	**Basecase ICERs (£ / QALY gained):** Cannot summarise results, but analysis could not conclude that newer AEDs were cost-effective or not cost-effective. **Analysis of uncertainty:** SA: 3.5% discounting for both costs and QALYs
Data sources				
Health outcomes: Transition probabilities relating to the effectiveness and tolerability of the different AEDs determined the likelihood of patients reaching a particular health outcome within the model and were derived from the systematic review of clinical effectiveness published in the HTA (Connock 2006). Other parameters including the				

proportions discontinuing treatment, time to discontinuation or withdrawal and probability of moving onto combination therapy at each stage were based on epidemiological literature (Connock 2006) and clinical advice. Proportions withdrawing due to adverse effects and lack of efficacy and proportions achieving seizure freedom were calculated from published trial data, adjusting the sample size for drop outs and length of follow-up. The proportion of patients achieving partial efficacy is assumed to include all remaining patients who neither withdrew for adverse effects of lack of efficacy nor achieved seizure freedom. To allow the proportion estimates to vary according to different stages of treatment (i.e first line, second line, etc) the trial data was used as 'anchor points' and various assumptions applied.

RCT data for newer AEDs consists of a single trial for each used as adjunctive therapy in more or less refractory populations. The trials included patients with a variable disease history, but performance of placebo in the trials is broadly similar thus the authors assumed the trial data to be reasonably representative of what might occur at fourth line treatment. Data for lamotrigine was available at two time points, as first line monotherapy and as later adjunctive therapy. Based on the studies' findings, the authors assumed that the proportions withdrawing due to adverse effects and lack of efficacy are constant across all stages of treatment for all AEDs. Also consistent with this data, the authors applied a constant factor of 0.4 to reflect the reduction in the proportion of patients achieving seizure freedom at each stage of treatment. They also allowed for a small increase in efficacy (a constant factor of approximately 1.10) when the drug is used in combination as compared to monotherapy.

Trial data for first-line carbamazepine monotherapy was used to form an 'anchor point' for other older AEDs (valproate, phenytoin, generic older AED). Meta-analyses of older drugs (Marson 2001; Tudur Smith 2002) suggest similar effectiveness with some differences in adverse effects with the order of preference being carbamazepine, valproate, phenytoin and others. The authors assumed this to be a rational order of preference and based estimates for valproate and phenytoin and a generic older AED on a slight increase in adverse effects (constant multiplier of 1.05) and slight decrease in effectiveness (constant multiplier of 0.95) by comparison with the drug used immediately before it in the strategy sequence.

Based on longer term time to treatment failure trends illustrated in Chadwick (1999) and clinical advice the authors assumed that unacceptable adverse effects will lead to earlier discontinuation of treatment, often within the titration period, than lack of efficacy. The majority of patients would discontinue treatment by 1 year due to lack of effect. These trends were built into the model using Weibull distributions with shape and location parameters 0.8 and 2.0 for withdrawal due to adverse effects and 1.2 and 6.0 for lack of efficacy.

The authors also assumed that patients will continue on AEDs which are beneficial with acceptable adverse effects but that at some point later on there will be further decisions to be made which may include discontinuation of the drug for various reasons. Time from the start of a treatment to the point where a change is made is assumed to follow a Weibull distribution (shape parameter 4 and location parameter 2). The authors have also assumed, based on clinical advice, that patients achieving seizure freedom who are willing to try withdrawing treatment will do so, on average, after 2 years of drug treatment.

Quality-of-life weights: Utility estimates for the modelled health states were not available from the published literature, therefore the authors sought the views of paediatric consultants concerning the quality of life of children with epilepsy. 25 clinical experts completed a modified version of the EQ-5D questionnaire.

Cost sources: Dosage and costs of AEDs were taken from the *British National Formulary* (2002). Other sources for costs included *NHS Reference Costs* (Department of Health 2002) and PSSRU's *Unit costs of health care and social care* (Netten 2002). Data on general resource use and costs associated with epilepsy diagnosis were obtained through a survey of 18 clinical experts.

Comments

Source of funding: UK NHS Research and Development Health Technology Assessment Programme.

Limitations: Due to a substantial lack of data on effectiveness of AEDs in populations of children, the analysis was highly speculative. The limited effectiveness data and complete lack of resource use and utility data make definitive conclusions impossible. Cost data for AEDs has changed substantially since the analysis was undertaken, with both lamotrigine and topiramate having become generic.

Although the analysis took into account all AEDs for which there was RCT evidence at the time, evidence for other AEDs licensed for adjunctive therapy in children (levetiracetam) has emerged since.

Other: The European Medicines Agency has recently issued guidance to indicate that in refractory focal epilepsies, the results of efficacy trials performed in adults could be extrapolated to children, provided the dose is established. On this basis, an analysis based solely upon efficacy data from a paediatric population is less in line with current standards than if it was based on all relevant RCT evidence in this population. However, as the resource use, costs and utilities for children may be different from adults, a separate analysis is nonetheless necessary.

Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable	

Abbreviations: ICER = incremental cost-effectiveness ratio

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

Hawkins N, Epstein D, Drummond M et al. Assessing the cost-effectiveness of new pharmaceuticals in epilepsy in adults: the results of a probabilistic decision model. *Med Decis Making.* 2005; 25(5):493-510. Ref ID: 7

Study details	Population & interventions	Health outcomes	Costs	Cost effectiveness
Analysis of first line monotherapy in newly diagnosed partial epilepsy				
Economic analysis: CUA **Study design:** Decision analytic model **Perspective:** UK NHS **Time horizon:** 15 years **Discounting:** Costs and QALYs, 6% and 1.5% per annum, respectively	**Population:** Patients with newly diagnosed partial epilepsy **Intervention 1:** CBZ **Intervention 2:** VPA **Intervention 3:** LTG **Intervention 4:** OXC **Intervention 5:** TPM	**Health outcomes incorporated:** response to drug, defined as both tolerating the drug and becoming seizure free; mortality **Mean total QALYs (95% CI)** CBZ: 9.392 VPA: 9.404 LTG: 9.382 OXC: 9.415 TPM: 9.430	**Cost components incorporated:** costs of general practitioner visits, outpatient visits and hospitalisations. **Mean total costs (95% CI)** CBZ: £4,428 VPA: £4,572 LTG: £6,133 OXC: £6,294 TPM: £7,838 **Currency & cost year:** 2002/03 UK pounds	**Basecase ICERs (£ / QALY gained):** CBZ: least cost VPA: £11,731 compared to CBZ LTG: dominated by CBZ and VPA OXC: extendedly dominated by TPM TPM: £126,519 compared to VPA **Analysis of uncertainty:** Probabilistic sensitivity analysis was performed. At a threshold of £20,000 per QALY, each AED has the following probability of being the most cost-effective: CBZ: 42% VPA: 46% LTG: 0% OXC: 12% TPM: 0%

				These figures indicate a large degree of uncertainty around this decision.
Analysis of second line monotherapy in refractory partial epilepsy				
Economic analysis: CUA **Study design:** Decision analytic model **Perspective:** UK NHS **Time horizon:** 15 years **Discounting:** Costs and QALYs, 6% and 1.5% per annum, respectively	**Population:** Patients with refractory partial epilepsy **Intervention 1:** CBZ **Intervention 2:** VPA **Intervention 3:** LTG	**Health outcomes incorporated:** response to drug, defined as both tolerating the drug and achieving a 50% reduction in seizure frequency compared with baseline; mortality **Mean total QALYs (95% CI)** CBZ: 8.865 VPA: 8.856 LTG: 8.856	**Cost components incorporated:** costs of general practitioner visits, outpatient visits and hospitalisations. **Mean total costs (95% CI)** CBZ: £5,599 VPA: £5,728 LTG: £6,749 **Currency & cost year:** 2002/03 UK pounds	**Basecase ICERs (£ / QALY gained):** CBZ: least cost VPA: dominated by CBZ LTG: dominated by CBZ **Analysis of uncertainty:** Probabilistic sensitivity analysis was performed. At a threshold of £20,000 per QALY, each AED has the following probability of being the most cost-effective: CBZ: 79% VPA: 21% LTG: 0%
Analysis of third line adjunctive therapy in refractory partial epilepsy				

Economic analysis: CUA **Study design:** Decision analytic model **Perspective:** UK NHS **Time horizon:** 15 years **Discounting:** Costs and QALYs, 6% and 1.5% per annum, respectively	**Population:** Patients with refractory partial epilepsy **Intervention 1:** placebo (monotherapy) **Intervention 2:** GBP **Intervention 3:** LTG **Intervention 4:** TGB **Intervention 5:** OXC **Intervention 6:** LEV **Intervention 7:** TPM	**Health outcomes incorporated:** response to drug, defined as both tolerating the drug and achieving a 50% reduction in seizure frequency compared with baseline; mortality **Mean total QALYs (95% CI)** Placebo: 8.716 GBP: 8.747 LTG: 8.746 TGB: 8.758 OXC: 8.794 LEV: 8.775 TPM: 8.777	**Cost components incorporated:** costs of general practitioner visits, outpatient visits and hospitalisations. **Mean total costs (95% CI)** Placebo: £5,064 GBP: £5,861 LTG: £5,926 TGB: £6,133 OXC: £6,400 LEV: £6,984 TPM: £7,026 **Currency & cost year:** 2002/03 UK pounds	**Basecase ICERs (£ / QALY gained):** Placebo: least cost GBP: extendedly dominated by OXC LTG: extendedly dominated by OXC TGB: extendedly dominated by OXC OXC: £17,095 compared to placebo LEV: dominated TPM: dominated **Analysis of uncertainty:** Probabilistic sensitivity analysis was performed. At a threshold of £20,000 per QALY, each AED has the following probability of being the most cost-effective: Placebo (monotherapy): 40% GBP: 2% LTG: 2% TGB: 2% OXC: 52% LEV: 2% TPM: 0% These figures indicate a large degree of uncertainty around this decision.

Data sources

Health outcomes: The probability of responding to different drugs was determined from a meta-analysis of the clinical trial intention-to-treat data. In the absence of any trial simultaneously comparing all the drugs, a random effects Bayesian hierarchical model was used to derive the absolute treatment differences based on the network of evidence. These data were used to determine response to treatment in the first 6-month treatment cycle.

Probabilities of treatment failure following the first cycle for monotherapy for newly diagnosed and refractory patients were estimated from the National General Practice Study of Epilepsy (NGPSE), a longitudinal cohort study. Probabilities of treatment failure during subsequent cycles for adjunctive therapy were determined from the results of an unpublished tiagabine open-label follow-up study (study No. M91-604/M91-604C; communication from NICE to Cephalon Ltd). These data were not specific to the drug under consideration and indicated that the probability of failure declined over time for patients who successfully completed the first cycle on the therapy for both monotherapy and combination therapy.

There is evidence that the age- and sex-adjusted death rate among people with epilepsy is more than twice as high as for the general population. There is also evidence indicating that being in 6-month remission may enhance survival. Therefore, the mortality rates used in the model are taken from the national and epilepsy-specific sources (Office of National Statistics 2000; Lhatoo 2001) and are conditional on whether the patient is seizure free.

Quality-of-life weights: QALYs were calculated by weighting the time patients spend in a health state by the value of health related quality of life of that disease state using health state preference (utility) data. These weights were sourced from a nonrandomized audit of 125 patients starting a new adjunctive AED, who complete the EQ-5D questionnaire after 6 months (Selai CE, Trimble M, Price ML. Evaluation of the relationship between epilepsy severity and utility. In: ISPOR Fifth Annual European Conference; 3-5 November 2002; Rotterdam, the Netherlands).

Cost sources: The use and cost of health care resources were conditional on whether a patient was seizure free and were estimated from a number of sources (Heaney 1998; Jacoby 1998; Unit Costs of Health and Social Care 2002; NHS Reference Costs 2002). AED dosage and costs were based on data from the *British National Formulary* (March 2002).

Comments

Source of funding: UK NHS Research and Development Health Technology Assessment Programme.

Limitations: The longer term data used to parameterise cycles subsequent to the first were applied generally to all drugs under evaluation because drug-specific longer term evidence was lacking. In other words, the transition probabilities used in the maintenance periods are not AED-specific, rather AED treatments are differentiated only by their initial effectiveness and adverse event profile. Cost data was up to date at the time of initial HTA publication, but is now out of date, particularly as the costs of some AEDs (lamotrigine and topiramate) have reduced dramatically after coming off patent. Estimates of the impact of seizure control on utility were based on a single small study. Because the analysis is based on short term trials in a long-lasting condition, the impact of chronic toxicity and harm from AEDs or potential for teratogenicity have not been accounted for.

Although the analysis took into account all AEDs for which there was RCT evidence at the time, evidence for other AEDs licensed for monotherapy (gabapentin and levetiracetam) and adjunctive therapy (eslicarbazepine, lacosamide, pregabalin, zonisamide) has emerged since. Furthermore, the evidence base for drugs used as monotherapy has increased, as has the evidence base for adjunctive therapies.

Other:

Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable	

Marson AG, Appleton R, Baker GA et al. A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial. *Health Technol Assess.* 2007; 11(37):1-108. Ref ID: 1496				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Analysis of patient data collected during the entire trial period				
Economic analysis: CUA and CEA **Study design:** RCT **Perspective:** UK NHS **Time horizon:** 2 years from randomisation **Discounting:** Costs, QALYs, number of seizures: 3.5% per annum	**Population:** Patients with newly diagnosed epilepsy for whom CBZ was chosen as standard drug; primarily adults with newly diagnosed partial seizures. **Intervention 1:** CBZ **Intervention 2:** GBP **Intervention 3:** LTG **Intervention 4:** TPM	**Health outcomes incorporated:** EQ-5D measurements of HRQoL; number of seizures **Mean total QALYs (95% CI):** based on 636 adult patients completing EQ-5D questionnaires CBZ: 1.477 (1.40 to 1.56) TPM: 1.501 (1.42 to 1.58) LTG: 1.564 (1.48 to 1.64) GBP: 1.491 (1.40 to 1.58) **Mean total seizures (95% CI)** based on 823 patients CBZ: 52.6 (36.0 to 69.2) TPM: 63.1 (32.9 to 93.3) LTG: 41.7 (28.0 to 55.4) GBP: 69.8 (38.9 to 100.7)	**Cost components incorporated:** Costs of AEDs; costs of managing adverse events requiring hospitalisation; costs of GP, nurse or other health professional contacts; social services contacts; use of ambulance service **Mean total costs (95% CI)** based on 636 adult patients completing EQ-5D questionnaires: CBZ: £1,266 (970 to 1482) TPM: £2,009 (1699 to 2319) LTG: £2,257 (1948 to 2566) GBP: £2,561 (2139 to 2984) **Mean total costs (95% CI)** based on 823 patients CBZ: £1,266 (1030 to 1502) TPM: £2,008 (1693 to 2322) LTG: £2,134 (1890 to 2378) GBP: £2,494 (2144 to 2844) **Currency & cost year:** 2005 UK pounds	**Basecase ICERs (£ / QALY gained):** CBZ: least cost TPM: extendedly dominated by LTG LTG: £11,851 compared to CBZ GBP: dominated by LTG **Basecase ICERs (£ / seizure avoided):** CBZ: least cost TPM: dominated by CBZ LTG: £80 compared to CBZ GBP: dominated by CBZ **Analysis of uncertainty:** Using different drug costs (varying from high to low estimates) did not change the overall pattern of results: The lowest value of the ICER for LTG is when the highest cost for CBZ and lowest cost for LTG are used (£11,149 per QALY and £74 per seizure avoided). The highest ICER for LTG is when the lowest cost for CBZ and highest cost for LTG are used (£14,042 per QALY and £96 per seizure avoided). Alternative assumptions made in the area under the curve approach to estimating QALYs did not impact the relative ICERs and pattern of results. At a willingness to pay threshold of £20,000 per QALY gained, bootstrapped baseline point estimates of the ICERs for newer drug

				(below) compared to CBZ results in the following probabilities of being most cost-effective: TPM: 40% LTG: 75% GBP: 20% At a willingness to pay threshold of £160, £400, £800 and £1,600 per seizure avoided, ICERs for newer drug (below) compared to CBZ results in the following probabilities of being most cost-effective, respectively: TPM: 17%, 22%, 24%, 25% LTG: 70%, 79%, 82%, 84% GBP: 8%, 13%, 15%, 16%
Analysis of patient data collected after the introduction of oxcarbazepine				
Economic analysis: CUA and CEA **Study design:** RCT **Perspective:** UK NHS **Time horizon:** 2 years from randomisation **Discounting:** Costs, QALYs, number of seizures: 3.5% per annum	**Population:** Patients with newly diagnosed epilepsy (recruited after 1 June 2001) for whom CBZ was chosen as standard drug; primarily adults with newly diagnosed partial seizures. **Intervention 1:** CBZ **Intervention 2:** GBP **Intervention 3:** LTG **Intervention 4:** TPM **Intervention 5:** OXC	**Health outcomes incorporated:** EQ-5D measurements of HRQoL; number of seizures **Mean total QALYs (95% CI):** based on 414 adult patients completing EQ-5D questionnaires CBZ: 1.491 (1.38 to 1.60) OXC: 1.611 (1.50 to 1.72) TPM: 1.541 (1.42 to 1.66) LTG: 1.563 (1.45 to 1.67) GBP: 1.480 (1.37 to 1.59) **Mean total seizures (95% CI)** based on 547 patients CBZ: 50.9 (26.7 to 75.2) OXC: 32.0 (17.8 to 46.3) LTG: 50.9 (27.3 to 74.5)	**Cost components incorporated:** Costs of AEDs; costs of managing adverse events requiring hospitalisation; costs of GP, nurse or other health professional contacts; social services contacts; use of ambulance service **Mean total costs (95% CI)** based on 414 adult patients completing EQ-5D questionnaires: CBZ: £1,095 (860 to 1330) OXC: £1,839 (1481 to 2197) TPM: £1,930 (1536 to 2324) LTG: £2,078 (1740 to 2416) GBP: £2,573 (1929 to 3216)	**Basecase ICERs (£ / QALY gained):** CBZ: least cost OXC: £6,200 compared to CBZ TPM: dominated by OXC LTG: dominated by OXC GBP: dominated by CBZ, OXC, TPM and LTG **Basecase ICERs (£ / seizure avoided):** CBZ: least cost OXC: £35 compared to CBZ LTG: dominated by CBZ and OXC TPM: dominated by CBZ and OXC GBP: dominated by CBZ and OXC **Analysis of uncertainty:** Using different drug costs (varying from high to low estimates) did not change the overall pattern of results: The lowest value of the ICER for OXC is when the highest cost for CBZ and lowest cost for LTG are used (£5,702

		TPM: 59.4 (25.3 to 93.5) GBP: 85.3 (35.1 to 135.4)	**Mean total costs (95% CI)** based on 547 patients CBZ: £1,151 (880 to 1423) OXC: £1,815 (1541 to 2089) LTG: £1,946 (1683 to 2209) TPM: £2,059 (1578 to 2539) GBP: £2,594 (2048 to 3139) **Currency & cost year:** 2005 UK pounds	per QALY and £31 per seizure avoided). The highest ICER for LTG is when the lowest cost for CBZ and highest cost for LTG are used (£6,351 per QALY and £36 per seizure avoided). Alternative assumptions made in the area under the curve approach to estimating QALYs did not impact the relative ICERs and pattern of results. At a willingness to pay threshold of £20,000 per QALY gained, bootstrapped baseline point estimates of the ICERs for newer drug (below) compared to CBZ results in the following probabilities of being most cost-effective: OXC: 83% TPM: 58% LTG: 59% GBP: 14% At a willingness to pay threshold of £160, £400, £800 and £1,600 per seizure avoided, ICERs for newer drug (below) compared to CBZ results in the following probabilities of being most cost-effective, respectively: OXC: 85%, 90%, 90%, 91% TPM: 27%, 33%, 35%, 37% LTG: 41%, 48%, 50%, 52% GBP: 5%, 8%, 10%, 10%
Data sources				
Health outcomes: EQ-5D questionnaires were administered to adults only at baseline, 1 year and 2 years. Estimation of QALYs for children was not possible because EQ-5D data were not collected from children. Total QALYs were estimated using an area under the curve approach, and in the base case, health benefits are assumed to occur at the mid-points of years 1 and 2. An alternative assumption wherein health benefits are assumed to occur at either the beginning or end of years 1 and 2 was employed in a sensitivity analysis. Quantification of seizures for the cost per seizure avoided analysis offered no description on seizure type or severity.				

Quality-of-life weights: Using the EQ-5D, UK tariff values representing quality of life weights were applied to health states.

Cost sources: To allow for the potential impact of high and low drug costs on the results, separate analyses were conducted using the most expensive and cheapest costs for CBZ and LTG. Adverse event data requiring hospitalisation were collected from individual patient forms and categorised by specialty and outpatient attendances or inpatient stays. Unit cost data were obtained from the TFR2A and TFR2B specialty and programme costs to the Department of Health by Trusts for the year ending March 2003. Costs were then inflated to 2005 prices through application of Hospital and Community Health Services Pay and Prices Index. Other cost data were obtained from PSSRU's Unit Costs of Health and Social Care (2005) and the Finance Department of Walton NHS Hospital Trust. Patient-reported resource use data were collected at 3 months, 1 and 2 years and captured resource use in the preceding 3-month period. Therefore, to estimate year one costs, the costs in months 10-12 were multiplied by three and added to costs for months 1-3. Year two costs were estimated by multiplying the cost in months 22-24 by four.

Comments

Source of funding: UK NHS Research and Development Health Technology Assessment Programme.

Limitations: The majority of patients had partial onset seizures and cryptogenic or symptomatic localisation-related epilepsy, but around 11% had either an idiopathic generalised epilepsy, another syndrome or were unclassified.

The postal approach to collecting quality of life data resulted in some non-response and loss to follow-up. The clinical results of the trial found that the differences between responders and non-responders for baseline quality of life profile and trial clinical outcomes are in line with previous research showing that responders to surveys are likely to make favourable reports and be more successful in their current status than non-responders. In other words, patients who responded to the EQ-5D questionnaires were 'healthier' than their non-responding counterparts and the implications of this responder bias needs to be kept in mind for interpretation of the cost per QALY analysis. Number of seizures experienced by patients is an important outcome, but it constitutes a narrow measure of 'benefit' in an economic evaluation in that it focuses on just one aspect of patient outcome.

Cost-effectiveness acceptability curves were generated for each drug compared to CBZ, but it would have been more appropriate to include all in the same graph, creating an acceptability frontier. However, it is very unlikely that this visual would have changed the fairly definitive results in favour of LTG in the first analysis and OXC in the second. Separation of the two analyses makes practical sense, but makes interpretation of the optimal AED in terms of cost-effectiveness slightly difficult. In the first analysis, LTG is very likely to be a cost-effective alternative to CBZ. However, when OXC is introduced later in the trial, it seems to be an even more cost-effective option compared to LTG.

The incremental cost per seizure avoided analysis is also difficult to interpret. As there is no established willingness to pay threshold for additional seizures avoided, it could be difficult to make use of this information. However, as the results of this analysis are in line with those from the cost per QALY analysis, interpretation is fairly straightforward even without an explicit threshold.

Although cost data was up to date at the time of evaluation, current costs in 2010 are quite different, particularly as the costs of some AEDs (lamotrigine and topiramate) have reduced dramatically after coming off patent.

Other:

Cost per QALY analysis:	**Overall quality*:** Potentially serious limitations	**Overall applicability**:** Partially applicable

Cost per seizure avoided analysis:	**Overall quality*:** Potentially serious limitations	**Overall applicability**:** Partially applicable

Spackman DE, Yeates A, Rentz A, Hutton J. The cost-effectiveness of zonisamide as adjunctive therapy in adult partial seizure epilepsy. *Journal of Medical Economics*. 2007; 10: 455-473.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: CUA **Study design:** Decision analytic model **Perspective:** Scottish National Healthcare System **Time horizon:** 15 years **Discounting:** Costs and QALYs, 3.5% per annum	**Population:** Adults with refractory focal epilepsy **Intervention 1:** Adjunctive levetiracetam (2000 mg/day) – Adjunctive lamotrigine (300 mg/day) **Intervention 2:** Adjunctive zonisamide (300 mg/day) – adjunctive lamotrigine (300 mg/day)	**Health outcomes incorporated:** 50% reduction in seizure frequency; withdrawal due to a 'treatment limiting event' (i.e. adverse event); mortality **Mean total QALYs (95% CI):** LEV – LTG: 7.897 ZNS – LTG: 7.923	**Cost components incorporated:** Direct healthcare costs including neurologist visits, GP visits, AEDs, management of weight loss, concentration problems, nausea/vomiting, rashes (including Stevens-Johnson syndrome). **Mean total costs (95% CI)** LEV – LTG: £15,610 ZNS – LTG: £15,630 **Currency & cost year:** 2004 UK pounds	**Basecase ICERs (£ / QALY gained):** LEV – LTG: least cost ZNS – LTG: £761 compared to LEV - LTG **Analysis of uncertainty:** A series of 1- and 2-way sensitivity analyses were undertaken: • Discounting rates • Reducing time horizons • Varying the proportion of patients who have <1 seizure per month • Varying the proportion of non-responding patients who have <1 seizure per month • Varying proportion of responders to levetiracetam and zonisamide • Varying utilities gained for responders, non-responders and those starting new treatments None of the above sensitivity analyses changed the conclusions arising from the base case (i.e. the ICER for ZNS – LTG never came close to the £20,000 per QALY gained threshold for cost-effectiveness). Varying the annual costs of each AED dramatically altered the results. When the cost of ZNS was halved, it

				dominated the LEV-based strategy. When the cost of ZNS was doubled, the ICER increased to £48,021 per QALY gained. When the cost of LEV was halved, the ICER for the ZNS-based strategy increased to £45,314 per QALY gained. When the cost of LEV was doubled, ZNS-based strategy dominates. When the costs of switching after second-line treatment is reduced, the ZNS-based strategy dominates.

Data sources

Health outcomes: Effectiveness data was derived from selected clinical trials of zonisamide (Brodie 2005), levetiracetam (pooled from Shorvon 2000, Cereghino 2000 and Betts 2000) and lamotrigine (Matsuo 1993). Longer term effectiveness data used in the maintenance period of the model was taken from an observational study (Selei 2005) that followed patients for up to 5 years after they started one of the newer AEDs. The same data are applied to all drugs in the maintenance period as intervention-specific information is lacking. In other words, the transition probabilities used in the maintenance periods are not AED-specific, rather AED treatments are differentiated only by their initial effectiveness and adverse event profile. Data on seizure frequency among responders were taken from a study of adjunctive treatment in refractory focal epilepsy by Guberman (2002). Mortality rates were estimated by combining estimates of death rates in the general population (from the General Register Office for Scotland 2004), the odds ratio of epilepsy-associated mortality (from Mohanraj 2004) and the relative risk of sudden death from epilepsy by seizure frequency (from Nilsson 1999). Data on the incidence of adverse events were taken from the clinical trials, with the exception of the incidence of Stevens-Johnson syndrome, which was taken from Messenheimer (1998).

Quality-of-life weights: Utility weights were taken from a prospective observational study of 125 patients by Selai (2005). Adverse events are assumed to impact utilities in the initial period of the model if they are treatment limiting, in which case the 'no response' utility value from the Selei study is assigned.

Cost sources: Estimates of resource use are based on the opinion of four Scottish clinicians. They were asked to estimate the number of neurologist visits, GP visits and EEGs they would expect for each patient, based on their seizure frequency. It was estimated that patients who experienced seizures would have 3 specialists visits per year and 2.5 to 5 GP visits per year (dependent on seizure frequency). It was also thought that EEGs are not performed routinely, so it was assumed that patients experiencing ≥1 seizure per month would have an EEG every 4 years and patients with <1 seizure per month were assumed to have no EEGs. Costs related to the management of four side effects were included in the model: weight loss, problems in concentration, nausea/vomiting and rashes.

Annual direct medical costs were obtained from various UK sources (BNF 2004; Netten 2003) and other sources(MEDTAP Unit Cost Database 2004; Chartered Institute of Public Finance and Accountancy /HFM 2003) and inflated to 2004 prices using Health and Community Health Services inflation indices (Netten 2003).

Comments

Source of funding: Eisai Ltd.

Limitations: The authors separate the first three months of treatment from the rest of the analysis because it is a period of greater resource use due to the requisite monitoring of dose titration and management of patients not responding to treatment. It is unclear how this impacts the results and conclusions of the study.

The same data are applied to all drugs in the maintenance period as intervention-specific information is lacking. In other words, the transition probabilities used in the maintenance periods are not AED-specific, rather AED treatments are differentiated only by their initial effectiveness and adverse event profile.

Other:

Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable	

Which AEDs are clinically effective and cost-effective for people with idiopathic generalised epilepsy?

Marson AG, Appleton R, Baker GA et al. A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial. *Health Technol Assess.* 2007; 11(37):1-108. Ref ID: 1496				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: CUA **Study design:** RCT **Perspective:** UK NHS **Time horizon:** 2 years from randomisation **Discounting:** Costs, QALYs, number of seizures: 3.5% per annum	**Population:** Patients (mean age 22.5, SD 14.0) with newly diagnosed epilepsy for whom VPA was chosen as standard drug; primarily adults with newly diagnosed generalised epilepsy. **Intervention 1:** Sodium valproate monotherapy (VPA) **Intervention 2:** Lamotrigine monotherapy (LTG) **Intervention 3:** Topiramate monotherapy (TPM)	**Health outcomes incorporated:** EQ-5D measurements of HRQoL; number of seizures **Mean total QALYs (95% CI)** based on 165 patients completing EQ-5D questionnaires: VPA: 1.648 (1.51 to 1.79) LTG: 1.701 (1.61 to 1.79) TPM: 1.809 (1.74 to 1.88) **Mean total seizures (95% CI)** based on 299 patients: VPA: 44.1 (17.4 to 70.9)	**Cost components incorporated:** Costs of AEDs; costs of managing adverse events requiring hospitalisation; costs of GP, nurse or other health professional contacts; social services contacts; use of ambulance service; **Mean total costs (95% CI)** based on 165 patients completing EQ-5D questionnaires: VPA: £1390 (369 to 2411) TPM: £1568 (1303 to 1842) LTG: £1906 (1405 to 2408) **Mean total costs (95% CI)** based on 299 patients: VPA: £1136 (529 to 1743) TPM: £1568 (1378 to 1757) LTG: £1761 (1466 to 2055) **Currency & cost year:** 2005 UK pounds	**Basecase ICERs (£ / QALY gained):** VPA: least cost TPM: £1,106 compared to VPA LTG: dominated by TPM **Basecase ICERs (£ / seizure avoided):** VPA: least cost TPM: dominated by VPA LTG: dominated by VPA **Subgroup analyses:** None **Analysis of uncertainty:** Using different drug costs (varying from high to low estimates) did not change the overall pattern of results: LTG was still dominated and TPM had an ICER of between £692 and £1,106 per QALY gained. The same cost variation did not alter the results of the cost per seizure avoided analysis in which VPA dominates both TPM and LTG. Using an alternative method to calculate the total QALYs (not using a half cycle correction) did not change the relative ICERs and thus the overall pattern of results in the cost per QALY analysis. Bootstrapping the baseline point estimate of ICERs for TPM relative to VPA results in a 95% probability of being cost-effective at a

		TPM: 75.1 (19.8 to 130.3) LTG: 120.9 (59.2 to 182.6)		willingness to pay threshold of £20,000 per QALY gained. Bootstrapping the baseline point estimate of ICERs for LTG relative to VPA results in a roughly 63% probability of being cost-effective at a willingness to pay threshold of £20,000 per QALY gained. Bootstrapping the baseline point estimate of ICERs for TPM relative to VPA results in a probability of being cost-effective of between 14% and 16% given a willingness to pay threshold of between £160 and £1600 per seizure avoided. Bootstrapping the baseline point estimate of ICERs for LTG relative to VPA results in a 1% probability of being cost-effective given a willingness to pay threshold of between £160 and £1600 per seizure avoided.
Data sources				
Health outcomes: EQ-5D questionnaires were administered to adults only at baseline, 1 year and 2 years. Estimation of QALYs for children was not possible because EQ-5D data were not collected from children. Total QALYs were estimated using an area under the curve approach, and in the base case, health benefits are assumed to occur at the mid-points of years 1 and 2. An alternative assumption wherein health benefits are assumed to occur at either the beginning or end of years 1 and 2 was employed in a sensitivity analysis. **Quality-of-life weights:** Using the EQ-5D, UK tariff values representing quality of life weights were applied to health states. **Cost sources:** To allow for the potential impact of high and low drug costs on the results, separate analyses were conducted using the most expensive and cheapest costs for VPA and LTG. Adverse event data requiring hospitalisation were collected from individual patient forms and categorised by specialty and outpatient attendances or inpatient stays. Unit cost data were obtained from the TFR2A and TFR2B specialty and programme costs to the Department of Health by Trusts for the year ending March 2003. Costs were then inflated to 2005 prices through application of Hospital and Community Health Services Pay and Prices Index. Other cost data were obtained from PSSRU's Unit Costs of Health and Social Care (2005) and the Finance Department of Walton NHS Hospital Trust. Patient-reported resource use data were collected at 3 months, 1 and 2 years and captured resource use in the preceding 3-month period. Therefore, to estimate year one costs, the costs in months 10-12 were multiplied by three and added to costs for months 1-3. Year two costs were estimated by multiplying the cost in months 22-24 by four.				

Comments		
Source of funding: UK NHS Research and Development Health Technology Assessment Programme. **Limitations:** The evidence from the bootstrapped ICERs is slightly misleading, as both LTG and TPM were only compared relative to VPA and not to one another. The cost-effectiveness acceptability estimates indicate that LTG has a reasonably high likelihood of being cost-effective compared to VPA, but it would seem from the ICER point estimates that LTG would have a very low likelihood of being cost-effective compared to TPM at any willingness to pay cost per QALY value. The incremental cost per seizure avoided analysis is also difficult to interpret. As there is no established willingness to pay threshold for additional seizures avoided, it could be difficult to make use of this information. However, as probabilities of LTG and TPM are extremely low, thus indicating little likelihood of cost-effectiveness compared with VPA, interpretation is fairly straightforward even without an explicit threshold. In this analysis, VPA is clearly dominant. Although cost data was up to date at the time of evaluation, current costs in 2010 are quite different, particularly as the costs of some AEDs (lamotrigine and topiramate) have reduced dramatically after coming off patent. **Other:** The results of the two different analyses (cost per QALY and cost per seizure avoided) seem slightly contradictory. The cost per seizure avoided analysis supports the recommendation that VPA should be the first-choice drug for IGE or unclassified epilepsy. However, the cost per QALY analysis suggests that there is a high probability that TPM is a cost-effective alternative to VPA. The authors explain that the seemingly contradictory result may be due to the QALY picking up effects on health related quality of life other than those attributable to seizures, or it may be due to some other phenomenon such as the unrepresentative patient sample on which the cost per QALY analysis was based.		
Cost per QALY analysis:	**Overall quality*:** Potentially serious limitations	**Overall applicability**:** Directly applicable
Cost per seizure avoided analysis:	**Overall quality*:** Potentially serious limitations	**Overall applicability**:** Partially applicable

Abbreviations: ICER = incremental cost-effectiveness ratio

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

Hawkins N, Epstein D, Drummond M et al. Assessing the cost-effectiveness of new pharmaceuticals in epilepsy in adults: the results of a probabilistic decision model. *Med Decis Making*. 2005; 25(5):493-510. Ref ID: 7

Study details	Population & interventions	Health outcomes	Costs	Cost effectiveness
Economic analysis: CUA **Study design:** decision analytic model **Perspective:** UK NHS **Time horizon:** 15 years **Discounting:** Costs – 6% Outcomes – 1.5%	**Population:** Adult patients with generalised seizure type (tonic-clonic); newly diagnosed and refractory <u>Newly Diagnosed</u> **Intervention 1:** Sodium valproate monotherapy **Intervention 2:** Lamotrigine monotherapy <u>Refractory Epilepsy</u> **Intervention 1:** Placebo adjunctive therapy **Intervention 2:** Topiramate adjunctive therapy	**Health outcomes incorporated:** Seizure freedom, 50% reduction in seizure frequency, mortality **Primary outcome measure:** QALYs (mean) <u>Newly Diagnosed</u> Sodium Valproate: 9.814 Lamotrigine: 9.748 <u>Refractory Epilepsy</u> Placebo: 8.737 Topiramate: 8.807	**Cost components incorporated:** Drug costs; costs of GP visits, outpatient visits and hospitalisations **Total costs (mean):** <u>Newly Diagnosed</u> Sodium Valproate: £4288 Lamotrigine: £6675 <u>Refractory Epilepsy</u> Placebo: £5064 Topiramate: £7471 **Currency & cost year:** 2002/03 UK pounds	**Basecase ICER (Intvn 2 vs Intvn 1):** <u>Newly Diagnosed</u> Lamotrigine dominated (more costly and less effective) by sodium valproate <u>Refractory Epilepsy</u> Topiramate has ICER of £34,417 compared to placebo **Subgroup analyses:** None undertaken **Analysis of uncertainty** Probabilistic sensitivity analysis was performed. At a threshold of £30,000 per QALY gained, sodium valproate has a 95% probability of being the best option for treating adult patients with a newly diagnosed generalised seizure type. At a threshold of £30,000 per QALY gained, adjunctive topiramate has a 41% probability of being the best option for treating adult patients with a refractory generalised seizure type, showing there is a large degree of uncertainty around this decision. Time horizon was lengthened and discounting rates for costs and outcomes were varied, but had little impact on the results of the base case.

Data sources

Health outcomes:
Effectiveness data was drawn from 3 RCTs: GSK (2001) compared lamotrigine and sodium valproate monotherapies in newly diagnosed idiopathic generalised epilepsy; Barrett et al. (1997) and Biton et al. (1999) both compared topiramate and placebo adjunctive therapies in refractory generalised tonic-clonic seizures.

Time dependency to treatment withdrawal was incorporated into the model using observational data from Lhatoo et al. (2001) and an open label study of Tiagabine HCl used in the treatment of focal epilepsy(1998).

Quality-of-life weights:

Utility weights were based on a non-randomised audit of 125 patients starting a new adjunctive AED who completed the EQ-5D questionnaire after 6 months by Selai et al. (2002).

Cost sources: The use and cost of health care resources were conditional on whether a patient was seizure free and were estimated from a number of sources (Heaney 1998; Jacoby 1998; Unit Costs of Health and Social Care 2002; NHS Reference Costs 2002). AED dosage and costs were based on data from the *British National Formulary* (March 2002).

Comments

Source of funding: UK NHS Research and Development Health Technology Assessment Programme.

Limitations: The longer term data used to parameterise cycles subsequent to the first were applied generally to all drugs under evaluation because drug-specific longer term evidence was lacking. In other words, the transition probabilities used in the maintenance periods are not AED-specific, rather AED treatments are differentiated only by their initial effectiveness and adverse event profile. Cost data was up to date at the time of initial HTA publication, but is now out of date, particularly as the costs of some AEDs (lamotrigine and topiramate) have reduced dramatically after coming off patent. Estimates of the impact of seizure control on utility were based on a single small study. Because the analysis is based on short term trials in a long-lasting condition, the impact of chronic toxicity and harm from AEDs or potential for teratogenicity have not been accounted for.

Although the analysis took into account all AEDs for which there was RCT evidence at the time, evidence for other AEDs (lamotrigine and levetiracetam) has emerged since.

Other: This was a publication arising out of the 2006 HTA of newer AEDs for epilepsy in adults.

Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable	

Abbreviations: ICER = incremental cost-effectiveness ratio

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

Which AEDs are clinically effective and cost-effective for people with Lennox-Gastaut syndrome?

Benedict A, Verdian L, Maclaine G. The cost-effectiveness of rufinamide in the treatment of Lennox-Gastaut Syndrome in the UK. *Pharmacoeconomics.* 2010; 28(3):185-199.				
Study details	**Population & interventions**	**Health outcomes**	**Costs**	**Cost effectiveness**
Economic analysis: CEA **Study design:** Decision analytic model with individual patient simulation **Perspective:** UK NHS and PSS **Time horizon:** 3 years **Discounting:** 3.5% for costs; 0% for outcomes	**Population:** Patients with Lennox-Gastaut syndrome **Intervention 1:** standard therapy **Intervention 2:** Add-on lamotrigine **Intervention 3:** Add-on topiramate **Intervention 4:** Add-on rufinamide	**Health outcomes incorporated:** median percent reduction in seizure frequency; non-responders; experience of adverse events; death **Percent of patients treated successfully measured by reduction in drop attack seizures (95% CI):** Standard therapy: 3.3% Lamotrigine: 5.2% Topiramate: 7.2% Rufinamide: 11.3% **Percent of patients treated successfully measured by reduction in total seizures (95% CI)** Standard therapy: 2.3% Lamotrigine: 6.9% Topiramate: 5.6% Rufinamide: 7.7%	**Cost components incorporated:** Direct medical costs including diagnostics, A+E visits, hospitalisation, adverse event management; personal social services **Mean total costs (95% CI):** Standard therapy: 51437 Lamotrigine: 50975 Topiramate: 50728 Rufinamide: 50985 **Mean total costs (95% CI)** Standard therapy: 38366 Lamotrigine: 37064 Topiramate: 38557 Rufinamide: 38828 **Currency & cost year:** 2006 GBP	**Basecase ICERs (£ / 1% increase in successfully treated patients on drop attack seizures):** Topiramate: least cost Lamotrigine: dominated by topiramate Rufinamide: £62 compared to topiramate Standard therapy: dominated by rufinamide **Basecase ICERs (£ / 1% increase in successfully treated patients on total seizures):** Lamotrigine: least cost Standard therapy: dominated by lamotrigine Topiramate: dominated by lamotrigine Rufinamide: £2151 compared to lamotrigine **Subgroup analyses:** None **Analysis of uncertainty:** Probabilistic sensitivity analysis indicates that at a willingness to pay of £250 for a 1% increase in the number of successfully treated patients in terms of drop attacks, the probability of rufinamide being optimal is >80%. In terms of total seizures, for rufinamide to have a >80% probability of being optimal, society has to be willing to pay £900 for a 1% increase in the number of successfully treated patients. One-way sensitivity analyses were conducted on the following parameters: rate of hospitalisation due to drop attacks, discount rate, PSS costs; time horizon.

				The cost-effectiveness of rufinamide was sensitive to decreases in rates of hospitalisation.

Data sources

Health outcomes: In the first 3-month cycle, patients were stratified into one of three health states based on their response to treatment: responder with greater than 75% reduction in seizure frequency, responder with 50-74% reduction in seizure frequency, non-responder. Treatment effect estimates were derived from a random effects indirect treatment comparison (ITC) undertaken in winBUGS using data from three RCTs: Glauser 2008, Motte 1997, Sachdeo 1999. The ITC also generated estimates for the proportion of patients experiencing a treatment-limiting adverse event. In all subsequent 3-month cycles for all drugs, transitions between health states were based on data from the open-label extension study following on from Glauser 2008. Age specific death rates were adjusted by standardised mortality ratio from Lhatoo 2001.

Quality-of-life weights: Utility weights were not applied in the model as no data was available. The primary outcome of modelling was percentage of patients successfully treated.

Cost sources: Estimates of resource use were obtained via a telephone survey of five physicians specialising in paediatric epilepsy in the UK. They were asked about drug use, the type and frequency of NHS contacts related to monitoring and switching treatments, hospitalisations due to seizure, treatment of adverse events and use of personal and social services. Resource use was differentiated based on clinical severity – mild (1 seizure per day), moderate (1-20 seizures per day) or sever (>20 seizures per day) – and seizure type – drop attacks, convulsive status epilepticus or non-convulsive status epilepticus).

Unit costs for diagnostics, A+E visits and PSS were obtained from NHS reference costs (2005/06) and PSSRU (2006). Unit drug costs were taken from the BNF (2007).

Comments

Source of funding: Agnes Benedict is an employee of UBC Health Care Analytics and received payment for this consultancy work from Eisai Ltd.

Limitations: Estimates of resource use were based upon the expert opinion of 5 physicians. One parameter informed by expert opinion related to the risk of hospitalisation arising from a drop attack seizure. The cost-effectiveness of rufinamide is sensitive to increased rates of hospitalisation, thus more definitive data is required. Only side effects associated with topiramate and lamotrigine carried costs and the authors did not report the proportion of patients experiencing particular adverse events, such as Stevens-Johnson syndrome. The authors highlight problems in the reporting of the clinical data, specifically which outcomes were not reported in different trials and where assumptions had to be made. The structure of the model appears to favour the outcomes reported in the trial comparing rufinamide to placebo (Glauser 2008) and it is unclear what assumptions were made for other drugs without the same outcomes reported. It is unclear how these assumptions may affect the results and conclusions of the analysis.

Other: Although the authors present reasons why QALYs were not used, the results do not lend themselves easily to decision-making using preferred NICE methods.

Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable	

Abbreviations: ICER = incremental cost-effectiveness ratio

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable

Verdian L, Yunni Y. Cost-utility analysis of rufinamide versus topiramate and lamotrigine for the treatment of children with Lennox-Gastaut Syndrome in the United Kingdom. *Seizure.* 2010; 19(1):1-11.

Study details	Population & interventions	Health outcomes	Costs	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic Markov model **Perspective:** UK NHS and PSS **Time horizon:** 3 years **Discounting:** 3.5% per annum for costs and benefits	**Population:** Children with Lennox-Gastaut syndrome **Intervention 1:** Adjunctive rufinamide (RUF) **Intervention 2:** Adjunctive lamotrigine (LTG) **Intervention 3:** Adjunctive topiramate (TPM)	**Health outcomes incorporated:** ≥75% reduction in drop attacks; ≥50% to <75% reduction in drop attacks; non-response; experience of adverse events **Mean total QALYs (95%CI):** TPM: 1.36 (1.21-1.53) LTG: 1.42 (1.27-1.57) RUF: 1.44 (1.30-1.59)	**Cost components incorporated:** Direct medical costs including diagnostics, A+E visits, hospitalisation, adverse event management; personal social services **Mean total costs (95% CI):** LTG: £21,783 TPM: £23,360 RUF: £24,992 **Currency & cost year:** 2007 GBP	**Basecase ICERs (£ / QALY):** Lamotrigine: least cost Topiramate: dominated by lamotrigine Rufinamide: £154,831 compared to lamotrigine (£20,538 compared to TPM) **Subgroup analyses:** None **Analysis of uncertainty:** Probability RUF is most cost-effective at £20K and £30K respectively: Compared to TPM: 52%, 65% Compared to LTG: 8%, 15% One way sensitivity analysis showed that the ICERs were most sensitive to changes in probabilities of treatment response during first 3 months of treatment.

Data sources

Health outcomes: In the first 3-month cycle, patients were stratified into one of three health states based on their response to treatment: responder with greater than 75% reduction in seizure frequency, responder with 50-74% reduction in seizure frequency, non-responder. Treatment effect estimates were derived from a fixed effects indirect treatment comparison (ITC) undertaken in winBUGS using data from three RCTs: Glauser 2008, Motte 1997, Sachdeo 1999. The ITC also generated estimates for the proportion of patients experiencing a treatment-limiting adverse event. In all subsequent 3-month cycles for all drugs, transitions between health states were based on data from the open-label extension study following on from Glauser 2008.

Quality-of-life weights: A separate study was performed to elicit utilities for the LGS health states, among 119 members of the UK general public, 'primarily' using a time trade-off exercise. Point estimates were not presented among the methods of this analysis. They were published as a separate poster presentation, but it is unclear exactly which utilities were used in the analysis, as 3 methods of elicitation (TTO, VAS, EQ-5D) and 3 sets of results were presented in abstract of the poster.

Cost sources: Estimates of resource use were obtained via a survey of physicians specialising in paediatric epilepsy in the UK. Other than drug dosing, no details on estimates of resource use were presented. Unit costs for diagnostics, A+E visits and PSS were obtained from NHS reference costs (2006/07) and PSSRU (2007). Unit drug costs were taken from the BNF (2007).

Comments
Source of funding: Lara Verdian is an employee of Eisai Ltd and all other contributors are/were employees of Eisai Ltd and Mapi Values. **Limitations:** There is a general lack of transparency regarding certain model inputs: • Probabilities of response and how they were derived: authors simply state a 'response rate was estimated,' but does not state method used • Resource use was gathered from a survey, but no specifics were provided • Utility data is not published and therefore impossible to validate • Probabilities of specific adverse events not published, but feed into costs of LTG and TPM strategies It is impossible to validate these inputs and unclear as to how they may affect the results and conclusions of the analysis. **Other:**

Overall quality*: Potentially serious limitations	**Overall applicability**:** Partially applicable	

Abbreviations: ICER = incremental cost-effectiveness ratio

*Very serious limitations / Potentially serious Limitations / Minor limitations; ** Directly applicable / Partially applicable / Not applicable