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The cost-effectiveness of newer drugs as add-on therapy for children with focal epilepsies

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Summary

Purpose: Epilepsies in children are complex diseases. Guidelines are needed on the appropriate use of newer versus older anti-epileptic drugs (AEDs). This paper presents an individual patient-sampling model to assess the cost-effectiveness of using newer AEDs as add-on therapy in line with UK prescribing guidance.
Methods: Identification of the relevant parameters and treatment pathways for the model were achieved by a systematic review of the literature and discussions with clinical experts. Data were obtained from the literature and supplemented with data elicited from paediatric neurologists. The model considered paediatric patients over the period of childhood from the age of diagnosis to 18 years.
Results: The results suggest that the older and newer AEDs are similar in terms of drug retention rates and the average time in 'good' treatment outcomes. In terms of cost, the results indicate a consistent increase in cost (compared to older AEDs) when all of the newer AEDs are considered. The decision analysis results indicate that there are no important health benefits from the use of newer AEDs when used as add-on therapy. However, the analysis also reveals that the uncertainties in the model are greater than the differences between the drug strategies.
Conclusions: To develop guidelines on the appropriate use of newer AEDs, better information is required from randomised controlled trials as there is insufficient data available in the public domain to accurately estimate the nature of the trade off between older versus newer AEDs.

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Introduction

A large proportion of epilepsy syndromes start in infancy or childhood.[1] The heterogeneous and complex nature of the condition presents a challenge for diagnosis as it depends on the type of seizure (there are many different types of focal and generalised epileptic seizure[2,3]) and aetiology (symptomatic, idiopathic and cryptogenic). Based on a review of many studies that adopted various definitions of the disease,[4] the prevalence of epilepsy in children (up to 15 years old) is about 5–7/1000. Some childhood epilepsies are relatively benign, but others have a detrimental impact on psychological, social and intellectual development, and in severe cases the effect on individual, carer(s) and family can be devastating. Important consequences for children and young people include not only the seizures themselves but also the impact of the condition and its effect upon social life, educational progress and mental health.

Following a diagnosis of epilepsy in childhood, Anti-epileptic drugs (AEDs) tend to be the first treatment option considered. Over 80% of children with epilepsy are treated with AEDs in the Netherlands and USA,[5,6] and it is likely that similar practice occurs in the United Kingdom (UK).[7] Since 1989, seven "newer" anti-epileptic drugs (AEDs) have become available in the UK: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin. The overall aim of AED treatment is to reduce epileptic seizure frequency and enhance patient's quality of life with as few adverse effects and as few co-medications as possible while minimising long-term detrimental effects. Few economic studies have explored the cost-effectiveness of AEDs, the analyses undertaken have focused more on the overall cost of epilepsy, the effect on mortality and the impact upon quality of life.[8] Studies focusing on the economics of childhood epilepsy are limited. A recent review[9] identified three US-based cost-outcome studies that measured among them; the effect of rectal diazepam used to treat severe seizures;[10] the impact of reducing the numbers of AEDs given as polytherapy;[11] the cost of administering a ketogenic diet.[12] None of the studies measured the cost-effectiveness of AED therapy in children newly diagnosed with epilepsy. As the treatment of children with epilepsy has considerations that are quite different from adults there is a need to build a model that exclusively considers AED therapy in children. This paper presents a new model that explores the cost-effectiveness of 'newer' AEDs in the UK, focusing on children from the age of 3–18 years with a new diagnosis of partial (i.e. focal) epilepsy with or without secondarily generalised seizures. Given that this paper is based on work commissioned for the National Institute of Clinical Excellence (NICE), consideration is only given to use of AEDs within their current United Kingdom marketing authorisation ("licensed" use). The newer AEDs that can be used as add-on therapies are lamotrigine, gabapentin, topiramate, oxcarbazepine and tiagabine. Vigabatrin is licensed for use as add-on therapy in partial epilepsy but is recommended for use only as a treatment of last resort owing to problematic adverse effects; we therefore did not include it in the analysis. In addition, we were also not able to consider tiagabine in our analysis due to lack of data. The model therefore reports results on the cost-effectiveness of four 'newer' AEDs for use as add-on therapy.

Methods

Decision problem

The 'newer' and 'older' AEDs are compared in terms of costs and benefits, with the latter judged according to the treatment objectives (i.e. seizure control and favourable adverse effect profile). In order to compare the cost-effectiveness of the 'newer' versus the 'older' AEDs, various drug sequences have been considered, based on published prescribing guidance in childhood epilepsy[13] and advice from clinical experts. The comparisons are between predefined drug sequences that contain exclusively 'older' AEDs (termed older AED strategy) or a combination of 'older' and 'newer' AEDs (termed newer AED strategy). The older AED strategy is illustrated in Fig. 1. We have assumed that all newly diagnosed patients with partial epilepsies requiring AED treatment start with monotherapy: carbamazepine followed by sodium valproate. Depending on the patient's 'response' to sodium valproate, they then receive either add-on therapy (sodium valproate and carbamazepine) or the next choice monotherapy (phenytoin). Clearly, each patient can potentially be subject to many different treatment pathways depending on the success or otherwise of current (and past treatment). In fact, the older AED strategy produces a possible 40 different drug sequences that are detailed in Table 1. Note that a drug will *not* be used as add-on therapy if in previous use it led to unacceptable adverse effects or poor seizure control. The unspecified generic older AED described in Fig. 1 contains features of carbamazepine, valproate and phenytoin, this is only considered for a patient who progresses to the end of the drug sequence before the age of 18. The older AED strategy represents the comparator (i.e. the baseline option) for the newer AED strategy.

The drug sequence representing the newer AED strategy is illustrated in Fig. 2. As with the older AED strategy many treatment pathways can be followed. The newer AEDs are considered only as first choice add-on therapy with sodium valproate. As in the older AED strategy, patients still initially receive carbamazepine and then sodium valproate; they then move onto sodium valproate plus the 'new AED' as add-on therapy or phenytoin as monotherapy. Separate analyses have been conducted for each new AED — combination therapy involving two or more newer AEDs is not considered. The analysis therefore explores the relative cost-effectiveness of each of the four newer AED strategies with the baseline option where no newer AEDs are available.

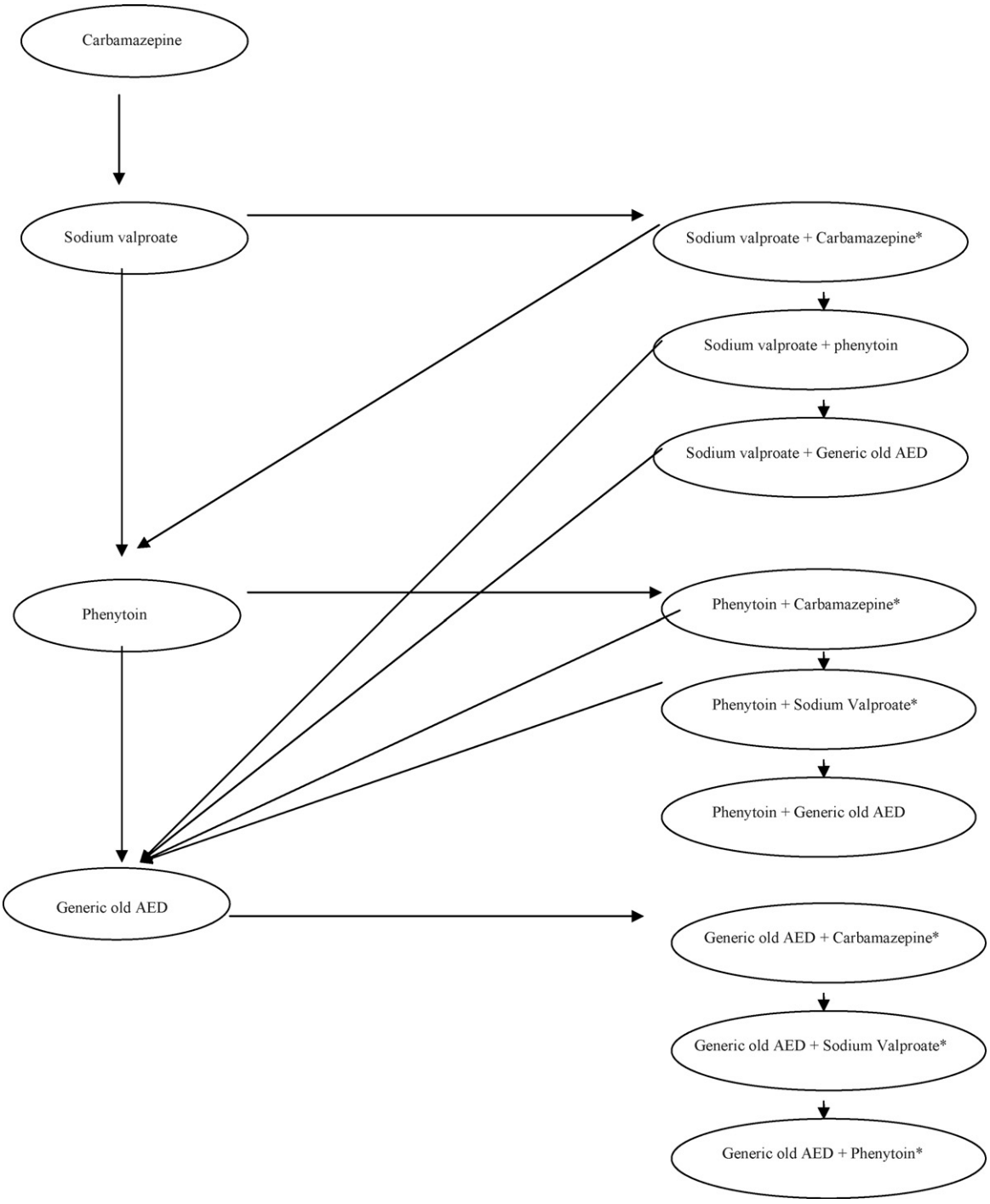

Figure 1 Older drug sequence. The symbol (*) denotes drug only used in combination if, in earlier use in this patient, it was not associated with unacceptable side-effects or unacceptable efficacy.

Table 1 Possible drug sequences from Fig. 2

Drug sequence
cbz
cbz—val
cbz—val—phy
cbz—val—phy—old
cbz—val—val/cbz
cbz—val—val/cbz—val/phy
cbz—val—val/cbz—val/phy—val/old
cbz—val—val/cbz—phy
cbz—val—val/cbz—val/phy—old
cbz—val—val/cbz—val/phy—val/old—old
cbz—val—phy—phy/cbz
cbz—val—phy—phy/cbz—phy/val
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cbz—val—phy—phy/cbz—phy/val—old—old/cbz
cbz—val—phy—phy/cbz—phy/val—old—old/cbz—old/val
cbz—val—phy—phy/cbz—phy/val—old—old/cbz—old/val—old/phy

The sequence of AEDs modelled in both the older and newer AED strategies were chosen based on published prescribing guidance[13] in childhood epilepsy and advice from clinical experts.

Model structure

The treatment pathways are modelled as clinical decisions using an individual sampling simulation model constructed in TreeAge DATA Professional software (Release 6). The model structure was chosen based on published criteria for model selection.[14] It was felt that an individual sampling model was appropriate as the drug treatment requires a sequence of drugs to be considered, the time frame modelled is potentially long (up to 15 years) and the model required consideration of individuals receiving any one drug for a variable length of time. The model structure is illustrated in Fig. 3. A patient enters the model with a new diagnosis of partial epilepsy. Personal characteristics for the individual (gender, age and the presence of learning difficulties) are then assigned to the patient through a process of repeated samplings from appropriate distributions for these characteristics. The rationale behind sampling for learning difficulties is that resource use and quality of life will differ between the two groups. A hypothetical cohort of children then progress through the model and follow different clinical pathways, based on the outcomes they experience and the clinical decisions made. The youngest patients at entry into the model are 3 years (infantile epilepsy is not considered) and the oldest are just under 18 years.

Within the model, the patient may experience one of four treatment outcomes:

1. Intolerable adverse effects, leading to early discontinuation (TOX).
2. Lack of effect on seizure rate, leading to early discontinuation (SEIZ).
3. Partial efficacy with tolerable or no adverse-effects (PART).
4. Complete seizure freedom with tolerable or no adverse-effects (SFREE).

Patients moving through the model will progress through the drug sequences, the rate is determined by the treatment outcomes experienced. Hence, patients who enter outcomes 1 or 2 will progress to receive the next choice monotherapy or opt to discontinue drug treatment; those entering into outcome 3 may stay on the current drug treatment, try the next choice monotherapy or try the next choice add-on therapy. If the patient achieves seizure freedom (outcome 4), it is assumed that after a given period of time (sampled in the model), withdrawal from drug treatment will be attempted. This assumption reflects a desire by patients to avoid long-term use of AEDs

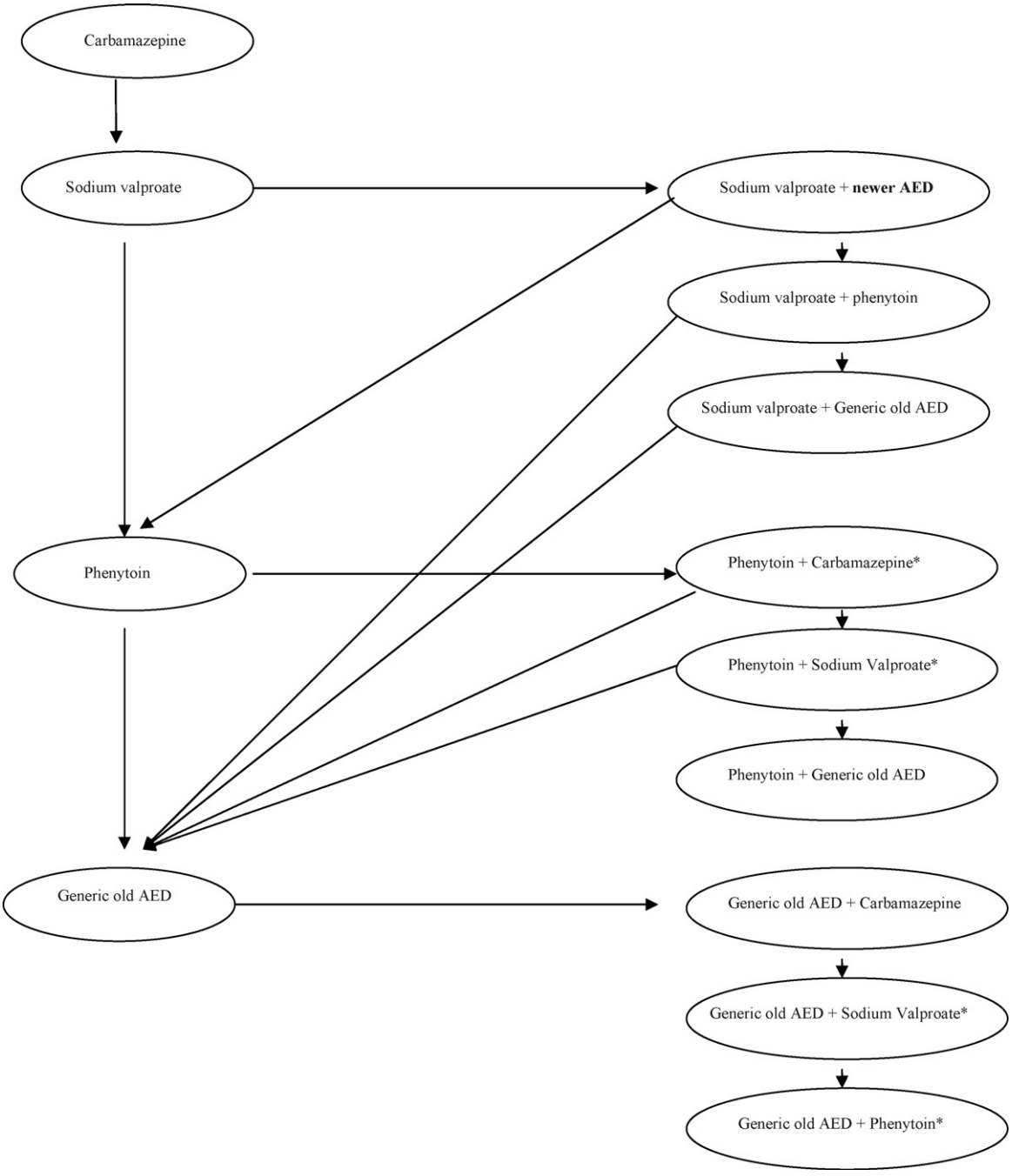

Figure 2 Newer drug sequence. The symbol (*) denotes drug only used in combination if, in earlier use in this patient, it was not associated with unacceptable side-effects or unacceptable efficacy.

and the fact that approximately one third of all epilepsies that start in childhood will, by puberty, have shown a natural remission.[15] Therefore, patients achieving seizure freedom will either remain on the current drug (if reluctant to withdraw) or will attempt the withdrawal process. Within the model, there are six possible health states, with associated costs (Cs) and effects (Us) to consider. Total costs and effects are then estimated for each patient according to which of these health states are experienced. In addition to the four outcomes listed above, there are two further states in the model:

- Patient has seizure freedom following withdrawal of drug therapy (WFREE).
- Patient is not seizure free but prefers to remain untreated (UNTRT).

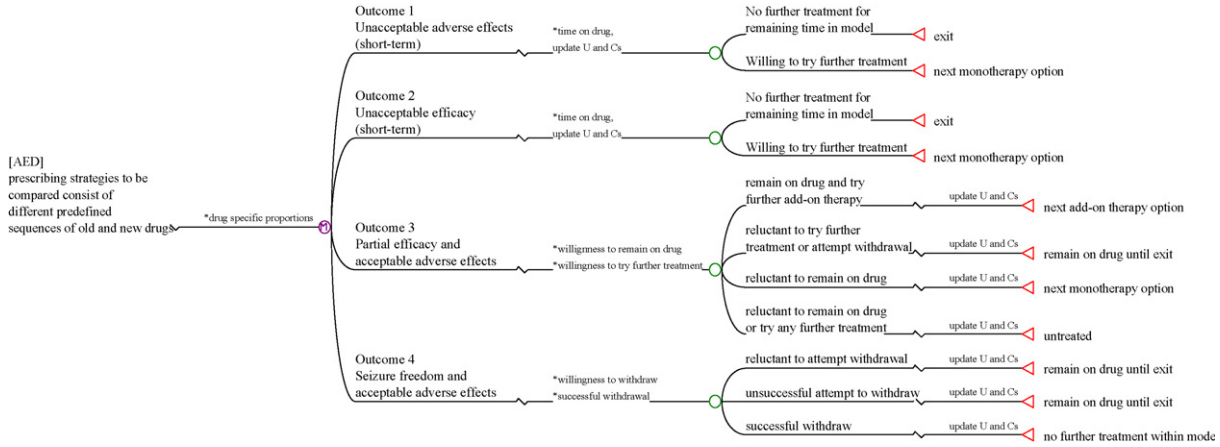

Figure 3 Patient pathway for a child with newly diagnosed partial (focal) epilepsies.

Model assumptions and data

Given the complex nature of partial epilepsies in children and the limitation of data from the published literature, several assumptions had to be made:

- Patients receiving alternative treatment in outcomes TOX and SEIZ switch drugs rather than receive add-on therapy.
- The willingness to try alternative treatment in outcome PART depends on the number of treatments tried at this point, as the number of drugs tried increases, the patient is more likely to try add-on therapy and less likely to try further monotherapy options.
- Patients achieving seizure freedom either continue with current therapy or withdraw, they do not switch treatments.
- If attempted withdrawal is unsuccessful, patients successfully reintroduce the original drug that achieved seizure freedom.
- Time to stopping an unsuccessful drug (outcomes TOX and SEIZ) is determined by the reasons for discontinuing and is independent of the drug.
- The same prescribing pattern is assumed for both boys and girls.
- Policy on discontinuing and withdrawal of drugs is the same for patients receiving monotherapy and add-on therapy, a patient achieving complete seizure freedom on a two drug combination would attempt to withdraw from both drugs.

Transition probabilities relating to the effectiveness and tolerability of the different AEDs determine the likelihood of patients reaching a particular outcome within the model. These were derived from the systematic review of clinical effectiveness.[7] Other clinical parameters for the model, such as the proportions discontinuing treatment, time to discontinuation or withdrawal, and likelihood of moving onto combination therapy at each stage, were estimated based on the epidemiological literature[7] and clinical advice. For the proportions of patients withdrawing due to adverse effects and lack of efficacy, and for proportions achieving seizure freedom, these were calculated from trial data by obtaining the numbers withdrawing for these reasons, adjusting the sample size for drop outs and for length of follow up. The proportion of patients achieving partial efficacy is assumed to include, from the trial data, all the remaining patients who did not withdraw for adverse effects or lack of efficacy and did not achieve seizure freedom. To allow the proportion estimates to vary according to different stages of treatment, i.e. first, second drug attempted, essentially the trial data available was used as 'anchor points' and then various assumptions applied.[7] The RCT data available for this model consist of a single trial for each newer AED used as add-on therapy in more or less refractory populations. The trials of add-on therapy all included patients with variable disease history, but the performance of placebo in these trials is broadly similar and so we have assumed that the trial data are reasonably representative of what will occur at fourth-line treatment. Lamotrigine was the only AED for which we have trial data at two different time points, as first line monotherapy and later use as add-on. The proportions withdrawing owing to toxicity are very similar in the two lamotrigine trials, as are the proportions withdrawing owing to lack of effect. We have therefore kept these parameters constant across all stages for all AEDs. Reducing the proportion achieving complete seizure freedom by a constant factor of 0.4 is consistent with the lamotrigine data, allowing for a small increase in efficacy when the drug is used in

Table 2 Proportions moving into the main model outcome states[a]

Outcome	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
Carbamazepine				
1	0.113	0.113	0.113	0.113
2	0.107	0.107	0.107	0.107
3	0.153	0.529	0.679	0.739
4	0.626	0.250	0.100	0.040
Valproate				
1	0.119	0.119	0.119	0.119
2	0.113	0.113	0.113	0.113
3	0.174	0.531	0.673	0.730
4	0.595	0.238	0.095	0.038
Phenytoin				
1	0.125	0.125	0.125	0.125
2	0.119	0.119	0.119	0.119
3	0.192	0.531	0.666	0.721
4	0.565	0.226	0.090	0.036
Lamotrigine				
1	0.062	0.062	0.062	0.062
2	0.131	0.131	0.131	0.131
3	0.238	0.579	0.716	0.770
4	0.569	0.227	0.091	0.036
Valproate + old AED				
1	0.131	0.131	0.131	0.131
2	0.105	0.105	0.105	0.105
3	0.110	0.503	0.660	0.723
4	0.654	0.262	0.105	0.042
Phenytoin + old AED				
1	0.137	0.137	0.137	0.137
2	0.110	0.110	0.110	0.110
3	0.131	0.504	0.653	0.713
4	0.622	0.249	0.009	0.040
Generic old AED				
1	0.131	0.131	0.131	0.131
2	0.124	0.124	0.124	0.124
3	0.208	0.503	0.659	0.710
4	0.537	0.215	0.086	0.034
Gabapentin + old AED				
1	0.081	0.081	0.081	0.081
2	0.266	0.266	0.266	0.266
3	0.252	0.492	0.588	0.627
4	0.401	0.160	0.064	0.026
Lamotrigine + old AED				
1	0.069	0.069	0.069	0.069
2	0.123	0.123	0.123	0.123
3	0.186	0.560	0.709	0.769
4	0.622	0.249	0.100	0.040
Oxcarbazepine + old AED				
1	0.143	0.143	0.143	0.143
2	0.062	0.062	0.062	0.062
3	0.225	0.567	0.704	0.759
4	0.570	0.228	0.091	0.036
Topiramate + old AED				
1	0.120	0.124	0.124	0.124

Table 2 (*Continued*)

Outcome	First-line treatment	Second-line treatment	Third-line treatment	Fourth-line treatment
2	0.190	0.194	0.194	0.194
3	0.010	0.377	0.560	0.634
4	0.680	0.305	0.122	0.049

[a] 1 = Intolerable adverse effects; 2 = lack of efficacy; 3 = partial efficacy with tolerable adverse effects; 4 = complete seizure freedom with tolerable adverse effects.

combination as compared with monotherapy. The data for first-line carbamazepine monotherapy are based on the trial data from Nieto-Barrera et al.[16] and Zamponi and Cardinali[17] combined. Meta-analyses of the older drugs[18,19] suggest that they are of similar effectiveness with some differences in toxicity, with the order of preference being carbamazepine, valproate, phenytoin and others. On the assumption that this is a rational order of preference, we have based estimates for valproate, phenytoin and older AED on a slight increase in toxicity and a slight decrease in effectiveness by comparison with the drug immediately before it in the sequence; we used a constant multiplier of 1.05 for withdrawal due to adverse effects and lack of efficacy and 0.95 for complete seizure freedom to drive estimates for valproate, phenytoin and older AED. Table 2 details the proportion estimates applied for each drug used as first, second, third and fourth line treatment.

Table 3 shows the proportions used for the various decisions in the model after the patient reaches one of the four main treatment outcomes. These estimates are based upon the limited literature available.

To calculate the time to 'treatment failure event' (withdrawal from drug due to adverse effects or lack of efficacy) within the model, the RCTs identified by the clinical effectiveness review were explored. Chadwick[20] provided useful separate survival curves for discontinuation due to adverse events and for overall time to withdrawal due to adverse events or lack of efficacy. However these curves are based on slightly different patient populations, and the printed plots are small, with thick lines and a small gap between the axis, making it especially difficult to get accurate estimates of the survival rates. It was therefore not possible to use the Chadwick paper to accurately estimate survival distributions and so we chose distributions which were both consistent with the Chadwick data and which accorded with clinical advice; that is that unacceptable adverse effects will tend to discontinuation earlier than discontinuation due to lack of effectiveness, often within the titration period, and that the majority of patients would discontinue by 1 year due to lack of effect. The distributions are both Weibull distributions with shape and location parameters 0.8 and 2.0 for adverse effects and 1.2 and 6.0 for lack of effect.

It is 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 (see Fig. 3). We have assumed that the time from start

Table 3 Proportions moving into secondary model states

Primary Outcomes[a]	Secondary Outcomes	First-line	Second-line	Third-line	Fourth-line and beyond
1	Try another drug	0.9	0.95	0.9	0.8
	No further drugs	0.1	0.05	0.1	0.2
2	Try another drug	0.9	0.95	0.9	0.8
	No further drugs	0.1	0.05	0.1	0.2
3	Continue	0	0.05	0.1	0.2
	Add-on	0	0.3	0.4	0.6
	No further drugs	0.1	0.05	0.1	0.2
	Try different drug	0.9	0.6	0.4	0
4	Continue indefinitely	0	0	0.1	0.2
	Withdraw unsuccessfully	0.5	0.5	0.45	0.4
	Withdraw unsuccessfully	0.5	0.5	0.45	0.4

[a] 1 = Intolerable adverse effects; 2 = lack of efficacy; 3 = partial efficacy with tolerable adverse effects; 4 = complete seizure freedom with tolerable adverse effects.

Table 4 Costs[a] associated with all AEDs considered in the model

AEDs	Cost per mg (pence)	Titration dose (per day)	Maintenance dose (per day)
Gabapentin	0.023	Age >12 years: 20 mg/kg Others: 275 mg	Age >12 years: 30 mg/kg Others: 1100 mg
Lamotrigine	0.016	Age <12 years: 1.5 mg/kg Others: 75 mg	Age < 12 years: 3 mg/kg Others: 150 mg
Oxcarbazepine	0.013	20 mg/kg	30 mg/kg
Topiramate	0.0146	2 mg/kg	7 mg/kg
Carbamazepine	0.00028	200 mg/day	1–5 years: 300 mg/day 6–10 years: 500 mg/day 11–18 years: 800 mg/day
Valproate	0.00028	Up to 20 kg: 20 mg/kg	Up to 20 kg: 20 mg/kg
Phenytoin	0.00089	Over 20 kg: 30 mg/kg 6 mg.kg	Over 20 kg: 35 mg/kg 6 mg/kg

[a] These unit costs are taken from the BNF (September 2002).

'of a' treatment to the point where a change is made (switch, add-on or discontinue drug treatment) will follow a Weibull distribution (shape parameter 4, and location parameter 2). This distribution gives few patients making a change within 6 months, with nearly two-thirds having made a change in 2 years. We have also assumed, in accordance with clinical advice that patients achieving complete seizure freedom who are willing to try to withdraw from drug treatment will do so, on average, after 2 years of drug treatment.

Data on drug dose and unit costs estimates were taken from routine UK sources[21–23] and are detailed in Table 4. Data on more general resource use and the costs associated with diagnosis of epilepsy were obtained from clinical experts. In order to obtain estimates of the resource use and costs to the NHS for an average child (with and without learning difficulties) within the health states defined in the model a survey of clinical experts was conducted. The resource items upon which data were collected included: GP consultations, outpatient consultations, Emergency Department visits, telephone calls to clinical departments from patients (and family) for advice and inpatient stays. Data were collected from 18 experts, summary of the annual cost associated with each health state is presented in Table 5.

An additional, more speculative, element to the project was the attempt to undertake a cost-utility analysis, requiring the use of Quality Adjusted Life Years (QALYs) i.e. life year gain weighted by a utility weight (perception of quality of life (QOL) with regard to health states). Suitable utility estimates for the modelled health states are not available from the literature. The views of paediatric consultants concerning the quality of life (QOL) of children with epilepsy were sought, 25 clinical experts completed a modified version of the EuroQOL EQ-5D instrument.[24] The utility values for each of the health states are presented in Table 6.

Analysis and presentation

Each outcome within the model has associated costs and effects that are accrued as the patient flows through the model. Once the patient exits the model the total cost and outcome for that patient

Table 5 Summary of annual cost for each health state (£)

Health states	With learning difficulties				Without learning difficulties			
	Mean	I-Q range			Mean	I-Q range		
		25	50	75		25	50	75
TOX	1725	804	1130	2321	1048	520	894	1328
SEIZ	1648	541	1300	2532	1365	374	757	1944
PART	343	196	327	438	322	145	281	411
SFREE	273	201	244	411	323	151	223	363
WFREE	177	109	175	348	210	130	155	369
UNTRT	677	135	218	789	620	152	218	732

Table 6 Utility[a] values for health states in model

Health states	With learning difficulties				Without learning difficulties			
	Mean	I-Q range			Mean	I-Q range		
		25	50	75		25	50	75
TOX	0.562	0.315	0.673	0.779	0.753	0.689	0.812	0.883
SEIZ	0.670	0.585	0.779	0.779	0.789	0.779	0.812	0.883
PART	0.782	0.779	0.779	0.788	0.915	0.883	1.000	1.000
SFREE	0.825	0.779	0.779	0.815	0.982	1.000	1.000	1.000
WFREE	0.850	0.779	0.815	1.000	1.000	1.000	1.000	1.000
UNTRT	0.702	0.583	0.779	0.779	0.845	0.804	0.883	0.912

[a] Quality of life value used to weight life years to estimate QALYs.

is then calculated. To account for the many different treatment pathways within the model and the likely small differences between older and newer AED strategies the model used 10,000 simulated patients for each run and estimated an average cost per patient at the end of the run. To give some indication of the sampling variability in the results the runs of 10,000 simulated patients were repeated 20 times for each drug strategy. For the incremental analysis, the costs (and outcomes) accrued by patients successfully treated on carbamazepine are excluded since these are common to both the baseline strategy and the newer drug strategies (i.e. all patients are treated initially with carbamazepine). Thus, the cost and outcome estimates presented are from the point of failure on carbamazepine. Another model output is the average time spent in each treatment outcome for the each drug sequence. The longer a patient spends on a drug (or drug combination) the more that drug is deemed to be effective and acceptable and so the retention rates (i.e. time to withdrawal) are also reported. In addition to the cost and 'time on outcome' comparisons, results are also presented in the form of incremental cost-effectiveness ratios (ICERs), where effectiveness is measured as QALYs.

The comparison of the 20 mean estimates of the cost and QALY scores for each newer drug strategy with the 20 mean estimates for the older drug strategy give a total of 400 estimates of the incremental cost, incremental QALY score and ICER. These are reported graphically as scatters on the cost-effectiveness plane and uncertainty in the appropriate threshold value of the ICER is explored using cost-effectiveness acceptability curves (CEACs). CEACs represent the probability that the drug strategy is cost-effective given different levels of willingness-to-pay for the health gains.

To adjust all results to the present value, future costs are discounted at 6% and future QALY gains at 1.5%.

Sensitivity analysis

The model was re-run using a common discount rate of 3.5% for both costs and benefits (current UK Treasury advice). In light of the information from the RCT evidence that there is no difference in effectiveness between the older and newer AEDs but that the new AEDs lead to fewer adverse effects, the model was re-run using the 'best' utility values for TOX and the 'worst' utility values for SEIZ, and vice versa. This was done in order to maximise the possible differences between the old and newer AEDs.

Results

If a patient is experiencing unacceptable adverse effects and poor efficacy then they will switch relatively quickly to an alternative drug. The model indicates that, without using the newer AEDs, patients spend an average of 1.7 and 2.5 years in outcomes 1 and 2, respectively. Patients spend a longer period in outcome 3 (3.8 years) but to achieve complete seizure freedom is relatively rare, on average only 0.7 years is spent in outcome 4. Table 7 reports the estimated average number of years per patient spent in each main treatment outcome, for the drug sequences considered. The results reveal no statistically significant differences between the drug strategies.

Fig. 4 displays the retention rates (i.e. the proportion of patients who remain on the drug in question over time) for each of the drug sequences considered in the model. The results show that at about 1.5 years, approximately one third of patients have withdrawn from the drug therapy (mainly because of adverse effect concerns). After 1.5 years, the withdrawal rate remains high as patients discover that the drug is lacking in efficacy. However, the rate of withdrawal slows once the AED therapy has been administered up to 3 years, as the

Table 7 Average time in treatment outcomes (years) [accrued from time of failure on carbamazepine]

	Outcome 1[a]			Outcome 2[a]			Outcome 3[a]			Outcome 4[a]		
	Average	S.D.[b]	95% CI	Average	S.D.	95% CI	Average	S.D.	95% CI	Average	S.D.	95% CI
Baseline	1.69	0.09	1.65–1.73	2.45	0.12	2.39–2.50	3.83	0.09	3.79–3.87	0.67	0.03	0.65–0.69
Gabapentin	1.65	0.06	1.62–1.68	2.57	0.13	2.52–2.63	3.78	0.08	3.74–3.82	0.66	0.03	0.64–0.67
Oxcarbazepine	1.66	0.11	1.62–1.71	2.45	0.11	2.4–2.5	3.87	0.09	3.83–3.91	0.65	0.03	0.64–0.66
Lamotrigine	1.65	0.08	1.61–1.68	2.46	0.15	2.4–2.53	3.88	0.1	3.84–3.93	0.66	0.03	0.64–0.68
Topiramate	1.65	0.08	1.61–1.69	2.51	0.1	2.47–2.56	3.83	0.09	3.79–3.87	0.67	0.02	0.66–0.68

[a] 1 = Intolerable adverse effects; 2 = lack of effect on seizure rate; 3 = partial efficacy with tolerable adverse effects; 4 = complete seizure freedom with tolerable adverse effects.
[b] S.D., standard deviation; 95% CI, 95% confidence interval.

patients who remain on the drug at that point are experiencing acceptable treatment outcomes. Fig. 4 demonstrates that there is little difference between the newer and older AEDs with respect to the retention rates.

With each run of the model, an estimate of the incremental cost and incremental QALY gains is obtained for the comparison of the new drug strategy in question and the baseline strategy. For the 20 runs of the model for each drug strategy, the standard deviation of the results remained constant (at 2.9) indicating that enough replications of the model had been run. Fig. 5 presents the results in the form of cost-effectiveness planes that display 400 (20×20) estimates of the ICERs. In all cases the baseline strategy is the point of comparison. These results support the 'time on outcome' and retention rate results in that there is no strong evidence to suggest that the newer AEDs are associated with important health benefits. However, Fig. 5 does indicate a consistent increase in cost for all of the newer AEDs considered. The scatter plots of ICERs can be used to construct CEACs for each new drug strategy. These are displayed in Fig. 6 and indicate that, for a willingness to pay of £150,000 per QALY, the probability that any of the newer AEDs is cost-effective is less than 50%. These results indicate that the use of new AEDs as first-choice add-on therapy does not lead to any cost-savings compared to the baseline strategy.

Re-running the models using the discount rate of 3.5% for both costs and QALYs makes very little difference to the overall results, the newer AEDs have a slightly higher cost. Varying the toxicity and efficacy rates to maximise the difference between the old and new AEDs strategy also does not have a marked impact on the overall results.

Discussion

The importance of the dual consideration of both adverse effects and efficacy (in terms of reduction in seizure rate) when considering the cost-effectiveness of AEDs is highlighted in the literature.[25–28] Both effects have been explicitly considered within the model reported in this paper. In addition, an important strength of this model is that its structure and the assumptions made regarding the clinical decision-making, mirror the realities of patient management of children with partial epilepsy. Unlike more conventional and commonly seen modelling approaches, such as Markov models,[29] the individual patient sampling model has no fixed time cycle and so can accommodate drugs being prescribed for highly variable lengths of time. In this

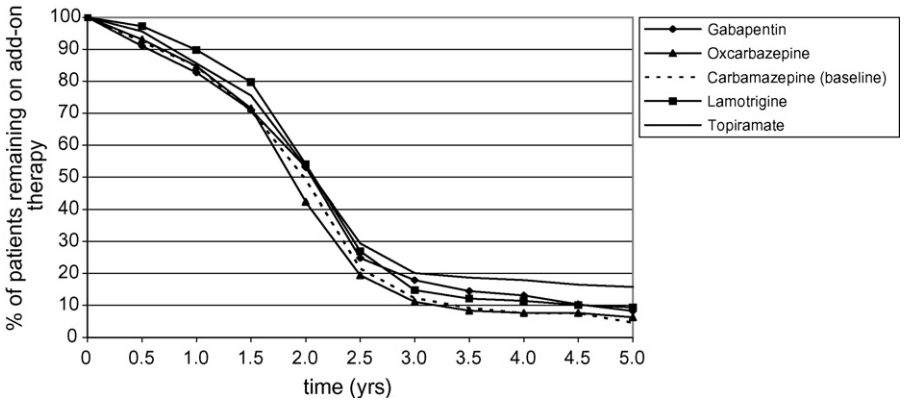

Figure 4 First-choice add-on drug retention rate (with valproate).

clinical situation, 'time to withdrawal' and retention rates are, therefore, important outcomes to consider when directly comparing the cost-effectiveness of different drug strategies. While the model has many strengths, it is necessary to recognise that an important weakness is its limited scope, for example, the effects of epilepsy surgery, re-diagnosis and mortality are not considered. The reason for this is primarily associated with the data limitations. The prescribing strategies considered within the model are also based on published prescribing UK guidance in childhood epilepsy and may not be applicable to other countries.

Direct comparison of the sequences of older and newer AEDs revealed no difference in terms of the average time spent in the treatment outcomes specified within the model. The model shows that patients spend a similar amount of time in all four outcomes across the drug strategies. Concentrating on the retention rate of the drugs also revealed little difference between the old and new drug strategies indicating that the new drugs are not producing a favourable outcome with respect to their adverse-effect and efficacy profile. One interpretation of our findings is that the uncertainty inherent within the model (i.e. random variation)

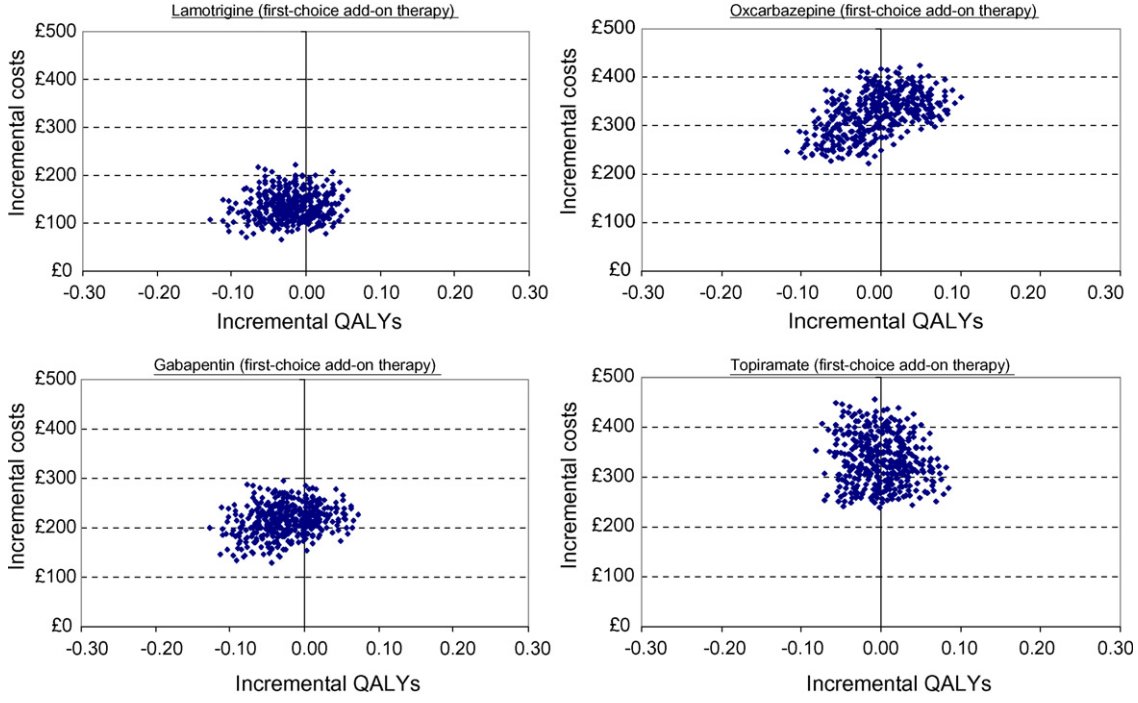

Figure 5 Cost-effectiveness planes presenting results for each new drug strategy (compared to baseline). Oxcarbazepine (first-choice add-on therapy); lamotrigine (first-choice add-on therapy); topiramate (first-choice add-on therapy). Gabapentin (first-choice add-on therapy).

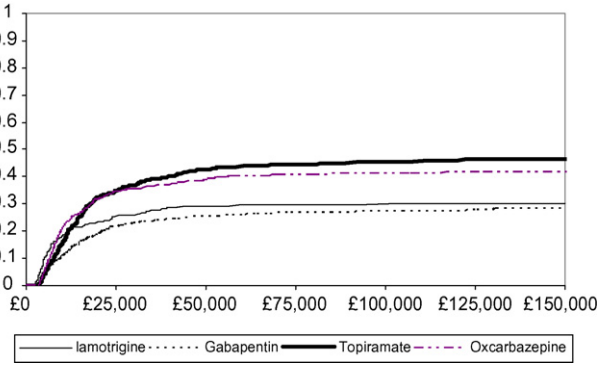

Figure 6 Cost-effectiveness acceptability curves for each new drug strategy (compared to baseline).

is greater than the differences between the newer and older AED strategies. Therefore, overall, the results do not suggest that the use of newer AEDs in any of the scenarios considered is clearly cost-effective, but similarly, do not indicate that they are clearly not cost-effective.

There is no other published evidence that reports the cost-effectiveness of older versus newer AEDs in children with focal epilepsies for us to draw comparison with. However, there are some studies which have looked at the cost-effectiveness of these drugs within an adult population and although the treatment objectives within this population are quite different, there may be some merit in comparing the results. Schacter et al.[30] compared carbamazepine and phenytoin with carbamazepine and tiagabine as add-on therapy in patients with partial epilepsy. The study found that phenytoin cost US$ 810 compared to US$ 958 for tiagabine and that both drugs (as add-on therapy) had similar efficacy. A recent review of the cost-effectiveness of older versus newer drugs in adults with partial epilepsy[31] found that beyond a willingness to pay threshold value of £10,000, it was not possible to determine which was the most cost-effective AED with any degree of certainty. While the above studies have focused on the use of AEDs in adult patients, the results are in line with those reported in this paper in that it is not possible to conclude that the newer AEDs are more cost-effective than the older AEDs.

Epilepsies in children comprise a complex group of diseases with many different syndromes, treatment options and outcomes. While the majority of children do respond well to the first treatment given, for the minority that do not, more evidence is required on the relative benefits and adverse effects of any treatment given. The limited trial-based information available suggests that the newer drugs, while no more effective than the older drugs, may be somewhat better tolerated. However, the analysis and results presented in this paper have demonstrated that there is insufficient data available to accurately estimate the nature of this trade-off, whether in terms of long-term treatment retention or utility. For any rational evidence-based prescribing strategy to be developed, better information is required in the form of randomised controlled trials and utility-based quality of life. Randomised controlled trials should be conducted from a public health perspective making relevant comparisons and incorporating outcomes of interest to clinicians and patients, with sufficiently long-term follow-up to determine reliably the clinical utility of different treatments, particularly with respect to treatment retention and the balance between effectiveness and tolerability. Randomised controlled trials should mirror clinical practice with respect to diagnosis, focusing on defined syndromes or; where no syndrome is identified, on groups defined by specific seizure type(s) and aetiology.

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