National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

Supplement 3: Cost effectiveness of antiseizure therapies for people with focal and generalised tonic-clonic seizures

NICE guideline tbc

Health economics

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Evidence reviews were developed by National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

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Contents

Cost effectiveness of antiseizure monotherapy and add-on therapy for people with focal and generalised tonic-clonic seizures

Introduction

Four economic models were created, to estimate the cost effectiveness of antiseizure medicines (ASMs), for the relevant review questions on monotherapy and add-on therapy for people with focal and tonic-clonic seizures. These models were:

1) Antiseizure monotherapy for people with a new diagnosis of epilepsy with confirmed focal onset seizures.
2) Antiseizure monotherapy for people with a new diagnosis of epilepsy with confirmed generalised tonic-clonic seizures with or without other generalised seizure types.
3) Antiseizure add-on therapy for people with focal onset epilepsy that have failed to respond to one or more antiseizure therapy, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus).
4) Antiseizure therapy for people with generalised tonic-clonic seizures that have failed to respond to one or more antiseizure therapy, or refractory generalised tonic-clonic seizures with or without other generalised seizure types (absence, myoclonus)

These economic models were largely based on the Network Meta-analyses (NMAs) conducted either as part of the Cochrane network meta-analysis of ASMs (Nevitt 2021) Cochrane Link discussed in evidence report E or as part of evidence report F. A full list of NMAs and the economic models they inform are available in Table 1. The list of included ASMs were those included in the NMAs and for model 3 will include ASMs which are not in the economic model. Reasons for these exclusions are discussed below.

Table 1: Summary of NMAs used to inform the economic models

NMA	Interventions	Economic model and accompanying evidence review
Number of studies = 89 Number of participants = 22,040 People with a new diagnosis of epilepsy with confirmed focal onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types.	• Carbamazepine • Eslicarbazepine acetate • Gabapentin • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Phenobarbitone • Phenytoin • Sodium valproate • Topiramate • Zonisamide	Model 1 & Model 2 Evidence Review E & Cochrane Link

NMA	Interventions	Economic model and accompanying evidence review
Number of studies = 99 Number of participants = 20,826 People with focal onset epilepsy for which one or more ASM has failed to respond, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus)	• Brivaracetam • Carisbamate • Cenobamate • Eslicarbazepine Acetate • Gabapentin • Lacosamide • Lamotrigine • Levetiracetam • Oxcarbazepine • Perampanel • Placebo • Pregabalin • Primidone • Retigabine • Rufinamide • Selurampanel (BGG492) • Sodium valproate • Tiagabine • Topiramate • Vigabatrin • Zonisamide	Model 3 Evidence report F
Number of studies = 8 Number of participants = 1,218 People with focal onset epilepsy for which one or more ASM has failed to respond, or refractory focal epilepsy with or without other generalised seizure types (absence, myoclonus)	• Brivaracetam • Lacosamide • Lamotrigine • Levetiracetam • Perampanel • Placebo • Topiramate	Model 4 Evidence report F

ASMs for monotherapy in focal and generalised tonic-clonic (GTC) seizures were included in the relevant economic models if they appeared in the Cochrane network meta-analysis of ASMs (Nevitt 2021). Cochrane Link ASMs in this NMA were selected by the report authors because they were currently licensed for use in the relevant group and were commonly used as monotherapy. Cochrane's methods are closely aligned to standard NICE methods, minor deviations (inclusion of unpublished and ongoing trials, the use of the original Cochrane risk of bias tool, use of GRADE only on main outcomes, defining primary and secondary

outcomes as opposed to critical and important and including countries from a broader range of income categories than the majority of the other reviews in the guideline). The majority of estimates from the NMA were considered of high certainty as evaluated by CINeMa.

ASMs were included in the economic model of add-on therapy if they were included in the NMAs of add-on ASMs reported in the accompanying clinical evidence review for add-on therapies in focal and GTC seizures (evidence report F) and had a licensed for use as an add-on therapy in this group. ASMs included in the NMA but not licensed were excluded from the economic model. Cenobamate, which had identified evidence in the NMA, was excluded from the economic model because it was under an ongoing health technology appraisal and was outside of the scope of this guideline. Placebo was excluded from the economic model as it was not considered a treatment option for this group where effective treatment has been identified with high quality randomised evidence. Placebo was used as a common comparator in the model to allow concordance with the clinical evidence review but results were presented compared to an active treatment. The choice of comparator does not alter the results or conclusions of the economic model. All these ASMs remained in the clinical evidence review and NMA to allow for indirect evidence informing included ASMs and evidence on placebo response.

The economic model builds upon the previous NICE economic model for Epilepsy guideline (https://www.nice.org.uk/guidance/cg137/documents/epilepsy-update-full-guideline-appendix-p2) which in turn adapted the economic model of Hawkins 2005. There were a few major differences between the updated and previous guideline models. Firstly, the economic models in the updated report do not attempt to split the population between adults and children and the economic models covered all age groups. The accompanying NMAs for this evidence report included a combined population of adults, children and young people. They did not present any analyses that split the population between children and adults and it was the committee's view that there was no benefit from splitting such groups for this review question. The previous NICE guideline model did not make recommendations which differentiated between children, young people or adults for treatment of either focal or GTC seizures. The previous economic model also found no difference in cost effectiveness when children were considered as a distinct group. Secondly, this economic modelling considers the cost effectiveness of treatment for both focal and GTC seizures as monotherapy and add-on. We also only considered the first line of treatment for both add-on and monotherapy as this perspective was best represented by the evidence from the NMAs. These were also considered as distinct models and we did not aim to model explicitly beyond the first treatment failure or withdrawal. Other changes and more contemporary data have been highlighted in the methods below where appropriate.

Methods

Interventions considered

A list of ASMs considered by the 4 economic models and their corresponding 3-letter abbreviation are presented in table 1 below. As discussed above ASMs were included if evidence was identified in the relevant NMA, were licensed for use in the UK, were considered an appropriate treatment option and were not already under consideration by an existing health technology assessment or were otherwise outside of the scope of this guideline. ASMs for which no evidence was identified in either the NMAs or economic evaluation may still be considered by the committee in forming their recommendations based on their experience and judgment. A common comparator for all models would have been beneficial in interpreting results. An ASM recommended for all populations in the previous guideline at any line (and therefore could be considered as used in current practice) and for which was included in the economic models was explored but none were identified which met all criteria. Carbamazepine was recommended for focal monotherapy and add-on as well as GTC monotherapy and was also the comparator in the previous NICE economic model. It was decided this would form the best comparator for these groups. Carbamazepine was also one of the comparator treatments used in the Cochrane NMA (Nevitt 2021). Lamotrigine was chosen as the comparator for GTC add-on model (for which no evidence on carbamazepine was identified) as it was widely used based on the committees experience and was recommended in the previous NICE guideline for this group. It should be noted that the choice of comparator has no impact upon the ranking or preferred choice of ASMs.

Table 2: List of Antiseizure medications considered by the economic model and their abbreviations

	FOCAL MONOTHERAPY	GTC MONOTHERAPY	FOCAL ADD-ON	GTC ADD-ON
COMPARATOR	Carbamazepine (CBZ)	Carbamazepine (CBZ)	Carbamazepine (CBZ)	Lamotrigine (LTG)
INTERVENTIONS	Gabapentin (GBP)	Gabapentin (GBP)	Brivaracetam (BRV)	Brivaracetam (BRV)
	Lacosamide (LCM)	Lacosamide (LCM)	Eslicarbazepine Acetate (ESL)	Lacosamide (LCM)
	Lamotrigine (LTG)	Lamotrigine (LTG)	Gabapentin (GBP)	Levetiracetam (LEV)
	Levetiracetam (LEV)	Levetiracetam (LEV)	Lacosamide (LCM)	Perampanel (PER)
	Oxcarbazepine (OXC)	Oxcarbazepine (OXC)	Lamotrigine (LTG)	Topiramate (TPM)

	Phenobarbital (PHB)	Phenobarbital (PHB)	Levetiracetam (LEV)
	Phenytoin (PHT)	Phenytoin (PHT)	Oxcarbazepine (OXC)
	Sodium Valproate (VPS)	Sodium Valproate (VPS)	Perampanel (PER)
	Topiramate (TPM)	Topiramate (TPM)	Phenytoin (PHT)
	Zonisamide (ZNS)		Pregabalin (PGB)
			Primidone (PRM)
			Sodium valproate (VPS)
			Tiagabine (TGB)
			Topiramate (TPM)
			Vigabatrin (VGB)
			Zonisamide (ZNS)

GTC: Generalised tonic-clonic

Population

The populations considered by the 4 economic models are identical to the populations specified in the relevant protocols and PICOs in the evidence review. In short, the 2 monotherapy models cover people with a new diagnosis of epilepsy with confirmed focal or GTC seizures. For the 2 add-on models, the population was people with epilepsy who failed to respond to one or more antiseizure therapy or who had focal or GTC refractory epilepsy.

The average age of the population and the proportion of male and females in the cohort was based on the SANAD-II trial of people with newly diagnosed focal epilepsy (Marson 2021). This study was included in the NMAs of monotherapy. It was considered that this recent, large, UK randomised controlled trial (RCT) would most accurately reflect the population under consideration. The study discussed in detail in clinical evidence review E compared levetiracetam and zonisamide to lamotrigine in 990 people with newly diagnosed focal epilepsy, being treated at UK epilepsy centres between 2013 and 2017. The study participants had a mean age of 40 years and were 57% male. These values were used for the cohort in the economic model. These values were not varied during PSA (PSA).

Model structure

The model structure, in terms of health states was identical to that of the previous guideline economic model which was adapted from Hawkins 2004. It was confirmed by the committee that this still represented a reasonable reflection of health states for epilepsy and of current practice. There are two model structures in the updated model having split apart the previous model into monotherapy and add-on. The model structures only differ between monotherapy and add-on and are identical between focal and GTC seizures. The reason for having two distinct models is because it better fitted the evidence which looked at the most effective treatment for first line monotherapy and add-on therapy. It also prevented the need to express a specific treatment pathway or ordering of ASMs at all subsequent lines. Such pathways or ASM ordering was outside of the scope of the evidence review although it was considered by the committee that such evidence was not available to make a systematic review in the area worthwhile.

The monotherapy model assumes that all people in the model cohort start off as newly diagnosed and had not received previous treatment for epilepsy i.e. they are treatment naïve. From this first state people can either become seizure free, not respond (they do not achieve seizure freedom) or withdraw either because of adverse events or lack of efficacy. People will remain in the ‘seizure free’ state in all future stages until they fail treatment. People who withdraw treatment or subsequently fail after being seizure free move to a holding state of state of ‘add-on therapy’. In the previous guideline model these people would transit to the add-on therapy model. However, to allow for 2 distinct models in our report costs and QALYs were added retrospectively from the add-on model for people in this holding state.

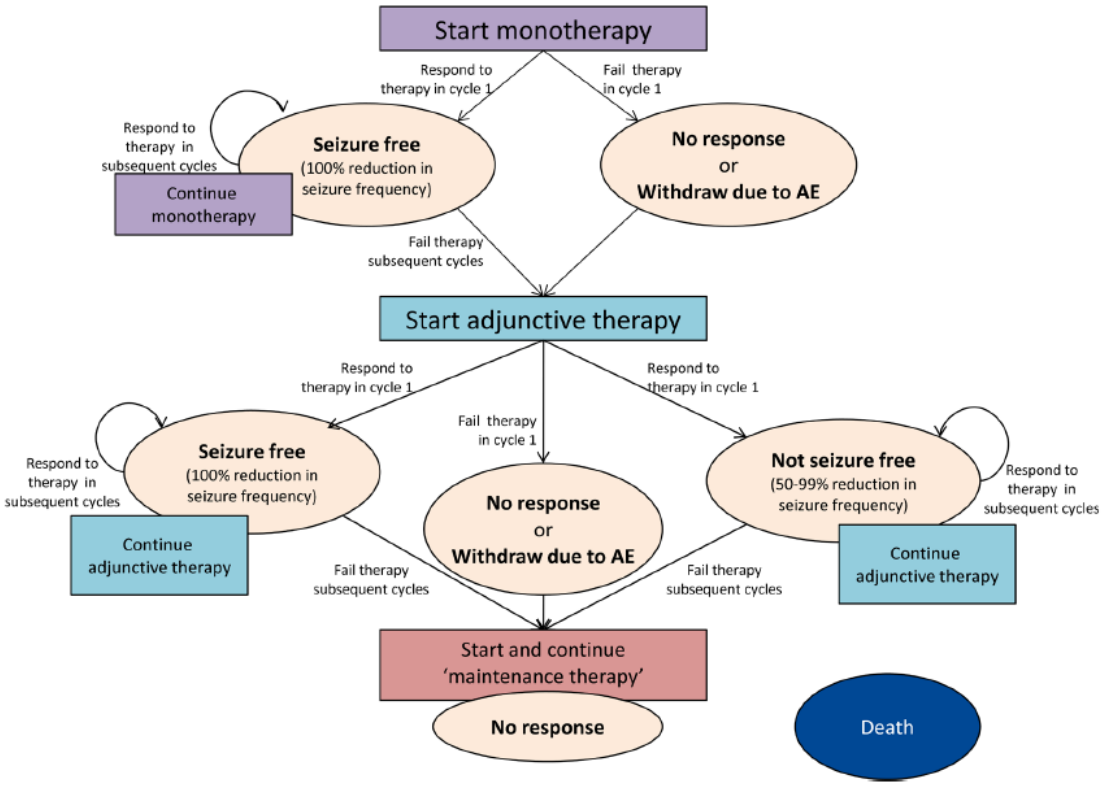
The add-on therapy model assumes that all people in the cohort have failed at least 1 monotherapy ASM or have refractory epilepsy. It is assumed that this is the first line of add-on therapy for people in the model cohort. The cohort can than transit to 1 of 4 health states. ‘Seizure free’, ‘not seizure free but responding’, ‘no response’ (≤50% reduction in seizure frequency), withdrawal due to adverse events and not seizure free but responding (>50% reduction in seizure frequency). People remain in either the seizure free or not seizure free but responding states until subsequent treatment failure. If treatment fails, then the cohort move into a holding state for maintenance therapy. The holding state again is used to prevent implicitly needing to suggest a pathway for subsequent lines of add-on treatment. This holding state is always assumed to be of higher cost and lower QALYs (other than death) than any other state in the model.

The cohort for both model structures can transit to the death state from any other state, during any cycle, other than from the two holding states. The model is configured though that death is captured in these states through the costs and QALYs assigned to them.

The model structures are presented in Figure 1. All states in the economic model are mutually exclusive and the cohort may only be in one state during any cycle. The economic component of the model is run in Microsoft Excel 2016. The models had a cycle length of 6 months and a time horizon of 15 years considered long enough to capture all important differences in terms of costs and outcomes between the ASMs being compared.

The model assumes that when a person fails monotherapy they will move onto add-on treatment. A proportion of people however will move onto a second line monotherapy before starting add-on therapy. This may continue in a small number of cases to future lines of monotherapy. The principles for this and discussed in section 4.1 Treatment with antiseizure medications of the recommendations.

Figure 1: Diagrammatic representation of the economic models taken from the previous guideline economic model



Parameters

Effectiveness of antiseizure medication

Response to and withdrawal from monotherapy in the first cycle of the model (monotherapy)

The first probability faced by the cohort in the economic model is that of withdrawal from monotherapy. For both focal and GTC seizures carbamazepine was used as the comparator ASM and a probability of withdrawal assigned to carbamazepine, for the first 36 months of the model, identical to that of the previous NICE economic model. This in turn estimated their probabilities from the SANAD I trial of monotherapy in people with focal seizures (Marson 2007).

Probability of withdrawal (PTW) from monotherapy for other ASMs during the first 36 months were calculated by altering the baseline probability for carbamazepine by the hazard ratio (HR) reported for the relevant ASM in the Cochrane NMA (Nevitt 2021). Probabilities were converted using the following formulae:

$$1 - e^{(-(Hazard\ ratio\ X\ \text{Baseline probability}))}$$

The usual proportional hazard assumptions were made about the hazard ratios for these calculations most importantly that it remains constant over the first 36 months of the model. Probability of treatment withdrawal for any reason during the first 36 months of the trial for focal seizures are shown in Table 3 and for GTC seizures in Table 4.

Table 3: Probability of treatment withdrawal during the first 36 months of the economic model- focal seizures

	GBP	LCM	LTG	LEV	OXC	PHB	PHT	VPS	TPM	ZNS	CBZ
HAZARD RATIO	1.21	0.95	0.79	0.80	1.03	1.56	1.14	1.08	1.19	0.93	1.00
0-6 MONTH	0.31	0.26	0.22	0.22	0.27	0.39	0.30	0.29	0.31	0.25	0.27
6-12 MONTH	0.12	0.10	0.08	0.08	0.11	0.16	0.12	0.11	0.12	0.10	0.10
12-18 MONTH	0.07	0.06	0.05	0.05	0.06	0.09	0.07	0.06	0.07	0.06	0.06
18-24 MONTH	0.08	0.06	0.05	0.06	0.07	0.10	0.08	0.07	0.08	0.06	0.07
24-30 MONTH	0.03	0.02	0.02	0.02	0.03	0.04	0.03	0.03	0.03	0.02	0.03

30-36 MONTH	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01	0.01

Table 4: Probability of treatment withdrawal during the first 36 months of the economic model- generalised tonic clonic seizures

	GBP	LCM	LTG	LEV	OXC	PHB	PHT	VPS	TPM	CBZ
HAZARD RATIO	1.29	1.04	1.19	0.99	1.26	1.29	0.97	0.99	1.07	1.00
0-6 MONTH	0.21	0.42	0.20	0.21	0.23	0.37	0.21	0.19	0.24	0.27
6-12 MONTH	0.08	0.17	0.07	0.08	0.09	0.15	0.08	0.07	0.09	0.10
12-18 MONTH	0.05	0.10	0.04	0.04	0.05	0.09	0.05	0.04	0.05	0.06
18-24 MONTH	0.05	0.12	0.05	0.05	0.06	0.10	0.05	0.05	0.06	0.07
24-30 MONTH	0.02	0.05	0.02	0.02	0.02	0.04	0.02	0.02	0.02	0.03
30-36 MONTH	0.01	0.02	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.01

Longer-term discontinuation probabilities of ASMs beyond the first 36 months of the economic model were taken from the previous NICE economic model which in turn took them from the observational NGPSE follow-up study (Manford 1992). The committee highlighted that this was a relatively old study but provided the most applicable and largest body of data on ASM discontinuation. It is likely that knowledge of titration and dosing has improved over this time so these values might overestimate the number of people discontinuing ASMs. Probabilities and relevant distributions for the PSA are presented in Table 5.

The values of the hazard ratios were varied in the PSA based on the point estimates and matrix of variance and covariance provided by the Cochrane study team. Assuming a multivariate normal distribution around the relative effectiveness estimates used for this parameter allowing for a distribution to be specified for ‘time to treatment withdrawal’ which accounts for the both the variance within ASMs and covariance between ASMs. This is important as it reflects that estimates of effectiveness of specific ASMs in the NMA are dependent of estimates of other ASMs.

Table 5: Long-term treatment failure probabilities and beta distributions for PSA

MONTHS	PROBABILITY WITHDRAWAL	ALPHA	BETA
12	0.0509	27.27	508.0
18	0.034	17.29	490.7
24	0.034	16.71	474.0
30	0.0184	8.74	465.3
36	0.0184	8.58	456.7
42	0.0184	8.42	448.3
48	0.0184	8.26	440.0
54	0.0163	7.17	432.8
60	0.0163	7.06	425.8
66	0.0163	6.94	418.8
72	0.0163	6.83	412.0
78	0.0067	2.78	409.2
84	0.0067	2.76	406.5
90	0.0067	2.74	403.7
96	0.0067	2.72	401.0

Probability of achieving 12-month remission (monotherapy)

The probability of achieving 12-month remission for monotherapy was conditional on having not failed monotherapy and was estimated subsequent to that probability. The estimation of this probability for carbamazepine was taken from the previous economic model which estimated the value from SANAD I (Marson 2007). These probabilities were adjusted using the same formulae as for treatment withdrawal but using the 12-month remission hazard ratios from the Cochrane NMA (Nevitt 2021) for the first 36 months of the model. Probabilities for the first 6 months is zero for all ASMs as 12-month remission cannot be achieved in 6 months. Probabilities are displayed in Table 6.

Table 6: Probability of achieving 12-month remission during the first 36 months of the economic model- focal seizures

	GBP	LCM	LTG	LEV	OXC	PHB	PHT	VPS	TPM	ZNS	CBZ
HAZARD RATIO	1.29	1.00	1.06	1.08	0.95	1.03	1.04	1.08	1.13	1.10	1.00
0-6 MONTH	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

6-12 MONTH	0.46	0.38	0.40	0.40	0.37	0.39	0.39	0.40	0.42	0.41	0.38
12-18 MONTH	0.31	0.25	0.27	0.27	0.24	0.26	0.26	0.27	0.28	0.27	0.25
18-24 MONTH	0.21	0.17	0.18	0.18	0.16	0.18	0.18	0.18	0.19	0.19	0.17
24-30 MONTH	0.14	0.11	0.12	0.12	0.10	0.11	0.11	0.12	0.12	0.12	0.11
30-36 MONTH	0.09	0.07	0.07	0.07	0.07	0.07	0.07	0.07	0.08	0.08	0.07

Table 7: Probability of achieving 12-month remission during the first 36 months of the economic model- generalised tonic clonic seizures

	GBP	**LCM**	**LTG**	**LEV**	**OXC**	**PHB**	**PHT**	**VPS**	**TPM**	**ZNS**	**CBZ**
HAZARD RATIO	1.29	1.04	1.19	0.99	1.26	1.29	0.97	0.99	1.07	1.29	1.00
0-6 MONTH	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
6-12 MONTH	0.46	0.39	0.44	0.38	0.45	0.46	0.37	0.38	0.40	0.46	0.38
12-18 MONTH	0.31	0.26	0.29	0.25	0.31	0.31	0.25	0.25	0.27	0.31	0.25
18-24 MONTH	0.21	0.18	0.20	0.17	0.21	0.21	0.17	0.17	0.18	0.21	0.17
24-30 MONTH	0.14	0.11	0.13	0.11	0.14	0.14	0.11	0.11	0.12	0.14	0.11
30-36 MONTH	0.09	0.07	0.08	0.07	0.09	0.09	0.07	0.07	0.07	0.09	0.07

The longer term probabilities are achieving 12-month remission are based on the treatment failure probabilities presented in Table 5. Where a person does not fail treatment in two successive 6-month cycles they will transit to the seizure free (12-month remission) state. Distributions around the 12-month remission hazard ratios used in the PSA are again calculated from variance covariance matrices provided by the Cochrane study authors. The assumptions around distributions are the same as for probability of treatment withdrawal.

Response to and withdrawal from add-on therapy during the first cycle (add-on)

For the first cycle of the model people in the model cohort are assumed seizure free.

The probability of withdrawal from add-on therapy for the first cycle are taken from the accompanying systematic review for add-on therapy using the estimated 'treatment withdrawal' percentages from the add-on NMA for focal and GTC seizures. It is important to note that these outcomes were not estimated comparatively and other issues with treatment withdrawal and adverse event outcomes discussed in detail in evidence review F for add-on therapy. Probabilities were included in the model at their point estimate and this event was assumed to occur first and not dependent on other factors so the probabilities were not adjusted for or dependent on other events. The values were varied using a beta distribution during PSA. Two ASMs, carbamazepine and phenytoin did not report withdrawal outcomes in any of the studies identified in the accompanying NMA. These were assigned the highest value reported by any other ASM (lacosamide) for the point estimate and given a uniform distribution varying the estimate 25% either direction from the mean. Probability of treatment withdrawal during the first cycle are presented in Table 8 alongside distributions used in PSA.

Table 8: Probability of withdrawal during the first cycle of the model (add-on)

ANTISEIZURE MEDICATION	PROBABILITY WITHDRAWL FIRST CYCLE	BETA DISTRIBUTION USED IN THE PSA	
		Alpha	Beta
BRIVARACETAM (BRV)	14.0%	197	1207
CARBAMAZEPINE (CBZ)	23.6%	Uniform	
ESLICARBAZEPINE ACETATE (ESL)	13.4%	85	548
GABAPENTIN (GBP)	10.3%	7	61
LACOSAMIDE (LCM)	23.6%	204	659
LAMOTRIGINE (LTG)	6.0%	102	1584
LEVETIRACETAM (LEV)	4.4%	49	1065
OXCARBAZEPINE (OXC)	11.5%	24	185
PERAMPANEL (PER)	12.0%	53	389
PHENYTOIN (PHT)	9.3%	159	1549
PREGABALIN (PGB)	6.5%	48	691
PRIMIDONE (PRM)	6.8%	138	1879
SODIUM VALPROATE (VPS)	7.1%	7	91
TIAGABINE (TGB)	9.6%	142	1336

TOPIRAMATE (TPM)	9.8%	67	620
VIGABATRIN (VGB)	23.6%	Uniform	
ZONISAMIDE (ZNS)	12.9%	62	418

Probability of achieving seizure freedom (add-on)

The probability of achieving seizure freedom (100% reduction in seizure frequency) with placebo was taken from the accompanying NMA for placebo (1%). This was then adjusted using the estimated odds ratio from the NMA to get probabilities for achieving seizure freedom for the active ASMs. Unlike for monotherapy these probabilities were not conditional on having not withdrawn from treatment as the estimates were taken from the same studies and the assumption made in the model that people would not withdraw from treatment if they achieved seizure freedom. The odds ratios used to estimate the probability of seizure freedom were varied in the PSA using WinBUGS convergence diagnostics and output analysis (CODA) output from the primary NMAs. 1000 iterations from the CODA, sampled after the burn in samples, were used in the model and full sets of odds ratios were sampled using a random number. CODA output lists all values from the full posterior distribution. Correlations in the odds ratios are preserved by sampling from the same iteration of the NMA (Dias 2013). No evidence was identified in the NMA for seizure freedom for two ASMs, carbamazepine and phenytoin and were not present in the CODA output. Both of these were conservatively assumed not to perform better than placebo for this outcome (odds ratio equal to 1) and a wide uniform distribution assigned between 0.03 and 5. No attempt was made to correlate these outcomes with the effectiveness of other ASMs included in the CODA output given a paucity of evidence identified to inform any correlation.

Probability of achieving 50% or greater reduction in seizure frequency and not withdrawing (add-on)

The probability of achieving a 50% or greater reduction in seizure frequency were again taken from the economic model with the baseline value for placebo again taken from the NMA (16%). The probabilities on this occasion were adjusted for having not withdrawn from treatment and having not achieved seizure freedom. This is because the 50% reduction in seizure frequency outcome is unlikely to be mutually exclusive from these other two outcomes. CODA from the primary NMAs were again used, in an identical manner to that of seizure freedom for the PSA. Whilst it would seem logical that there is some correlation between seizure freedom and 50% reduction in seizure frequency outcomes (i.e. if seizure freedom was to increase so would 50% reduction in seizure frequency) the NMAs were run

separately and any such correlation is not captured. Given the low estimates for seizure freedom it was not thought this would significantly impact upon the outputs of the PSA.

Longer term probabilities of seizure free and 50% reduction in seizure freedom (add-on)

Discontinuation after the first year of the model are taken from the previous NICE guideline model who in turn estimated them from Hawkins 2005 study which was an open-label follow-up study of tiagabine. The data was not specific to just tiagabine and showed that the probability of discontinuation of add-on ASMs decreased the longer that treatment was successful either through seizure freedom or a greater than 50% reduction in seizures. The authors of the previous economic model then estimated a beta distribution from a hypothetical cohort of 100 people. The discontinuation probabilities and their beta distributions are presented in Table 9.

Table 9: Probability of discontinuation of add-on therapy after the first cycle of the economic model

MONTHS	MEAN	DISTRIBUTION USED IN THE PSA	
		Alpha	Beta
12	0.126	9.97	90.03
18	0.148	10.42	89.58
24	0.131	5.35	94.65
30	0.1	6.29	93.71
36	0.104	4.88	95.12
42	0.054	2.47	97.53
48	0.063	2.47	97.53
54	0.049	2.47	97.53
60	0.025	2.47	97.53
66	0.025	2.47	97.53
72	0.025	2.47	97.53
78	0.025	2.47	97.53
84	0.025	2.47	97.53
90	0.025	2.47	97.53
96	0.025	2.47	97.53
102	0.025	2.47	97.53
108	0.025	2.47	97.53

114	0.025	2.47	97.53
120	0.025	2.47	97.53
126	0.025	2.47	97.53
132	0.025	2.47	97.53
138	0.025	2.47	97.53
144	0.025	2.47	97.53
150	0.025	2.47	97.53

Death

Death can occur in any cycle from any state (excluding the death state) in the economic model other than for the two holding states ('maintenance therapy' and 'add-on therapy'). The baseline probability of death was taken from the Office of National Statistics (ONS) National Life Tables for 2017-2019 the latest available at the time of writing. The baseline probabilities reported by ONS were weighted based on the split of male and females in the model cohort and the assumed age (40 years plus 1 year for every two model cycles).

These weights were then adjusted using standardised mortality rates (SMRs) calculated by the previous NICE economic model based on reported deaths and hazard ratios from NGPSE study calculated from observed deaths. These SMRs were stratified, by age, in intervals of 10 years. Two age intervals were used for the economic model representing the age of the cohort throughout the model 40-49 years and 50-59 years. As a starting age of 40 years was assumed for the model cohort this would adequately cover the cohort for the entirety of the time horizon of the models. The SMRs were further split into seizure free and 'not seizure free'. The baseline probabilities of death were adjusted using these SMRs. The seizure free was applied to the 'seizure free' and '12-month remission' states. All other non-dead and non-holding states were adjusted for the 'not seizure free' SMR. These values were fixed during PSA. The SMR are presented in Table 10.

Table 10: Standardised mortality rate by age and seizure status

Age	SMR seizure free	SMR not seizure free
40-49 years	3.00	4.28
50-59 years	6.12	8.74

Adverse events

Adverse events were not explicitly included in the economic model. Adverse events were collected inconsistently across studies and it was often not clear whether events had not occurred or if they were not captured. The definition and required severity of adverse events also differed across studies. The impact of adverse events on continuation of treatment and quality of life was also likely to differ between individuals. It was therefore difficult to make comparisons between treatments based on our narrative adverse event data. It was also highlighted that adverse events could be controlled or removed with careful titration of ASMs or through treatment withdrawal. It was therefore considered that the actual costs of adverse events would be relatively small and would not impact upon the results or conclusions of the model.

Adverse events were indirectly captured in the model through the treatment withdrawal outcomes, which would capture withdrawal due to adverse events as well as through lack of efficacy. Adverse events were considered during the committee's interpretation of the economic evidence and making of recommendations.

Costs and resource use

Only costs incurred by the NHS & PSS were included in the economic model. These costs include medication costs, costs of contact with healthcare services (emergency department visit etcetera) and costs of switching ASM treatment after treatment failure. Unlike the previous NICE model we did not cost the price of starting a ASM as this was assumed to be equal across all intervention and thus zero out during incremental analysis. Nearly all of this cost would consist of medical appointments (GP, consultant neurologist etc) and the committee did not believe these would differ by ASM.

Medication costs and resource use

Costs of medication were taken from the BNF (accessed 11/03/2021). We assumed the cost of the ASM was equal to the NHS indicative price as this was most likely to reflect the true cost incurred by the NHS. The BNF alternatively reports the Drug Tariff price, the amount usually reimbursed to dispensers, which may not accurately reflect hospital prices where prescribing would take place. The NHS indicative price and drug tariff were equal for all the ASMs other than gabapentin, lamotrigine, oxcarbazepine, phenobarbital, pregablin, primidone, sodium valproate, topiramate and zonisamide. In all cases the drug tariff price was greater than the NHS indicative price. The dosage assumed for all ASMs was the median range reported by the BNF after full titration. For all ASMs the recommended dosage for both focal and GTC seizures was identical in both mono- and add-on therapy. During the

titration period, dosage may be well below this range but titration will almost certainly be achieved in the first cycle of the model so any underestimation of costs would be small. Costs were only applied in model states where treatment has continued. All ASMs in the model are widely prescribed and there is much certainty around the unit costs of the ASMs. Given that the dosages are given in ranges and ASM dosage is likely to differ by individual the costs were varied above and below the estimated value by 25% using a uniform distribution during PSA. The median ASM dosage and cost per 6-month cycle are shown in Table 11 for monotherapy and Table 12 for add-on therapy.

Table 11: Median daily dosage and 6-monthly costs for antiseizure medication considered by the economic model for monotherapy

ANTISEIZURE MEDICATION	6 MONTH COST	MEDIAN DAILY DOSE
CARBAMAZEPINE (CBZ)	£40.93	1000mg
GABAPENTIN (GBP)	£17.12	2250mg
LACOSAMIDE (LCM)	£940.26	400mg
LAMOTRIGINE (LTG)	£18.03	350mg
LEVITERACETAM (LEV)	£73.61	1750mg
OXCARBEZAPINE (OXC)	£100.99	1500mg
PHENOBARBITAL (PHB)	£26.09	120mg
PHENYTOIN (PHT)	£325.20	450mg
SODIUM VALPROATE (VPS)	£123.04	1750mg
TOPIRAMATE (TPM)	£41.59	300mg
ZONISAMIDE (ZNS)	£83.75	400mg

Table 12: Median daily dosage and 6-monthly costs for antiseizure medication considered by the economic model for add-on therapy

ANTISEIZURE MEDICATION	6 MONTH COST	MEDIAN DAILY DOSE
BRIVARACETAM (BRV)	£528.47	125mg
CARBAMAZEPINE (CBZ)	£40.93	1000mg
ESLICARBAZEPINE ACETATE (ESL)	£1,034.88	1000mg

GABAPENTIN (GBP)	£17.12	2250mg
LACOSAMIDE (LCM)	£587.66	250mg
LAMOTRIGINE (LTG)	£14.43	150mg
LEVETIRACETAM (LEV)	£84.13	2000mg
OXCARBAZEPINE (OXC)	£100.99	1500mg
PERAMPANEL (PER)	£608.75	8mg
PHENYTOIN (PHT)	£325.20	450mg
PREGABALIN (PGB)	£17.32	450mg
PRIMIDONE (PRM)	£818.94	1125mg
SODIUM VALPROATE (VPS)	£123.04	1750mg
TIAGABINE (TGB)	£712.83	37.5mg
TOPIRAMATE (TPM)	£41.59	300mg
VIGABATRIN (VGB)	£449.26	2500mg
ZONISAMIDE (ZNS)	£83.75	400mg

Cost of switching antiseizure medication

The cost of switching medication were based on resource use estimated in the previous NICE economic model and unit costs from NHS Cost Collection 2019/20 (The Department of Health 2021) or for GP appointments from the Unit Costs and Health and Social Care 2020 (Curtis & Burns 2020). The health resources required to switch medication are presented in Table 13. All costs from the NHS Cost Collection were varied using a gamma distribution during PSA based on the mean and number of observations underpinning the estimate. The cost of a GP appointment was not varied although it only made up a small part of the total cost of switching medication.

Table 13: Health service use for switching medication following treatment failure

HEALTH SERVICE USE	UNIT COST	NUMBER OF VISITS	NHS COST COLLECTION CURRENCY CODE
GP APPOINTMENT	£39.00	3 (monotherapy) 4 (add-on)	Not applicable
NEUROLOGY OUTPATIENT INITIAL VISIT	£215.11	1	WF01A

NEUROLOGY OUTPATIENT FOLLOW-UP	£174.10	1 (monotherapy) 2 (add-on)	WF01B
PHONE-CALL FOLLOW-UP	£89.64	2	WF01C

Non-medication related health care resource use and costs

Health care resource use and costs unrelated to the cost of medication were assumed to consist of GP visits, inpatient hospital stays, emergency department visits and appointments with a neurologist consultant. The costs of these are again taken from the NHS Cost Collection with the cost of a GP visits from Curtis & Burns 2020. Again, these costs were varied in sensitivity analysis using a gamma distribution and the number of observations submitted apart from GP visits, which again was fixed. GP visits make up an even smaller part of total costs than for switching medication.

The frequency of using the above resources was based on whether an individual was seizure free or not seizure free with people who were not seizure free using healthcare resources more often.

This difference in service use according to whether individuals are seizure free or not seizure free has been estimated from data reported in a large UK prevalence study on epilepsy (Jacoby 1998). Jacoby 1998 was a cross-sectional study of 1,341 people with epilepsy and their uptake of healthcare services in the UK using GP health records. These data were recorded relative to the different health and social care settings (for example, inpatient, outpatient or community care settings); according to severity of the epilepsy (for example, seizure frequency reported in the last year by people with epilepsy); and by age groups (for example, adults and children). According to this study, people with epilepsy who experienced one or more seizures in a year reported higher use of all services than individuals who were seizure free in the last year, although the differences were greater for adults than for children. Total cost for the health state per cycle were calculated by multiplying the probability of using a healthcare service, by the number of visits and the unit cost. These probabilities were not varied during PSA.

Table 14: Probabilities of using healthcare services by seizure frequency.

USE OF HEALTHCARE SERVICES	Seizure Free	Not Seizure Free	Number of visits	Unit cost	Currency code
EMERGENCY DEPARTMENT VISIT	0.02	0.27	1	£220.22	VB08Z
INPATIENT STAY	0.01	0.16	3	£2,301.79	AA26F
NEUROLOGY OUTPATIENT INITIAL VISIT	0.18	0.49	1	£215.11	WF01A
NEUROLOGY OUTPATIENT INITIAL VISIT	0.18	0.49	2	£174.10	WF01B
GP APPOINTMENT	0.18	0.61	1	£39.00	Not applicable

Health related quality of life

Three utility values were used for the health model ‘seizure free’, ‘not seizure free’, ‘greater than 50% seizure reduction’ and ‘dead’. The health utilities for ‘seizure free’ and ‘not seizure free’ were taken from Väätäinen 2020 who in turn estimated their value from unpublished EQ-5D-3L data from the SANAD I study used to inform the baseline values of this economic evaluation (Marson 2007). The EQ-5D-3L responses were scored using the UK population tariff. The values reported from the SANAD study were 0.869, 0.805, 0.623 and zero for ‘seizure free’, ‘greater than 50% seizure reduction’, ‘not seizure free’, and ‘dead’. These values were halved to reflect the 6-month cycle length and multiplied by the time spent in each health state. These values were varied using a uniform distribution during PSA. The states were given a hierarchy during PSA so that ‘seizure free’ states would always have a utility equal or greater than the ‘greater than 50% seizure reduction’ state which in turn would be greater than the ‘not seizure free state’

Sodium Valproate

Given the teratogenic risk associated with sodium valproate it should only be considered in women and girls able to have children (including young girls who are likely to need treatment when they are old enough to have children), when other treatment options are unsuccessful and after a full discussion of the risks and benefits, including risks to the unborn and after taking into account the likelihood of pregnancy and putting in place a pregnancy prevention programme, if appropriate. Therefore, as sodium valproate may not be the most appropriate treatment in a large proportion of this population where sodium valproate was strongly

returned as one of the preferred choices in the economic evaluation the model was re-run without sodium valproate as an option.

Discount Rate

All health outcomes were discounted at a rate of 3.5% per annum in line with the NICE guidelines manual after the first year of the model.

Probabilistic sensitivity analysis

PSA was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values. The distributions used are presented in the individual tables of the report. The results of the PSA are presented as cost effectiveness acceptability curves (CEACs) which show the probability of an ASM being the preferred (cost effective) at different cost per QALY thresholds.

Net Monetary Benefit

All results are presented as incremental net monetary benefit (INMB). INMB is a representation of cost effectiveness where incremental QALY gains, compared to the comparator intervention, are converted into a monetary value by multiplying by a willingness to pay per QALY. For example, if an intervention had a QALY gain of 0.5 compared to the comparator and the willingness to pay or threshold per QALY was £20,000, the monetary value of the QALY gain would equal £10,000. INMB is then calculated by subtracting total incremental cost from this incremental monetary value of the QALYs gained. For our analysis the threshold is set equal to £20,000 per QALY (unless otherwise stated) the value below which NICE conventionally recommends interventions. Interventions, which report a positive INMB, are cost effective compared to the comparator with those reporting a negative value not being cost effective. The ‘preferred’ intervention would be the one which reports the highest INMB. All interventions are also ranked based on their INMB with 1 indicating the preferred option i.e. that with the highest INMB value. These rankings remain in the same order regardless of the removal of other interventions and can therefore be used to make direct comparisons between any two or more ASMs.

Results

Monotherapy for focal seizures

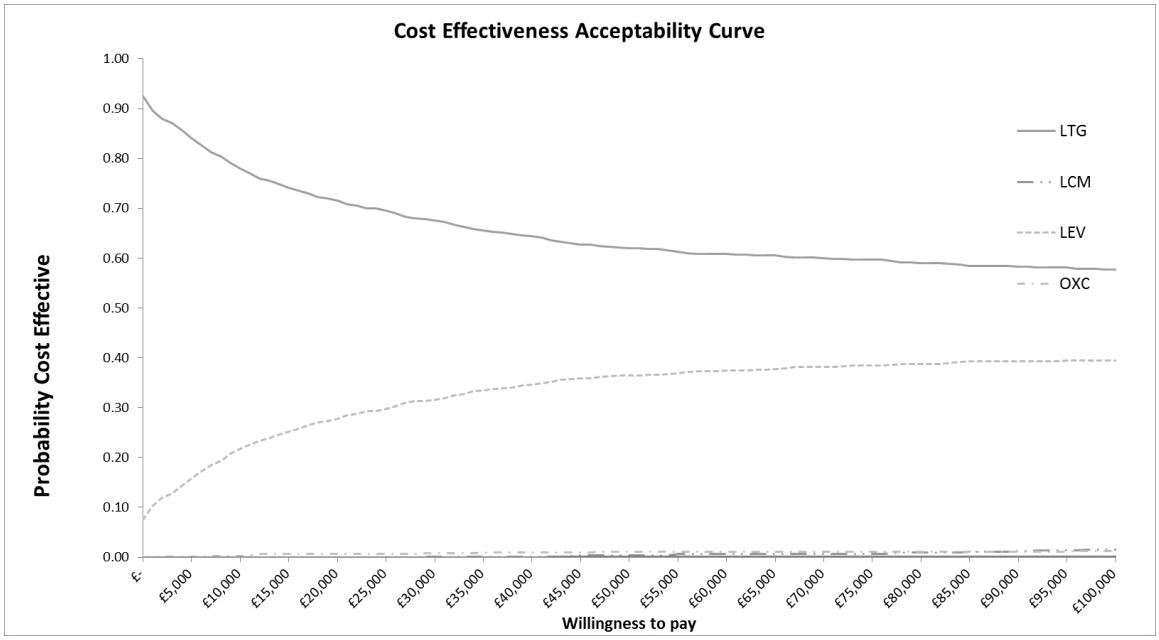
Table 15 presents the base-case results of the ASMs considered for monotherapy in people with focal seizures. Under the base-case assumptions, lamotrigine is estimated as both the least costly and the most effective (highest QALYs) resulting in the highest INMB across the 11 ASMs considered when a £20,000 per QALY threshold is considered. In the absence of lamotrigine, levetiracetam becomes the least costly and most health improving. The same is also true for zonisamide when both lamotrigine and levetiracetam are excluded from the analysis. This suggests that outcomes (QALYs) and costs are negatively correlated and that improved outcomes lead to lower costs through lower healthcare resource utilisation. This may indicate that ASMs that are more effective, and prevent treatment withdrawal (either through lack of efficacy or adverse events), will be the most cost effective and highlights the importance of taking into account individual considerations and expectations.

Table 15: Base-case results for monotherapy in people with focal seizures assuming £20,000 per QALY threshold ordered by ranking (1 indicates preferred option)

	TOTAL COST	TOTAL QALY	INCREMENTAL COST	INCREMENTAL QALY	INMB	RANK
LAMOTRIGINE	£15,437	8.82	-£1,773	0.16	£4,946	1
LEVITERACETAM	£16,294	8.81	-£916	0.15	£3,945	2
ZONISAMIDE	£17,298	8.72	£87	0.05	£ 980	3
CARBAMAZEPINE	£17,210	8.66	Reference	Reference	0	4
OXCARBEZAPINE	£18,182	8.64	£972	-0.02	-£1,422	5
SODIUM VALPROATE	£18,716	8.61	£1,505	-0.05	-£2,555	6
GABAPENTIN	£18,134	8.53	£924	-0.13	-£3,555	7
TOPIRAMATE	£18,341	8.54	£1,131	-0.12	-£3,588	8
PHENYTOIN	£21,516	8.57	£4,306	-0.09	-£6,172	9
PHENOBARBITAL	£20,129	8.33	£2,919	-0.34	-£9,646	10
LACOSAMIDE	£28,797	8.70	£ 11,587	0.04	-£10,875	11

Figure 2 presents the cost effectiveness acceptability curve (CEAC) for ASMs considered as monotherapy in people with focal seizures. For ease of reading only 4 ASMs are presented as all other ASMs reported a zero probability of being cost effective at all values of willingness to pay per additional QALY in the model. At a threshold of £20,000 per additional QALY lamotrigine has a 73% probability of being the preferred option with a 27% probability of levetiracetam being the preferred option. Oxcarbazepine has less than a 1% probability of being the preferred option at the same threshold. Lacosamide has a probability of 1% only above thresholds of £55,000 per QALY.

Figure 2: Cost effectiveness acceptability curve for antiseizure medications considered as monotherapy for people with focal seizures



Add-on therapy for focal seizures

Table 16 shows the base-case results for the add-on model for people with focal seizures. Differences in QALYs differs by only 0.03 across all interventions equivalent to 11 days in perfect health. Assuming a £20,000 per QALY threshold levetiracetam becomes the preferred option. Without levetiracetam, which is one of the preferred options for monotherapy (and therefore may not be an option for add-on therapy) topiramate becomes the preferred option under the base-case assumptions.

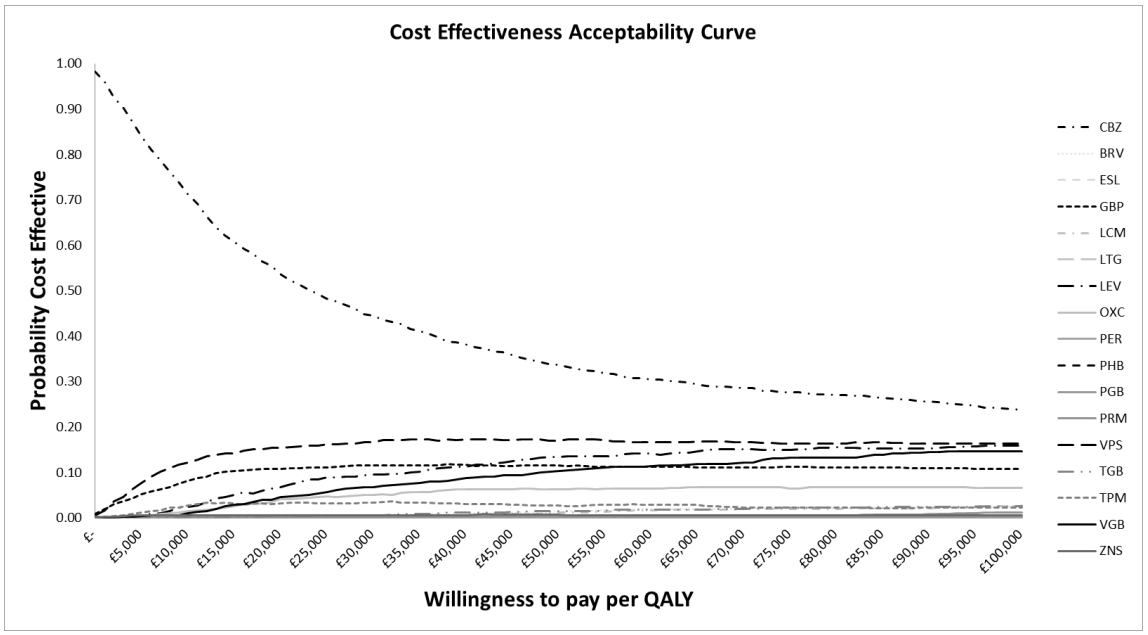
Table 16: Base-case results for add-on therapy in people with focal seizures assuming £20,000 per QALY threshold ordered by ranking (1 indicates preferred option)

	Total cost	Total QALY	Incremental Cost	Incremental QALY	INMB	Rank

Levetiracetam	£11,474	6.84	£352	0.03	£170	1
Topiramate	£11,333	6.83	£211	0.01	£51	2
Carbamazepine	£11,122	6.82	Reference	Reference	£-	3
Oxcarbazepine	£11,553	6.83	£432	0.01	-£163	4
Gabapentin	£11,383	6.82	£261	0.00	-£237	5
Pregablin	£11,358	6.82	£236	-0.00	-£250	6
Sodium valproate	£11,632	6.83	£511	0.01	-£255	7
Lamotrigine	£11,373	6.81	£251	-0.00	-£284	8
Zonisamide	£11,527	6.82	£405	-0.00	-£415	9
Phenytoin	£12,330	6.81	£1,208	-0.00	-£1,282	10
Brivaracetam	£12,819	6.83	£1,697	0.01	-£1,405	11
Perampanel	£12,977	6.82	£1,856	0.01	-£1,728	12
Vigabatrin	£13,301	6.84	£2,179	0.02	-£1,734	13
Primidone	£12,861	6.81	£1,740	-0.00	-£1,767	14
Tiagabine	£13,195	6.81	£2,073	-0.00	-£2,119	15
Lacosamide	£13,567	6.83	£2,445	0.01	-£2,232	16
Eslicarbazepine Acetate	£14,321	6.82	£3,199	0.00	-£3,140	17

Figure 3 shows the CEACs for ASMs considered by the economic model for people with focal seizures. The model shows carbamazepine as the preferred option at all values of willingness to pay per QALY up to £100,000. Carbamazepine had the highest point estimate for '50% reduction in seizure freedom' in the economic model with favourable but very wide confidence intervals. The direct evidence for carbamazepine in the accompanying NMA was based on two relatively old studies with a high risk of bias. Without carbamazepine no other ASM had more than a 15% probability of being the preferred option at a threshold of £20,000 per QALY. At the £20,000 per QALY threshold in the absence of carbamazepine, sodium valproate, gabapentin and levetiracetam were the preferred options in that order.

Figure 3: Cost effectiveness acceptability curves results for add-on therapy in people with focal seizures assuming £20,000 per QALY threshold



Monotherapy for GTC seizures

Table 17 presents the base-case results for ASMs considered in the economic model. Under the base-case assumptions lamotrigine comes out as the preferred choice with sodium valproate ranked second when a £20,000 per QALY threshold is assumed. Sodium valproate is the most effective intervention with lamotrigine being the least costly. Lacosamide was estimated to have the least QALYs and highest costs for this group reflecting the unfavourable point estimates for 12-month remission and time to treatment failure.

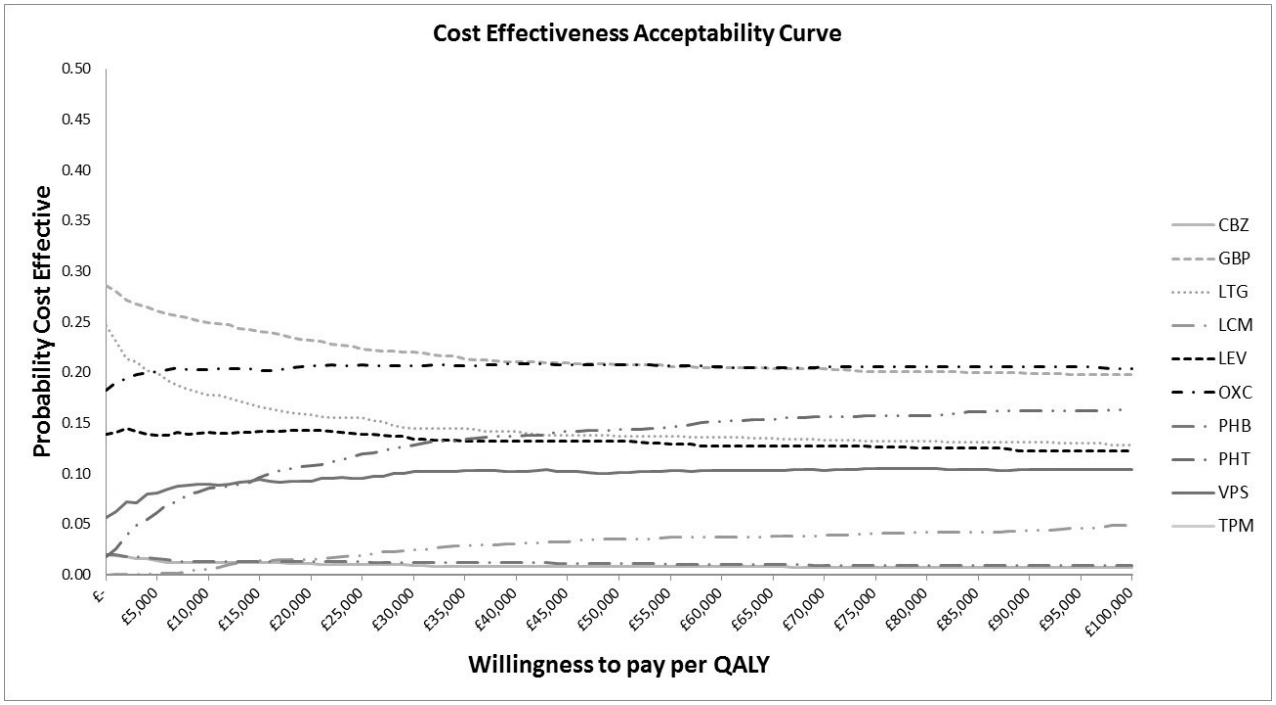
Table 17: Base-case results for monotherapy in people with GTC seizures assuming £20,000 per QALY threshold ordered by ranking (1 indicates preferred option)

	TOTAL COST	TOTAL QALY	INCREMENTAL COST	INCREMENTAL QALY	INMB	RANK
LAMOTRIGINE	£14,719	8.90	-£2,491	0.24	£7,214	1
SODIUM VALPROATE	£16,057	8.92	-£1,153	0.26	£6,410	2
GABAPENTIN	£15,064	8.86	-£2,146	0.20	£6,105	3
LEVITERACETAM	£15,897	8.86	-£1,314	0.20	£5,240	4
OXCARBEZAPINE	£16,771	8.80	-£439	0.14	£3,265	5
TOPIRAMATE	£16,540	8.74	-£670	0.07	£2,161	6

PHENYTOIN	£19,739	8.83	£2,529	0.17	£898	7
CARBAMAZEPINE	£17,210	8.66	Reference	Reference	0	8
PHENOBARBITAL	£19,592	8.38	£2,382	-0.28	-£7,937	9
LACOSAMIDE	£29,503	8.24	£12,293	-0.42	-£20,768	10

Figure 4 shows the CEAC for monotherapy in people with GTC seizures. The flatness of the curves reflect the wide confidence intervals for a number of ASMs considered in this analysis. No ASM has a greater than 25% probability of being the preferred option at a threshold of £20,000 per QALY. Sodium valproate which is the current first line ASMs in this group for people it is not contraindicated has a 10% probability of being the preferred intervention in this group although this is likely to be a function of the uncertainty around the other ASMs considered. Lacosamide, phenobarbital, topiramate and zonisamide never have greater than 5% probability of being the preferred option for all QALY thresholds between £0 and £100,000.

Figure 4: Cost effectiveness acceptability curves for monotherapy in people with focal seizures assuming £20,000 per QALY threshold



Add-on therapy for GTC seizures

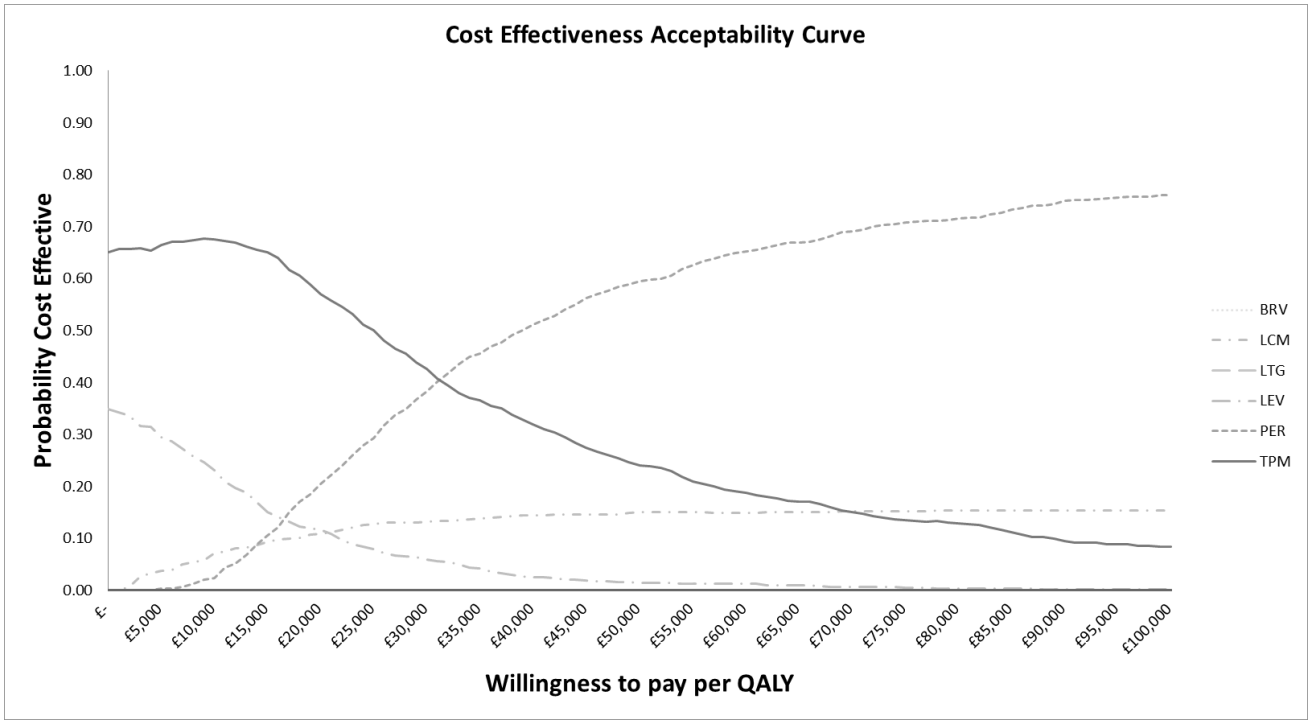
Table 18 shows the base-case results for ASMs considered by the economic model. Under the base-case assumptions levetiracetam is the most effective intervention and the second least costly. It is the preferred option when a £20,000 per QALY threshold is assumed.

Table 18: Base-case results for add-on therapy in people with GTC seizures assuming £20,000 per QALY threshold ordered by ranking (1 indicates preferred option)

	Total cost	Total QALY	Incremental Cost	Incremental QALY	INMB	Rank
Levetiracetam	£11,299	6.88	£150	0.06	£1,146	1
Topiramate	£11,180	6.85	£31	0.03	£584	2
Lamotrigine	£11,149	6.82	Reference	Reference	0	3
Lacosamide	£13,503	6.82	£2,354	-0.00	-£2,367	4
Perampanel	£13,787	6.83	£2,638	0.01	-£2,477	5
Brivaracetam	£14,145	6.83	£2,996	0.01	-£2,806	6

Figure 5 presents the CEAC for ASMs considered for add-on therapy in people with GTC seizures. At a threshold of £20,000 per QALY topiramate is the preferred option with a 57% probability of being the cost effective option. This is followed by perampanel (20.5%), levetiracetam (11.6%) and lacosamide (10.9%). Brivaracetam and lamotrigine had a zero probability of being the preferred option for all threshold values for cost per QALY.

Figure 5: Cost effectiveness acceptability curve for antiseizure medications considered as add-on therapy for people with GTC seizures



Sodium valproate

Sodium valproate was not the preferred choice in any of the economic analyses above and other options had very similar or greater probabilities of being the most cost effective intervention. Cost and clinically effective alternative choices were identified in all the economic models and additional analyses removing this ASM from consideration were not undertaken.

Discussion

The evidence in the economic model was strongest for ASMs for monotherapy in focal seizures and supported the clinical evidence in lamotrigine being the first line therapy in this group. The strength of results differed to Marson 2021 economic evaluation of lamotrigine, levetiracetam and zonisamide (discussed in detail in evidence review E) which found a greater than 99% probability of lamotrigine being the preferred option at a £20,000 per QALY threshold compared to 73% in this model. This model used results from the NMA reported by Nevitt 2021 (which included Marson 2021) which estimated much closer estimates for comparisons between lamotrigine and levetiracetam for inputs 'time to 12-month remission' and 'time to treatment withdrawal' than the SANAD II trial. When point estimates and confidence intervals from Marson 2021 were used in this model, lamotrigine also achieved probabilities greater than 99% for being the preferred option. The committee noted that there was a difference in outcomes from Nevitt 2021 (an NMA producing high quality estimates) and Marson 2021 (a recent, UK RCT with low risk of bias) and consequently the certainty around lamotrigine and levetiracetam being the preferred options. Importantly the probability of levetiracetam being the preferred option differed between Marson 2021 (less than 1% probability) compared to 27% in this model. The committee however considered that under both sets of results levetiracetam should remain a first line treatment given it is the second preferred option in both economic analyses and the shorter titration time may make it more appropriate for people where this would be of clinical benefit.

Evidence around add-on and GTC seizures was less certain given the wide confidence and credible intervals estimated from the various NMAs. For monotherapy in GTC seizures, no ASM was clearly demonstrated to be more cost effective than sodium valproate the current first line treatment for people for whom it is not contraindicated. Clinical evidence from the NMAs and QALY outcomes from the model also suggested sodium valproate as the most effective intervention. There were also no clear preferred therapies for ASMs for add-on in focal and GTC seizures although the evidence suggested a number of ASMs that may not be cost effective and therefore should not be considered as first line treatments.

Being conscious not to implicitly recommend a pathway of ASMs our model only looked at first line treatments. This may have led to small QALY values in the add-on treatments given that this group may rapidly move onto second and further lines of treatment. The results from this economic evaluation and the NMAs have been used to extrapolate to further lines of treatment in the forming of recommendations whilst being conscious that they did not cover population groups at this stage of the treatment pathway. This was done given the absence of evidence considering how the ordering of drugs in any treatment pathway impact upon

their relative effectiveness. The economic model avoided needing to make such assumptions given the use of these holding states.

The models showed a strong link between effectiveness and cost effectiveness. Very few of the ASMs considered are ‘on patent’ anymore and 6-monthly costs between them are relatively small. ASMs are likely to be cost effective if people continue on them and the time to treatment failure, either due to lack of efficacy or adverse events, is lengthened. It is important for efficient allocation of healthcare resources, that the individual treatment aims and outcomes of people are understood when planning treatment.

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1