# National Institute for Health and Care Excellence

Draft for consultation

# Epilepsies in children young people and adults

## [E] Monotherapy for generalised tonic-clonic and focal onset seizures

*Epilepsies in children, young people and adults*

*Evidence reviews underpinning recommendations 5.1.1 to 5.1.4 and 5.2.1 to 5.2.3*

*November 2021*

*Draft for consultation*

*These evidence reviews were developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists*

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ISBN:

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# Monotherapy for generalised tonic-clonic seizures and focal onset seizures

## Review question

This evidence report contains information on 2 reviews relating to monotherapy antiseizure medications (ASMs) for generalised tonic-clonic seizures and focal onset seizures (with or without evolution to bilateral tonic-clonic seizures).

- What ASMs are effective in the treatment of generalised tonic-clonic seizures?
- What ASMs are effective in the treatment of focal onset seizures?

### Introduction

Focal onset seizures are defined as those that originate within a network limited to one hemisphere. They may be discretely localised or more widely distributed. Clinical manifestations will depend on the area of the brain involved in the seizure, and the function it subserves, for example, seizures from the occipital lobe will have visual manifestations. Focal seizures are also defined as to whether awareness is retained; if awareness of the event is impaired for any portion of the seizure, then the seizure is classified as a focal seizure with impaired awareness whereas if the awareness is retained throughout it is a focal aware seizure. Such seizures may evolve during the clinical course of the seizure to tonic-clonic seizures – these are labelled as focal to bilateral tonic-clonic seizures (previously called secondarily generalised tonic seizures).

Generalised tonic-clonic seizures are defined as originating at some point within, and rapidly engaging, bilaterally distributed networks. Tonic means there is generalised stiffening, and clonic repetitive jerking. In a generalised tonic-clonic seizure there will be no warning, there will be sudden generalised stiffening of the body followed by repetitive jerking of all limbs. This seizure type is common amongst many different epilepsy types. The aim of this review is to determine which monotherapy antiseizure medications improve outcomes in people with epilepsy who have focal onset or generalised tonic-clonic seizures.

### Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

**Table 1: Summary of the protocol (PICO table)**

| | |
|---|---|
| **Population** | People with a new diagnosis of epilepsy with confirmed focal onset seizures or generalised tonic-clonic seizures with or without other generalised seizure types. |
| **Intervention** | The following ASMs will be considered:<br>• Carbamazepine<br>• Eslicarbazepine acetate<br>• Gabapentin<br>• Lacosamide<br>• Lamotrigine<br>• Levetiracetam<br>• Oxcarbazepine<br>• Phenobarbitone<br>• Phenytoin<br>• Sodium valproate<br>• Topiramate<br>• Zonisamide |
| **Comparison** | Any of the above |
| **Outcome** | **Critical**<br>• Time to treatment withdrawal (treatment failure)<br>**Important**<br>• Time to 12-month remission<br>• Time to 6-month remission<br>• Time to first seizure<br>• Incidence of adverse events |

*ASM: antiseizure medication*

For further details see the review protocol in appendix A.

## Methods and process

During the development of this guideline, a registered Cochrane protocol (Nolan 2014) was identified which matched the committee's intended PICO. The Cochrane review team completed their review (Nevitt 2021) during guideline development and presented their results to the committee which used them to make recommendations. 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) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence.

There were changes between the protocol (Nolan 2014) and the review update (Nevitt 2021), these are discussed in detail in the 'Differences between protocol and review' section in the forthcoming Cochrane review (Nevitt 2021). The main differences were the addition of

lacosamide and eslicarbazepine acetate to the interventions considered and a change in approach to judging the certainty of the evidence

Declarations of interest were recorded according to NICE's conflicts of interest policy.

## Clinical evidence

### Included studies

One Cochrane review and individual patient data (IPD) network meta-analysis including data from 89 randomised controlled trials (RCTs) involving 22,040 participants was considered in this report (Nevitt 2021). IPD was available for 39 RCTs recruiting 14,789 participants (67% of total participants, 43% of total RCTs). Fifty RCTs involving 7,251 participants (33% of total participants, 57% of total RCTs) did not provide IPD and aggregate data was used, where possible, in a sensitivity analysis.

The Cochrane review is summarised in Table 2 and the results of the review summarised in the 'Summary of the evidence' section of this report, however full details of the Cochrane review including methods, literature search strategy, study selection flow chart, forest plots and Confidence in Network Meta-Analysis (CINeMA) summary of findings tables are available in the forthcoming Cochrane review (Nevitt 2021). CINeMA was considered to have rigorous methodology to assess the confidence in the NMA outcomes and had many advantages over the GRADE approach including not being able to produce incoherent results (Welton 2020).

### Excluded studies

See the forthcoming Cochrane review (Nevitt 2021) for the list of excluded studies with reasons for their exclusions

## Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

**Table 2: Summary of included studies**

| Study | Population | Interventions | Comparator | Outcomes |
|---|---|---|---|---|
| Nevitt 2021<br><br>Systematic review and IPD NMA | Number of studies = 89<br><br>Number of participants = 22,040 | • Carbamazepine<br>• Eslicarbazepine acetate<br>• Gabapentin<br>• Lacosamide<br>• Lamotrigine<br>• Levetiracetam<br>• Oxcarbazepine<br>• Phenobarbitone<br>• Phenytoin<br>• Sodium valproate<br>• Topiramate<br>• Zonisamide | • Each Other | • Time to treatment withdrawal (treatment failure)<br>• Time to 12-month remission<br>• Time to 6-month remission<br>• Time to first seizure<br>• Incidence of adverse events |

*IPD: individual patient data; NMA: network meta-analysis*

See the forthcoming Cochrane review (Nevitt 2021) for full evidence tables.

## Summary of the evidence

In general, lamotrigine and levetiracetam were more effective than other ASMs for 'time to treatment failure' for people with focal seizures. Very few differences were shown for the other outcomes with carbamazepine more effective than gabapentin for 'time to 12-month remission' and sodium valproate for 'time to 6-month remission'. Older drugs in general (including phenobarbitone, oxcarbazepine and phenytoin) tended to be more effective for 'time to first seizure'.

For people with generalised tonic-clonic seizures no ASMs were more effective than sodium valproate for 'time to treatment failure' although there was no difference between sodium valproate, lamotrigine and levetiracetam.

The most commonly reported adverse events across all ASMs were drowsiness/fatigue, headache or migraine, gastrointestinal disturbances, dizziness/faintness and rash or skin disorders; however reporting of adverse events was inconsistent

## Quality assessment of studies included in the evidence review

See the forthcoming Cochrane review (Nevitt 2021) for CINeMA tables.

## Economic evidence

### Included studies

One study was included in this evidence review (Marson 2021).

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

### Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in supplementary material 2.

## Summary of studies included in the economic evidence review

One study was identified for inclusion in this evidence review (Marson 2021). This is an economic evaluation conducted alongside a RCT involving 990 people comparing ASMs for people with newly diagnosed focal epilepsy. The RCT was conducted at 65 centres across the UK between 2013 and 2017 with costs reported for the 2019/20 cost year and compared levetiracetam and zonisamide to lamotrigine. The study reports outcomes in terms of QALYs calculated from participant completed EuroQol-5 Dimension (EQ-5D) questionnaires scored using the UK tariff. The study took an NHS & personal social services (PSS) perspective.

The study shows lamotrigine to be cost saving and health improving in the base-case dominating the other options. At a £20,000 per QALY threshold lamotrigine has a greater than 99.9% probability of being the preferred option. This was the case in the adult subgroup analysis but not for people under the age of 16 (levetiracetam is cost saving and health improving; zonisamide less costly and less effective [ICER=£10,186 saved per QALY lost] when both compared to lamotrigine). From the sensitivity analyses lamotrigine remained dominant apart from when QALYs were valued using the epilepsy specific NEWQOL-6D (levetiracetam becomes the preferred option at a £20,000 per QALY threshold) and when complete cases only are used in the analysis where lamotrigine remains the preferred option but levetiracetam becomes cost saving.

The study is directly applicable to the review question being a recent UK RCT, taking a NHS&PSS perspective and reporting QALYs calculated from the EQ-5D using the UK

population tariff. The study closely followed the NICE reference case and is judged to only have minor limitations.

See the economic evidence tables in appendix H and economic evidence profiles in appendix I.

## Economic model

One economic model was created to answer the review questions for both monotherapy and add-on therapy. See supplementary material 4. A summary of the model for monotherapy for both focal and GTC seizures is summarised below.

The economic model was a Markov model based upon the outcomes from the forthcoming Cochrane review (Nevitt 2021). The model estimated the cost effectiveness of gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, sodium valproate and topiramate to a comparator of carbamazepine in people with newly diagnosed focal or GTC seizures. For focal seizure zonisamide was also considered.

*Overview of methods*

A decision-analytic model in the form of a Markov model based on the model from the previous NICE guideline was constructed to evaluate the relative cost effectiveness of different monotherapies for newly diagnosed epilepsy. Short term effectiveness data was almost entirely taken from the relevant NMAs with longer term data coming from UK observational studies. The model cohort was based on a recent UK RCT. Quality of life was based on an individual's seizure status but was estimated using the EQ-5D and UK population preference weights. The perspective of the analysis was that of NHS and Personal and Social Services (PSS). National UK unit costs were used with a cost year of 2019/2020. All costs and outcomes were discounted at a rate of 3.5% per annum.

*Results*

Monotherapy for focal seizures

In the base-case lamotrigine was estimated as both the least costly and the most effective (highest QALYs). 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.

From the probabilistic sensitivity analysis 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. All other ASMs had a less than 1% probability at all values.

Monotherapy for GTC seizures

Under the base-case assumptions lamotrigine is 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.

From the probabilistic sensitivity 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 effectiveness estimates of 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.

## Evidence statements

- There was evidence from 1 UK cost utility analysis alongside an RCT (n=990) showing lamotrigine to be cost saving and health improving in people with newly diagnosed focal epilepsy compared to levetiracetam and zonisamide. Lamotrigine had a greater than 99% probability of being cost effective at the NICE lower cost effectiveness threshold of £20,000 per QALY gained. This evidence was directly applicable to the NICE decision-making context and only had minor limitations.

- There was evidence from the guideline economic analysis showing that lamotrigine and levetiracetam were the preferred ASMs compared to carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, sodium valproate, topiramate and zonisamide in people with newly diagnosed focal epilepsy. From the probabilistic sensitivity analysis 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 most cost effective option. All other ASMs had a less than 1% probability. This evidence was directly applicable to the NICE decision-making context and only had minor limitations.

- There was evidence from the guideline economic analysis showing that lamotrigine was the preferred ASM followed by sodium valproate under the base-case assumptions in people with newly diagnosed epilepsy with GTC seizures. The analysis compared these ASMs to carbamazepine, gabapentin, lacosamide, levetiracetam, oxcarbazepine, phenobarbital, phenytoin and topiramate. However, during probabilistic sensitivity analysis no ASM had a probability greater than £20,000 per QALY of being the cost effective option. This evidence was directly applicable to the NICE decision-making context and only had minor limitations.

## The committee's discussion of the evidence

### Interpreting the evidence

#### *The outcomes that matter most*

Time to treatment withdrawal (treatment failure) was identified as a critical outcome to evaluate monotherapy for people with focal onset and generalised tonic-clonic seizures. This was considered an outcome that combined both the effectiveness of the intervention as well as tolerability as it will capture withdrawal for both lack of efficacy and for adverse events. It is an outcome which is dependent on choices made by the person using the treatment as definitions of treatment failure, especially in regards to adverse events, will differ widely within this population. For example, some people will be willing to have more severe adverse events than others in return for no or fewer seizures. Additionally, it is also the main outcome recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (ILAE) for evaluating monotherapy in this population. This outcome was calculated in three ways: time to 'treatment failure for any reason'; 'time to treatment withdrawal due to lack of efficacy' and 'time to treatment withdrawal due to adverse events'.

Important outcomes were time to 6-month and 12-month remission, time to first seizure and incidence of adverse events as these outcomes cover both treatment effectiveness (reducing seizures) or tolerability which are important in treatment decisions.

***The quality of the evidence***

The quality of the evidence for this review was assessed using the Confidence in Network-Meta-Analysis (CINeMA) approach. The certainty of outcomes were downgraded based on within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence (inconsistency).

For focal seizures the NMA gave high certainty evidence for time to treatment withdrawal for all interventions considered. The same was also the case for the 'time to 6-month remission' and 'time to 12-month remission outcomes'. For 'time to first seizure' the evidence was judged to be moderate to high.

For generalised tonic-clonic seizures where the evidence was more limited the certainty of the critical outcome of time to treatment withdrawal was moderate for all interventions. Certainty was also deemed moderate for the 'time to remission' and 'time to first seizure outcomes'.

There was no indication of important inconsistency (incoherence) between the NMA results and the direct evidence. The quality of the evidence was not downgraded for inconsistency for any outcome assessed in the NMA.No formal assessment of quality was undertaken for the incidence of adverse events which were reported narratively. A number of weaknesses were identified for this outcome in particular differences in reporting and definitions of adverse events between different studies. It is important to note these weaknesses are particularly important when making any comparison between therapies based on these incidences.

***Benefits and harms***

The common comparators considered by the committee for this analysis were carbamazepine and lamotrigine for focal seizures and sodium valproate for generalised tonic-clonic seizures. This was because they were previously recommended in NICE guidance as first line monotherapy for this population.

The committee agreed, based on their experience, that prior to starting antiseizure medication there should be a discussion with the person, their family and carers, if appropriate, about an individualised antiseizure medication strategy according to their seizure type, treatment goals and the preferences of the person and their family or carers as appropriate. Treatment plans should be regularly reassessed, and its agreement should include a transparent explanation of the epilepsy type, severity and duration of adverse effects that the person with epilepsy may experience and how should these be managed. The person, their family and carers, should also be made aware that they should be taking the least amount of medicines as possible to be effective due to the side effects of polypharmacy.

**Monotherapy for focal seizures**

For focal seizures there was high quality evidence that lamotrigine and levetiracetam were most effective in increasing the time to treatment withdrawal and in particular time to withdrawal due to adverse events, suggesting they were better tolerated and more effective than other options. Other newer drugs like zonisamide and lacosamide had a point estimate indicating they were more effective than carbamazepine for time to treatment withdrawal but their 95% confidence intervals passed the line of no effect.

The evidence showed no difference in the 'time to 6-month remission' and 'time to 12-month remission' and found gabapentin, levetiracetam, lamotrigine, sodium valproate and zonisamide all had worse outcomes than carbamazepine for time to first seizure. Older drugs in general (including phenobarbitone, phenytoin and oxcarbazepine) were effective for this outcome. The committee highlighted that time to first seizure was likely to be captured in the time to treatment withdrawal outcome especially where the first seizure led to withdrawal.

The committee therefore gave greater weight time to treatment withdrawal outcome when results were contradictory between outcomes as people will have different priorities in terms of their treatment as discussed in the 'The outcomes that matter most' section.

Overall the results of the NMAs suggested that lamotrigine and levetiracetam were the most effective first line monotherapy treatments for focal seizures. Carbamazepine, oxcarbazepine and zonisamide appeared to be the next most effective. The precise choice between these options will be dependent on the preferences and the particular circumstances of the person receiving treatment.

**Monotherapy for generalised tonic-clonic seizures**

For generalised tonic-clonic seizures, sodium valproate was more effective than carbamazepine, lacosamide, phenobarbital, and topiramate. There was no evidence of sodium valproate being more effective than any other intervention for 'time to 6-month remission', 'time to 12-month remission' or time to first seizure.

The committee acknowledged the risks associated with sodium valproate if prescribed to women and girls who are able to have children and, as a result, recommended that lamotrigine or levetiracetam should be used as first-line treatment in this population. Lamotrigine and levetiracetam were the ASMs that appeared to be closest in efficacy to sodium valproate for the outcome of time to treatment withdrawal for any reason with comparative hazard ratios just above 1 and relatively narrow confidence intervals. Nonetheless, the committee agreed that in some cases, for example, if women have tried other medication and it has not worked, sodium valproate should be available as an option. The committee agreed that sodium valproate should only be prescribed after a full and clear discussion with the girl or woman, ensuring she understands all the potential risks and benefits. If sodium valproate is prescribed, clinicians must follow MHRA guidance, which includes enrolment in a pregnancy prevention programme, if appropriate.

Where sodium valproate was unsuccessful in boys and men; girls under 10 years old or women who are unable to have children, lamotrigine and levetiracetam should be available as an option (as above) as these medications were closest in effectiveness to sodium valproate.

The committee discussed the evidence on adverse events and their importance in making choices about medication. Adverse events were reported inconsistently in the identified evidence. Studies often had differing included adverse events, level of severity or whether it was reported as a percentage of participants or total incidents of adverse events. The committee also agreed that, for most ASMs, adverse events could be managed by careful titration and dosage changes. Whilst acknowledging that adverse events were an important component of deciding on the most appropriate therapy, the impact of different portfolios of adverse events were likely to impact on individuals differently especially in terms of whether they would lead to treatment withdrawal. They noted that it is therefore important to discuss the possibility of adverse events when considering the best treatment option.

**Cost effectiveness and resource use**

The committee acknowledged high quality evidence from a bespoke economic model for this topic and also a recent economic evaluation conducted alongside a UK RCT evaluating the cost effectiveness of interventions for this topic (Marson 2021).

Marson 2021 compared levetiracetam and zonisamide to lamotrigine in people with newly diagnosed focal epilepsy. The economic evaluation was conducted alongside the SANAD II trial of 990 people. The study was considered directly applicable to the review question and had minor limitations and closely followed the NICE reference case. The study found lamotrigine to have an almost certain probability (>99.9%) of being the most cost effective option and was cost saving and health improving in all but a small number of sensitivity

analyses. The study authors concluded that only lamotrigine should be routinely used first line in this patient group.

The bespoke economic model, based on the accompanying NMA and considering all ASMs of interest for this review question, estimated that for people with newly diagnosed focal seizures the most cost effective option was again lamotrigine although the difference in probability of being the preferred option compared to levetiracetam was less (73% versus 27%). Zonisamide was the intervention with the third highest probability of being cost effective. This conclusion was again robust to sensitivity analysis.

The committee acknowledged the difference in the strength of conclusions between the two pieces of evidence. It was identified that a key driver of the results of the bespoke model was time to treatment withdrawal. For this outcome, in Marson 2021 lamotrigine was more effective than levetiracetam whilst there was no difference in the Cochrane NMA. When the values from Marson 2021 for time to treatment withdrawal were used in the bespoke economic model the results and sensitivity analysis were concordant.

Only the bespoke economic model considered cost effectiveness for generalised tonic-clonic seizures. In this analysis sodium valproate was the less costly and most effective treatment and this conclusion was robust to sensitivity analysis.

The committee noted that the majority of costs were associated with subsequent treatment either through needing to change treatment following withdrawal or through hospitalisation. Only a small proportion of costs were as a result of treatment itself. This highlighted the importance of considering peoples' preferences, especially in regards to adverse events where the person is largely in control of the outcome, as reducing treatment failure was likely to be cost effective. This also emphasised that where an ASM was the preferred choice in that the person was less likely to withdraw from it, it was also likely to be the less costly and more cost effective approach.

**Other factors the committee took into account**

The committee highlighted the discordance between the Cochrane NMA and the results of the most applicable (recent multi-centre UK) RCT and economic evaluation to the review question (Marson 2021), which assessed the effectiveness and cost effectiveness of levetiracetam, zonisamide and lamotrigine for newly diagnosed focal epilepsy. In particular differences in results for time to treatment withdrawal consequently leading to differences in cost effectiveness outcomes for people with focal seizures. Marson 2021 had lamotrigine as the preferred first line treatment for patients with focal epilepsy but the Cochrane NMA and bespoke economic model had little difference between lamotrigine and levetiracetam.

The committee acknowledged that the NMA and individual RCT had different perspectives and that the NMA included outcome data from Marson 2021 as well other direct and indirect evidence which explains any differences between the two. Direct evidence (2 studies including Marson 2021) in the NMA accounted for only 23.7% of the total evidence in comparing lamotrigine and levetiracetam for time to treatment failure highlighting the large additional evidence provided from indirect comparisons. Whilst the evidence hierarchy and committee gave greater weight to a NMA, especially as the results were of high certainty, given the direct applicability of the individual RCT and the accompanying economic evaluation the committee also considered it in isolation.

The committee also discussed the need for a shorter titration period when an effective dose is needed to be achieved sooner. Levetiracetam has a significantly shorter titration time than lamotrigine which would make it a more preferable approach in such circumstances.

Given the uncertainty about the best evidence for the critical outcome of time to treatment withdrawal and the issues about time to titration the committee considered it reasonable to

have both lamotrigine and levetiracetam as first line treatments for newly diagnosed focal seizures.

The committee recommended multiple potential drugs at each line of treatment for focal seizures. When deciding upon the best treatment alongside the person it should be considered and explained that some drugs which are generally poorly tolerated but are effective may require more careful titration and monitoring than alternatives. Contraindications for the drugs should also be carefully considered in decision making for example when considering treatment for people with depression.

The committee noted that, in line with the BNF carbamazepine and oxcarbazepine should not be offered to people of European or Japanese family background because of the risks of serious complications, unless the person meets the pre-treatment screening advice for people from these groups. In addition, in line with the MHRA, the committee emphasised that long-term treatment with carbamazepine and sodium valproate can cause decreased bone mineral density and increased risk of osteomalacia. The committee noted that appropriate supplementation should be considered for those at risk.

## Recommendations supported by this evidence review

This evidence review supports recommendations 5.1.1 to 5.1.4 and 5.2.1 to 5.2.3.

# References

## Clinical evidence

### Nevitt 2021

Nevitt SJ, Sudell M, Tudur Smith C, Marson AG, Cividini S. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD011412. DOI:10.1002/14651858.CD011412.pub4. See abstract available during consultation for details of the forthcoming Cochrane review.

### Nolan 2014

Nolan SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network metaanalysis. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD011412. DOI: 10.1002/14651858.CD011412. Available in https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011412/full

## Economic evidence

### Marson 2021

Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, Tudur-Smith C, Plumpton C, Hughes DA, Williamson P, Baker GA. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. The Lancet. 2021 Apr 10;397(10282):1363-74.

## Other references

### Welton 2020

Welton, NJ, Phillippo, D, Owen, R, Jones, H, Dias, S, Bujkiewicz, S, Ades, AE & Abrams, KR DSU Report. CHTE2020 Sources and Synthesis of Evidence; Update to Evidence Synthesis Methods. March 2020 http://nicedsu.org.uk/wp-content/uploads/2020/11/CHTE-2020_final_20April2020_final.pdf

# Appendices

## Appendix A – Review protocol

**Review protocol for review questions:**

**What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?**

**What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?**

See Cochrane review protocol: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011412/full

# Appendix B – Literature search strategies

## Literature search strategies for review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

See abstract available during consultation for details of the forthcoming Cochrane review (Nevitt 2021).

# Appendix C – Clinical evidence study selection

**Study selection for review questions:**

**What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?**

**What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?**

See abstract available during consultation for details of the forthcoming Cochrane review (Nevitt 2021).

# Appendix D – Clinical evidence tables

## Evidence tables for review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

See abstract available during consultation for details of the forthcoming Cochrane review (Nevitt 2021)..

# Appendix E – Forest plots

## Forest plots for review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

See abstract available during consultation for details of the forthcoming Cochrane review (Nevitt 2021).

# Appendix F – GRADE tables

## GRADE summary of findings tables for review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

See abstract available during consultation for details of the forthcoming Cochrane review (Nevitt 2021).

# Appendix G – Economic evidence study selection

## Economic evidence study selection for review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

A single economic search was undertaken for all topics included in the scope of this guideline. See Supplement 2 for further information.

# 1 Appendix H – Economic evidence tables

## 2 Economic evidence tables for review questions:

## 3 What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

## 4 What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

5 **Table 3: Economic evidence tables for monotherapy for generalised tonic-clonic and focal onset seizures**

| Study country and type | Intervention and comparator | Study population, design and data sources | Costs and outcomes (descriptions and values) | Results | Comments |
|---|---|---|---|---|---|
| **Author and year:** Marson 2021<br>**Country**: UK<br><br>**Type of economic analysis**: Cost utility<br><br>**Source of funding:** National Institute for Health Research Health Technology Assessment programme | **Intervention in detail:** Levetiracetam (LEV) Zonisamide (ZNS)<br>**Comparator in detail:** Lamotrigine (LTG) | **Population characteristics:** People over the age of 5 with a diagnosis of focal epilepsy, had a history of two unprovoked seizures requiring antiseizure medication. Participants had to have never been treated with antiseizure medicine before apart from for emergencies in the previous two weeks.<br>Mean age: 39.3 years<br>Female: 43%<br>Learning disability: 5%<br>Median days since first seizure: 327<br>Median total number seizures reported: 6 | **Mean cost per participant (95%CI):**<br>Intervention:<br>LEV: £5104 (4,450-6,141)<br>ZNS: £5400 (4,659-6,770)<br>Control:<br>LTG :£4,042 (3,626-4,983)<br>Difference:<br>Vs LEV: £1,062<br>Vs ZNS: £1,358<br><br>**Primary measure of outcome:** QALY measured using the EQ-5D-3L with UK tariff scores<br><br>**Mean outcome per participant (95%CI):** | **ICERs:** LTG dominant (cost saving and health improving) compared to ZNS and LEV<br>**Probability of being cost effective**: LEV/ZNS<0.01% probability of being cost effective at a £20,000 per QALY threshold<br>**Subgroup analysis**:<br>*≥16 years of age:* LTG cost saving and health improving compared to both LEV and ZNS<br>*<16 years of age:* LEV cost saving and health improving compared to LTG. ZNS less costly and less effective than LTG (ICER=£10,186 per QALY lost) | **Currency**: Pound Sterling<br><br>**Cost year**: 2019/20<br><br>**Time horizon**: 24 months (48 in sensitivity analysis)<br><br>**Discounting**: 3.5% for both costs and outcomes<br><br>**Applicability**: Directly applicable<br><br>**Limitations**: Minor limitations<br><br>Other comments: |

| Study country and type | Intervention and comparator | Study population, design and data sources | Costs and outcomes (descriptions and values) | Results | Comments |
|---|---|---|---|---|---|
| | | Median days since most recent seizure: 13<br>**Modelling approach:** Economic evaluation conducted alongside an RCT<br>**Source of baseline data:** SANAD II RCT discussed in detail in the accompanying Cochrane review. SANAD II was a UK RCT involving 990 participants in 65 centres between 2013 and 2017. The trial compared levetiracetam and zonisamide to lamotrigine in people with newly diagnosed focal epilepsy.<br>**Source of effectiveness data:** As above<br>**Source of cost data**: Resource use in secondary care was collected using routine hospital episode statistics and case report form records<br>**Source of unit cost data:** | Intervention:<br>LEV:1.474(1.393-1.523)<br>ZNS:1.502(1.418-1.566)<br>Control:<br>LTG:1.605(1.547-1.651)<br>Difference:<br>Vs LEV: -0.131<br>Vs ZNS: -0.103 | **Sensitivity analysis:**<br>QoL measured using EQ-VAS and the NEWQOL-6D<br><br>Time horizon increased from 24 to 48 months<br><br>Discount rate of 0% and 6% for QALYs and costs<br><br>Unadjusted analysis (mean results used no regression)<br><br>Complete cases only<br><br>Per protocol analysis<br><br>Treating blank values as missing rather than zero in costs<br><br>LTG remains cost saving and health improving other than for when NEWQOL-6D is used (LEV is preferred option at a £20,000 per QALY threshold) and for the complete case analysis (LEV becomes cost saving but LTG | |

| Study country and type | Intervention and comparator | Study population, design and data sources | Costs and outcomes (descriptions and values) | Results | Comments |
|---|---|---|---|---|---|
| | | Care: NHS reference costs 2017-18 & NHS National Tariff 2017-18.<br>Drug costs: British National Formulary & prescription costs analysis 2018 | | still preferred option at a £20,000 per QALY threshold) | |

*EQ-5D: EuroQOL-5 dimension LEV: Levetiracetam, LTG: Lamotrigine, NEWQOL-6D: Quality of life in newly diagnosed epilepsy- 6 dimension PSA: Probabilistic sensitivity analysis QALY: Quality adjusted life-year, QoL: Quality of Life, RCT: Randomised controlled trial ZNS: Zonisamide*

# Appendix I – Economic evidence profiles

## Economic evidence profiles for review questions:

## What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

## What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

**Table 4: Economic evidence profiles for monotherapy for generalised tonic-clonic and focal onset seizures**

| Study and country | Limitations | Applicability | Other comments | Incremental costs | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|---|---|
| **Author and year:** Marson 2021<br>**Country**: UK | Minor limitations[1] | Directly applicable[2] | **Type of economic analysis:** Cost utility<br>**Time horizon**: Up to 48 months<br>**Primary measure of outcome:** QALY | LTG Vs LEV: £1,062<br>LTG Vs ZNS: £1,358 | LTG Vs LEV: -0.131 QALYs<br>LTG Vs ZNS: -0.103 | LTG cost saving and health improving | **Deterministic sensitivity analyses**: LTG the preferred option in all analyses except for the <16 years of age subgroup and when |

| Study and country | Limitations | Applicability | Other comments | Incremental costs | Incremental effects | ICER | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | | | | NEWQOL-6D was used to measure quality of life.<br>**PSA**: >99.9% probability that LTG is the preferred intervention |

*LEV: Levetiracetam, LTG: Lamotrigine, NEWQOL-6D: Quality of life in newly diagnosed epilepsy- 6 dimension PSA: Probabilistic sensitivity analysis QALY: Quality adjusted life-year, ZNS: Zonisamide*

1. *No major limitations identified*
2. *The study is a recent UK study in the applicable patient group closely following the NICE reference case*

# Appendix J – Economic analysis

## Economic evidence analysis for review questions: review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

One economic model was created to answer the review questions for both monotherapy and add-on therapy. See supplementary material 3.

# Appendix K – Excluded studies

## Excluded studies for review question review questions:

### What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?

### What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?

See abstract available during consultation for details of the forthcoming Cochrane review (Nevitt 2021).

## Economic studies

A single economic search was undertaken for all topics included in the scope of this guideline. No economic studies were identified which were applicable to this review question. See supplementary material 2 for details.

# Appendix L – Research recommendations

**Research recommendations for review questions:**

**What antiseizure medicines (ASMs) are effective in the treatment of generalised tonic-clonic seizures?**

**What ASMs (individually or in combination) are effective in the treatment of focal onset seizures?**

No research recommendations were made for this review question.