

## Epilepsies in children, young people and adults

### [G] Effectiveness of antiseizure therapies in the treatment of absence seizures

*NICE guideline NG217*

*Evidence reviews underpinning recommendations 5.3.1 to 5.3.6 in the NICE guideline*

*April 2022*

*Final*

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



In January 2025, the [section on the Committee's discussion of the evidence](#) in this evidence review was updated following changes to recommendations that were made by a working group after Medicines and Healthcare products Regulatory Agency (MHRA) Drug Safety Updates. The following MHRA updates were considered:

- [guidance on the use of valproate](#),
- [valproate use in people younger than 55 years](#),
- [valproate use in women and girls](#), and
- [valproate use in men](#).

Additionally, the working group also took into account the impact of the [MHRA drug safety update concerning the use of topiramate](#).

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# Effectiveness of antiseizure therapies in the treatment of absence seizures

## Review question

What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?

## Introduction

Absence seizures are a form of generalised epileptic seizure, characterised by behavioural arrest with lack of awareness. Typical absences are sudden in onset, last a short duration of time (5 to 10 seconds), and stop abruptly. They are associated with a characteristic electroencephalogram (EEG) pattern of regular 3 to 4 per second spike and wave activity. They are characteristic of several epilepsy syndromes: in children, childhood absence epilepsy where they occur multiple times per day, and later onset juvenile absence epilepsy where they occur less frequently. In adults they may be a feature of juvenile myoclonic epilepsy. They may be seen in other epilepsy syndromes with other seizure types. Atypical absence seizures may be less obvious, last longer, and be associated with more variable patterns on EEG. They typically do not occur in isolation, but with other seizure types as part of more complex epilepsies. The aim of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have absence seizures.

## Summary of the protocol

Please 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)**

<b>Population</b>	People with confirmed epilepsy with absence seizures
<b>Intervention</b>	<p>The following treatments and their combinations will be considered:</p> <ul style="list-style-type: none"> <li>• Acetazolamide</li> <li>• Clobazam</li> <li>• Clonazepam</li> <li>• Ethosuximide</li> <li>• Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures)</li> <li>• Lamotrigine</li> <li>• Levetiracetam</li> <li>• Methsuximide/mesuximide</li> <li>• Sodium Valproate</li> <li>• Topiramate</li> <li>• Zonisamide</li> </ul>
<b>Comparison</b>	<ul style="list-style-type: none"> <li>• Any of the above and their combinations</li> <li>• No treatment/placebo</li> </ul>

<b>Outcomes</b>	<p><b>Critical</b></p> <ul style="list-style-type: none"> <li>• Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment).</li> <li>• 24 hour EEG seizure freedom</li> <li>• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)</li> <li>• Adverse events, as assessed by: <ul style="list-style-type: none"> <li>◦ % of patients with reported side effects (trial defined adverse and serious adverse effects)</li> <li>◦ treatment cessation due to adverse event (dichotomous outcome only)</li> <li>◦ mortality</li> </ul> </li> </ul> <p><b>Important</b></p> <ul style="list-style-type: none"> <li>• Neuropsychological changes (IQ testing, or other validated tools)</li> <li>• Health-related quality of life (validated tools only)</li> </ul>
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EEG: electroencephalogram; IQ: intelligence quotient

For further details see the review protocol in appendix A.

## Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](#). Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

## Clinical evidence

### Included studies

Seven studies (reporting on six randomised controlled trials [RCTs]) were identified for inclusion in this review. Four studies reporting on 3 RCTs compared ethosuximide to sodium valproate (Callaghan 1982, Glauser 2010, Glauser 2013, Sato 1982); 3 studies reporting on 2 RCTs compared lamotrigine to sodium valproate (Coppola 2004, Glauser 2010, Glauser 2013); 1 RCT compared levetiracetam to placebo (Fattore 2011); 1 RCT compared lamotrigine to placebo (Frank 1999) and 2 studies reporting on 1 RCT compared ethosuximide to lamotrigine (Glauser 2010, Glauser 2013).

The included studies are summarised in Table 2 to Table 6.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

### Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

## Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2 to Table 6.

**Table 2: Summary of included studies. Comparison 1: ethosuximide versus sodium valproate**

Study	Population	Intervention	Comparison	Outcomes
Callaghan 1982  RCT  Ireland	N = 28 people with typical absence seizures  Mean age: ESM: 8 years (range 4 to 14)  VPA: 9 years (range 5 to 15)	<u>Ethosuximide</u> n=14  Initial dose of 250mg/day  Dose increased by 250mg/day to a maximum 1500mg/day as required	<u>Sodium valproate</u> n=14  Initial dose of 400mg/day  Dose increased by 200mg/day to a maximum of 2400mg/day	<ul style="list-style-type: none"> <li>• Seizure remission (complete, partial, no remission)</li> <li>• EEG response - normal</li> <li>• Adverse events - any</li> </ul>
Glauser 2010  Multi-centre RCT  US  Reports 20 week follow-up data	N = 453 people with absence seizures ( <i>three-arm trial</i> )  Mean age: not provided	<u>Ethosuximide</u> n=156  250mg capsules or 250 mg per 5 ml of syrup.  Highest allowable daily dose of 60mg/kg (to a maximum of 2000mg).	<u>Sodium valproate</u> n=148  25mg capsules or 125mg dose of sprinkles.  Highest allowable daily dose of 60mg/kg (to a maximum of 3000mg).	<ul style="list-style-type: none"> <li>• Freedom from treatment failure</li> <li>• Adverse events (serious adverse events; intolerable adverse effects)</li> <li>• Study drug discontinued</li> <li>• Withdrawal from study</li> <li>• Attentional dysfunction (proxy outcome for neuropsychological changes)</li> </ul>
Glauser 2013  See Glauser 2010  Reports 12 month follow-up data	See Glauser 2010	See Glauser 2010	See Glauser 2010	<ul style="list-style-type: none"> <li>• Freedom from treatment failure</li> <li>• Adverse events (serious adverse events; intolerable adverse effects)</li> <li>• Attentional dysfunction (proxy outcome for neuropsychological changes)</li> <li>• Withdrawal from study</li> </ul>
Sato 1982  Cross-over RCT; only	N = 45 people with absence seizures	<u>Ethosuximide plus placebo</u>	<u>Sodium valproate plus placebo</u>	<ul style="list-style-type: none"> <li>• Seizure freedom</li> </ul>



Study	Population	Intervention	Comparison	Outcomes
period 1 was reported and synthesised	(treatment naive n=16; refractory n=29)	n=23 (treatment naive n=9, refractory n=14)	n=22 (treatment naive n=7, refractory n=15)	
US	First line therapy (naive) and add-on therapy (refractory)	Dosing schedule group 1: Daily dose of 250-1500mg  Dosing schedule group 2: Daily dose of 250 to 1500mg	Dosing schedule group 1: Initial dose of 15-20mg/kg for 5 days, increased to maximum of 30mg/kg if 12 hour telemetered EEG still showed generalised spike-wave discharges.  Dosing schedule group 2: Initial dose of 12.5 to 20mg/kg, with a dosage increase every 2 days for 2 weeks up to a maximum daily dosage of 60mg/kg.	
	Mean age: 11.7 years (range 4 to 18)	Naive patients with 100% seizure control and refractory patients with at least 80% control during the first 6 weeks of treatment were not crossed over to alternative treatment because of ethical concerns regarding withdrawal of effective medications. Instead, they were maintained on the same drug for 3 months in a double-blind manner.  Only those patients who did not 'respond' as described above; or experienced serious adverse reactions to the first therapy were crossed over to the alternative treatment.	Naive patients with 100% seizure control and refractory patients with at least 80% control during the first 6 weeks of treatment were not crossed over to alternative treatment because of ethical concerns regarding withdrawal of effective medications. Instead, they were maintained on the same drug for 3 months in a double-blind manner.  Only those patients who did not 'respond' as described above; or experienced serious adverse reactions to the first therapy were crossed over to the alternative treatment.	

EEG: electroencephalogram; ESM: ethosuximide; RCT: randomised controlled trial; VPA: sodium valproate

**Table 3: Summary of included studies. Comparison 2: lamotrigine versus sodium valproate**

Study	Population	Intervention	Comparison	Outcomes
Coppola 2004  RCT  Italy	N = 38 people with absence seizures  Mean age: VPA: 7.5 years (range 3 to 13)  LTG: 7.5 years (range 4 to 12)	<u>Lamotrigine</u> n=19  Initial dose of 0.5mg/kg/day for 2 weeks, followed by 1.0mg/kg/day for 2 weeks. Doses then increased by 1mg/kg/day every 5 days until seizures were under control	<u>Sodium valproate</u> n=19  Initial dose of 10mg/kg/day and increased by 5mg/kg/day every 3 days until seizures were under control	<ul style="list-style-type: none"> <li>• Seizure freedom (1, 3 and 12 months)</li> <li>• Adverse events - any</li> <li>• Treatment cessation due to adverse events</li> <li>• Withdrawal from study</li> </ul>
Glauser 2010  Multi-centre RCT  US  Reports 20 week follow-up data	N = 453 people with absence seizures ( <i>three-arm trial</i> )  Mean age: not provided	<u>Lamotrigine</u> n=149  5mg and 25mg chewable tablets. Maximum dose of 12 mg/kg up to a maximum of 600mg/day	<u>Sodium valproate</u> n=148  25mg capsules or 125mg dose of sprinkles.  Highest allowable daily dose of 60mg/kg (to a maximum of 3000mg).	<ul style="list-style-type: none"> <li>• Freedom from treatment failure</li> <li>• Adverse events (serious adverse events; intolerable adverse effects)</li> <li>• Study drug discontinued</li> <li>• Withdrawal from study</li> <li>• Attentional dysfunction (proxy outcome for neuropsychological changes)</li> </ul>
Glauser 2013  See Glauser 2010  Reports 12 month follow-up data	See Glauser 2010	See Glauser 2010	See Glauser 2010	<ul style="list-style-type: none"> <li>• Freedom from treatment failure</li> <li>• Adverse events (serious adverse events; intolerable adverse effects)</li> <li>• Attentional dysfunction (proxy outcome for neuropsychological changes)</li> <li>• Withdrawal from study</li> </ul>

LTG: lamotrigine; RCT: randomised controlled trial; VPA: sodium valproate

**Table 4: Summary of included studies. Comparison 3: levetiracetam versus placebo**

Study	Population	Intervention	Comparison	Outcomes
Fattore 2011  Multi-centre RCT	N = 59 people with absence seizures	<u>Levetiracetam</u> n=38  Initial dosage of 10mg/kg/day for 3	<u>Placebo</u> n=21	<ul style="list-style-type: none"> <li>• Responder status (free from clinical seizures on days 13 and 14; and</li> </ul>

Study	Population	Intervention	Comparison	Outcomes
Italy	Mean age LEV: 8.7 years (range 4.9 to 13)  Placebo: 7.9 years (range 4 to 15)	days followed by 15mg/kg/day for 4 days. If accepted and seizures contin- ued dosage in- creased to 20mg/kg/day and maintained until day 14	Equivalent tablet or liquid formulation given.	<ul style="list-style-type: none"> <li>free from EEG sei- zures on day 14)</li> <li>• Patients free from clinical and EEG seizures (days 4 – 7; days 11 - 14)</li> <li>• 50% reduction vs baseline in total duration of EEG seizures on day 14</li> <li>• Adverse events (any; serious; thought to be re- lated to treatment; leading to discon- tinuation)</li> </ul>

EEG: electroencephalogram; LEV: levetiracetam; RCT: randomised controlled trial

**Table 5: Summary of included studies. Comparison 4: lamotrigine versus placebo**

Study	Population	Intervention	Comparison	Outcomes
Frank 1999  RCT  US	<p>N=45 people with absence seizures re- cruited; n=29 randomised after dose escalation and took part in dose esca- lation phase. n=28 people with absence seizures ana- lysed (1 pa- tient in lamotrigine group with- drew con- sent).</p> <p>Mean age: LTG: 6.9 years (SD 2.3)</p> <p>Placebo: 8.8 years (SD 3.1)</p>	<p><u>Lamotrigine</u> n=14</p> <p>Initial dose of 0.5mg/kg/day for 2 weeks, followed by 1mg/kg/day for 2 weeks. Following increases by 1mg/kg/ day ac- cording to re- sponse, maximum dose of 15mg/kg/day.</p> <p>Chewable 5mg, 25 and 100mg tables</p>	<p><u>Placebo</u> n=14</p> <p>Patients who became seizure free after dose escalation phase were random- ised to LTG or pla- cebo – LTG was ta- pered over 2 weeks. Placebo lasted 4 weeks</p>	<ul style="list-style-type: none"> <li>• Remained seizure free at end of pla- cebo controlled phase</li> <li>• Adverse events - leading to with- drawal from study</li> </ul>

EEG: electroencephalogram; LTG: lamotrigine; RCT: randomised controlled trial; SD: standard deviation

**Table 6: Summary of included studies. Comparison 5: ethosuximide versus lamotrigine**

Study	Population	Intervention	Comparison	Outcomes
Glauser 2010  Multi-centre RCT  US  Reports 20 week follow-up data	N = 453 people with absence seizures ( <i>three-arm trial</i> )  Mean age: not provided	<u>Ethosuximide</u> n=156  250mg capsules or 250 mg per 5 ml of syrup.  Highest allowable daily dose of 60mg/kg (to a maximum of 2000mg).	<u>Lamotrigine</u> n=149  5mg and 25mg chewable tablets or 25mg tablets.  Highest allowable daily dose of 12mg/kg (to a maximum of 600 mg).	<ul style="list-style-type: none"> <li>• Freedom from treatment failure</li> <li>• Adverse events (serious adverse events; intolerable adverse effects)</li> <li>• Study drug discontinued</li> <li>• Withdrawal from study</li> <li>• Attentional dysfunction (proxy outcome for neuropsychological changes)</li> </ul>
Glauser 2013  See Glauser 2010  Reports 12 month follow-up data	See Glauser 2010	See Glauser 2010	See Glauser 2010	<ul style="list-style-type: none"> <li>• Freedom from treatment failure</li> <li>• Adverse events (serious adverse events; intolerable adverse effects)</li> <li>• Attentional dysfunction (proxy outcome for neuropsychological changes)</li> <li>• Withdrawal from study</li> </ul>

RCT: randomised controlled trial

See the full evidence tables in appendix D and forest plots in appendix E.

## Summary of the evidence

Across all the comparisons identified in this review, the majority identified a clinically important difference in at least one of the outcomes reported. For example, the comparison lamotrigine versus sodium valproate showed a clinically important benefit in relation to the number of people who were seizure free at 1 month and at 3 months and received sodium valproate, and in relation to scores on the Conners' Continuous Performance Test, which favoured those who received lamotrigine. When compared to placebo, those who received levetiracetam showed an improved EEG response on days 11 to 14. When compared to placebo, lamotrigine showed a clinically important benefit in relation to the number of patients who were seizure free at 4 weeks. The comparison ethosuximide versus lamotrigine showed a clinically important benefit in relation to the number of patients who were seizure free at 16 or 20 weeks or at 12 months for those who received ethosuximide.

There is a high level of uncertainty in the data presented and these findings should not therefore be considered to be definitive results. This uncertainty comes from the quality of the evidence, with the majority of results being assessed as very low, low or moderate quality. Outcomes were most often downgraded due to risk of bias, with limited information provided regarding randomisation and allocation concealment. Outcomes were also downgraded due to

imprecision and the majority of studies only included a small number of participants; further limiting confidence in the data.

A small number of outcomes were rated as being of high quality, indicating that the true effect for these treatments are similar to those calculated in this review. This was the case for the comparison of ethosuximide versus sodium valproate, for which there was high quality evidence that sodium valproate was more effective than ethosuximide in relation to improvements in the symptoms of attention deficit disorder (Conners' Continuous Performance Test score > 0.60) at 12 month follow-up. There was also high quality evidence showing an important difference for sodium valproate compared to lamotrigine in relation to improvements in the symptoms of attention deficit disorder at the 16 or 20 week follow-up point; as well as freedom from treatment failure at the 16 or 20 week follow-up and the 12 month follow-up. There was also high quality evidence indicating that ethosuximide provides important benefits (when compared to lamotrigine) in relation to freedom from treatment failure at 16 or 20 weeks and at 12 months.

Uncertainty in the data is further exacerbated by the absence of evidence on health-related quality of life, as well as a number of antiseizure therapies included in the review protocol.

### **Quality assessment of clinical outcomes included in the evidence review**

See the clinical evidence profiles in appendix F.

### **Economic evidence**

#### **Included studies**

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

#### **Excluded studies**

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

### **Summary of studies included in the economic evidence review**

No studies were identified which were applicable to this review question.

### **Economic model**

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

## **The committee's discussion of the evidence**

### **Interpreting the evidence**

#### **The outcomes that matter most**

The committee agreed that seizure freedom should be a critical outcome for this review as this is considered to be the main objective of treatment for children with absence seizures. 24-hour EEG seizure freedom was also included as a critical outcome as absence seizures show a specific pattern on EEG which usually improves or resolves with effective treatments. The committee also agreed that time to discontinuation of treatment or change of medication, and adverse events should be included as critical outcomes to ensure that data on treatment acceptability and tolerability were included.

Neuropsychological changes and health related quality of life were also included as important outcomes as deterioration in these may suggest adverse treatment effects.

#### **The quality of the evidence**

The committee were presented with data on 5 different comparisons, however, meta-analysis was only possible for 1 outcome in 1 comparison due to variation in the interventions and measurement of outcomes. All data presented related to children and young people under the age of 18 years. The quality of the evidence for this review was assessed using GRADE methodology. The majority of outcomes were considered very low, low or moderate quality indicating uncertainty in the reliability of the data. This was with the exception of some of the outcomes reported by Glauser 2010 and Glauser 2013, which were considered high quality; mainly as a result of a low risk of bias and more precise estimates. Outcomes were most often downgraded due to risk of bias, with limited information provided regarding randomisation and allocation concealment. Outcomes were also downgraded due to imprecision and the majority of studies only included a small number of participants; further limiting confidence in the data.

No studies reported on the outcome health-related quality of life.

#### **Benefits and harms**

The committee used the evidence presented and their clinical knowledge and expertise to make recommendations.

No evidence was identified which reported on the effectiveness of ASMs as treatment for absence seizures in people over 18 years; however, the committee agreed that, for recommendations on adults, it was appropriate to extrapolate from the evidence on children and young people given the similar pathophysiology in both age groups.

The committee agreed that, prior to starting antiseizure therapy there should be a discussion with the person, their family and carers, if appropriate, about a 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 seizure 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 being on numerous medications.

The committee emphasised that monotherapy should be used in the first instance. When starting alternative antiseizure medications, the dose of the new antiseizure medication should be slowly increased, whilst the existing antiseizure medication is tapered off. When starting add-on antiseizure medications, the additional antiseizure medication should be carefully titrated, in line with the BNF guidance, adverse events monitored, and there should be a frequent treatment review.

### **Absence seizures (including childhood absence epilepsy)**

There was some evidence which indicated that ethosuximide improves freedom from treatment failure in people with absence seizures (including childhood absence epilepsy). Although this evidence was generally of low quality, there was some high quality evidence which also showed that ethosuximide had an important benefit in relation to this outcome (when compared to lamotrigine, at 16/20 weeks follow-up, and at 12 months follow-up). The committee therefore agreed that this should be a strong recommendation, particularly as ethosuximide is the most widely used ASM in the treatment of absence seizures (including childhood absence epilepsy) and is associated with seizure remission.

Evidence was also identified which suggested that sodium valproate was effective in the treatment of absence seizures (including childhood absence epilepsy). Although the evidence was generally of low quality, the committee agreed to make a recommendation stating that sodium valproate can be offered as second-line alternative or add-on treatment given its association with extended seizure freedom (when compared to lamotrigine). Furthermore, the committee highlighted that sodium valproate is commonly used in clinical practice. The committee discussed in detail the risks associated with use of sodium valproate in women and girls who are able to have children. There was some evidence which suggested that lamotrigine and levetiracetam were effective in the treatment of absence seizures (including childhood absence epilepsy). It was noted that there is [safety advice by the Medicines and Healthcare products Regulatory Agency \(MHRA\) on the use of valproate, valproate use by women and girls](#) and [valproate use by men](#). This provides specific advice and criteria for its usage. Given the evidence that lamotrigine or levetiracetam were effective, it was decided in January 2025 that they should all be options as second-line monotherapy or add-on treatment for absence seizures. In relation to reproductive risks with sodium valproate, MHRA safety measures in women and girls able to have children and precautionary advice for boys and men were highlighted to ensure they are followed, discussed and reviewed. It was decided that if the first choice of treatment is unsuccessful, another one of these options should be tried and if that is also unsuccessful, the third option should be tried.

The committee noted that although other antiseizure medications are used in clinical practice and may benefit some people, it should be highlighted that some can exacerbate seizures.

### **Absence seizures with other seizure types**

For boys and men; girls aged under 10 years who are unlikely to need treatment when they are old enough to have children, and women who are unable to have children with absence seizures with other seizure types, the committee agreed to recommend sodium valproate as first-line treatment given its association with higher remission rates and tolerability in children and young people. As the evidence also indicated that lamotrigine and levetiracetam are effective, and given the MHRA drug safety advice for sodium valproate it was agreed to recommend a choice of sodium valproate, lamotrigine and levetiracetam as first-line treatment for absence seizures with other seizure types (or at risk of these). In relation to reproductive risks with sodium valproate, MHRA safety measures in women and girls able to have children and precautionary advice for boys and men were highlighted to ensure they are followed, discussed and reviewed. Lamotrigine and levetiracetam were recommended as a

choice because, compared to sodium valproate, lamotrigine was shown to be less effective for seizure control, but there were no differences between both ASMs for adverse events and treatment withdrawal. Furthermore, when lamotrigine was compared with placebo, it showed to be more effective for seizure control and no adverse events were reported in neither of the trial arms. There was a placebo-controlled trial for levetiracetam, which showed better seizure control in people who received levetiracetam and no clinically important differences in terms of adverse events. It was decided that if the first choice of treatment is unsuccessful, another one of these options should be tried and if that is also unsuccessful, the third option should be tried.

As there was evidence for ethosuximide in children and young people, the committee agreed to include this drug as an add-on treatment if first-line treatment is unsuccessful. The committee believed that ethosuximide may be needed in some situations, for example, in cases of absence seizures co-existing with other seizure types.

As there was evidence of effectiveness, the committee felt that it was necessary to make a recommendation stating that sodium valproate may be prescribed to women and girls of childbearing age, however they agreed that the recommendation should emphasise that this should be seen as a 'last resort' and must be done only after discussion of the risks and benefits. If sodium valproate is prescribed to women and girls able to have children, clinicians must follow MHRA guidance, which includes ensuring the continuous use of highly effective contraception and the enrolment of the girl or woman in a [pregnancy prevention programme](#), if appropriate.

The committee noted that although other antiseizure medications are used in clinical practice and may benefit some people, it should be highlighted that some can exacerbate seizures.

### **Cost effectiveness and resource use**

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

These recommendations represent current practice and therefore no resource impact is anticipated. Other than levetiracetam where a third line treatment is needed, the recommended antiseizure medications are identical to those of the previous NICE guideline. It is not anticipated that there will be any change in the use of levetiracetam as a result of these recommendations as it is already used in clinical practice in such circumstances.

### **Other factors the committee took into account**

In line with the MHRA, the committee emphasised that long-term treatment with 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 5.3.1-5.3.6.



## References

### **Callaghan 1982**

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### **Coppola 2004**

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### **Fattore 2011**

Fattore, C., Boniver, C., Capovilla, G., Cerminara, C., Citterio, A., Coppola, G., Costa, P., Darra, F., Vecchi, M., Perucca, E., A multicenter, randomized, placebo-controlled trial of levetiracetam in children and adolescents with newly diagnosed absence epilepsy, *Epilepsia*, 52, 802-809, 2011

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Glauser T, Cnaan A, Shinnar et al., Ethosuximide, Valproic Acid and Lamotrigine in Childhood Absence Epilepsy: Initial Monotherapy Outcomes at 12 months *Epilepsia*. 2013 January ; 54(1): 141–155. doi:10.1111/epi.12028

### **Glauser 2010**

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# Appendices

## Appendix A – Review protocols

**Review protocol for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

**Table 7: Review protocol**

Field	Content
PROSPERO registration number	CRD42019159420
Review title	Effectiveness of antiseizure therapies for absence seizures
Review question	What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?
Objective	<p>The objective of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have absence seizures.</p> <p>This review will determine the effectiveness of antiseizure therapies given alone (monotherapy) or as add-ons (combination therapy).</p>
Searches	<p>The following databases will be searched:</p> <ul style="list-style-type: none"> <li>• CDSR</li> <li>• CENTRAL</li> <li>• DARE</li> <li>• HTA</li> <li>• MEDLINE &amp; MEDLINE In-Process and Other Non-Indexed Citations</li> <li>• Embase</li> <li>• EMCare</li> </ul> <p>Searches will be restricted by:</p>

Field	Content
	<ul style="list-style-type: none"> <li>• Date: No date limit</li> <li>• English language studies</li> <li>• Human studies</li> <li>• RCT and systematic review study design filter</li> </ul>
Condition or domain being studied	Epilepsy with absence seizures
Population	<p>Inclusion</p> <ul style="list-style-type: none"> <li>• People with confirmed epilepsy with absence seizures</li> </ul> <p>Exclusion</p> <ul style="list-style-type: none"> <li>• Newborn babies (under 28 days) with acute symptomatic seizures</li> </ul>
Intervention/Exposure/Test	<p>The following antiseizure therapies and their combinations will be considered:</p> <ul style="list-style-type: none"> <li>• Acetazolamide</li> <li>• Clobazam</li> <li>• Clonazepam</li> <li>• Ethosuximide</li> <li>• Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures)</li> <li>• Lamotrigine</li> <li>• Levetiracetam</li> <li>• Methsuximide/mesuximide</li> <li>• Sodium Valproate</li> <li>• Topiramate</li> <li>• Zonisamide</li> </ul>
Comparator/Reference standard/Confounding factors	<ul style="list-style-type: none"> <li>• Any of the above and their combinations</li> <li>• No treatment/placebo</li> </ul>
Types of study to be included	<ul style="list-style-type: none"> <li>• Systematic review of RCTs</li> <li>• RCTs</li> </ul>

Field	Content
Other exclusion criteria	<ul style="list-style-type: none"> <li>• Studies with a mixed population (this is, including children and young people with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported</li> <li>• Studies with a mixed population (this is, including people with epilepsy with different seizure types) will be excluded, unless subgroup analysis for epilepsy with absence seizures has been reported.</li> <li>• Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias</li> </ul>
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care)
Primary outcomes (critical outcomes)	<ul style="list-style-type: none"> <li>• Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment)</li> </ul> <p><i>Due to anticipated heterogeneity in reporting of seizure freedom, data will be extracted as presented within included studies. Where a study reports multiple variants then all data will be extracted. For decision making priority will be given to data presented as “time to 12 months seizure freedom”, (this is time to event: HR or mean time) followed by “achievement of 12 months seizure freedom” (RR). Minimum follow up data of 3 months will be included.</i></p> <ul style="list-style-type: none"> <li>• 24 hour EEG seizure freedom</li> <li>• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)</li> <li>• Adverse events, as assessed by: <ul style="list-style-type: none"> <li>○ % of patients with reported side effects (trial defined adverse and serious adverse effects)</li> <li>○ treatment cessation due to adverse event (dichotomous outcome only)</li> <li>○ mortality</li> </ul> </li> </ul>
Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> <li>• Neuropsychological changes (IQ testing, or other validated tools)</li> </ul>

Field	Content
	<ul style="list-style-type: none"> <li>• Health-related overall quality of life (measured using validated tools only)</li> </ul> <p>Outcomes are in line with those described in the core outcome set for epilepsy <a href="http://www.comet-initiative.org/studies/searchresults">http://www.comet-initiative.org/studies/searchresults</a></p>
Data extraction (selection and coding)	<p>All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria. Duplicate screening will not be undertaken for this review question.</p> <p>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and will include: study setting; design; aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion criteria; details of intervention and controls; study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias.</p> <p>Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria, once the full version has been checked, will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reasons for its exclusion.</p> <p>All data extraction will be quality assured by a senior reviewer. Draft included and excluded studies tables will be circulated to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair.</p>
Risk of bias (quality) assessment	<p>Quality assessment of individual studies will be performed using the following checklists:</p> <ul style="list-style-type: none"> <li>• ROBIS tool for systematic reviews</li> <li>• Cochrane RoB tool v.2 for RCTs</li> </ul> <p>The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.</p>
Strategy for data synthesis	<p>Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively.</p> <p><u>Data synthesis</u></p>

Field	Content
	<p>Where possible pairwise meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios for dichotomous outcomes. Peto odds ratio will be used for outcomes with zero events in one arm and &lt;1% events in the other. Risk difference will be used for outcomes with zero events in both arms. Mean differences or standardised mean differences will be presented for continuous outcomes.</p> <p><u>Heterogeneity</u></p> <p>Heterogeneity in the effect estimates of the individual studies will be assessed using the I<sup>2</sup> statistic. I<sup>2</sup> values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively.</p> <p><u>In the presence of heterogeneity, sub-group analysis will be conducted:</u></p> <ul style="list-style-type: none"> <li>• according to the risk of bias of individual studies</li> <li>• study location</li> </ul> <p>Exact sub-group analysis may vary depending on differences identified within included studies</p> <p>If heterogeneity cannot be explained using these methods, random effects model will be used. If heterogeneity remains above 75% and cannot be explained by sub-group analysis. Reviewers will consider if meta-analysis is appropriate given characteristics of included studies.</p> <p><u>Minimal important differences (MIDs):</u></p> <p>Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes</p> <ul style="list-style-type: none"> <li>• For risk ratios: 0.8 and 1.25.</li> <li>• For continuous outcomes: <ul style="list-style-type: none"> <li>○ For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm.</li> <li>○ For two studies: the MID is calculated as +/-0.5 times the mean of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used.</li> </ul> </li> </ul>

Field	Content														
	<ul style="list-style-type: none"> <li>○ For three or more studies (meta-analysed): the MID is calculated by ranking the studies in order of SD in the control arms. The MID is calculated as <math>\pm 0.5</math> times median SD.</li> <li>○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries.</li> </ul> <p><u>Validity</u></p> <p>The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: <a href="http://www.gradeworkinggroup.org/">http://www.gradeworkinggroup.org/</a></p>														
Analysis of sub-groups (stratification)	<p>Stratification</p> <p>If data is available, results will be presented separately by:</p> <ul style="list-style-type: none"> <li>• Those with and without learning difficulties/disabilities</li> <li>• Age of onset (<math>\leq 10</math> years and <math>&gt; 10</math> years old)</li> <li>• Eyelid myoclonia</li> <li>• Photosensitivity</li> <li>• Typical and atypical absence seizures</li> </ul>														
Type and method of review	<table> <tr> <td><input checked="" type="checkbox"/></td><td>Intervention</td></tr> <tr> <td><input type="checkbox"/></td><td>Diagnostic</td></tr> <tr> <td><input type="checkbox"/></td><td>Prognostic</td></tr> <tr> <td><input type="checkbox"/></td><td>Qualitative</td></tr> <tr> <td><input type="checkbox"/></td><td>Epidemiologic</td></tr> <tr> <td><input type="checkbox"/></td><td>Service Delivery</td></tr> <tr> <td><input type="checkbox"/></td><td>Other (please specify)</td></tr> </table>	<input checked="" type="checkbox"/>	Intervention	<input type="checkbox"/>	Diagnostic	<input type="checkbox"/>	Prognostic	<input type="checkbox"/>	Qualitative	<input type="checkbox"/>	Epidemiologic	<input type="checkbox"/>	Service Delivery	<input type="checkbox"/>	Other (please specify)
<input checked="" type="checkbox"/>	Intervention														
<input type="checkbox"/>	Diagnostic														
<input type="checkbox"/>	Prognostic														
<input type="checkbox"/>	Qualitative														
<input type="checkbox"/>	Epidemiologic														
<input type="checkbox"/>	Service Delivery														
<input type="checkbox"/>	Other (please specify)														
Language	English														
Country	England														
Anticipated or actual start date	20 February 2020														

Field	Content		
Anticipated completion date	21 April 2021		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Piloting of the study selection process	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Formal screening of search results against eligibility criteria	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Data extraction	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Risk of bias (quality) assessment	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	Data analysis	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Named contact	<p>5a. Named contact National Guideline Alliance</p> <p>5b Named contact e-mail <a href="mailto:epilepsies@nice.org.uk">epilepsies@nice.org.uk</a></p> <p>5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance</p>		
Review team members	The National Guideline Alliance technical team		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.		
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's		



Field	Content
	declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of <a href="#">Developing NICE guidelines: the manual</a> . Members of the guideline committee are available on the NICE website: <a href="https://www.nice.org.uk/guidance/indevelopment/gid-ng10112">https://www.nice.org.uk/guidance/indevelopment/gid-ng10112</a>
Other registration details	Not applicable
URL for published protocol	<a href="https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=159420">https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=159420</a>
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Epilepsy; Absence seizures
Details of existing review of same topic by same authors	Not applicable
Additional information	Not applicable
Details of final publication	<a href="http://www.nice.org.uk">www.nice.org.uk</a>

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: The Database of Abstracts of Reviews of Effects; EEG: Electroencephalogram; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; HTA: Health Technology Assessment; IQ: Intelligence quotient; MID: minimal important difference; NICE: National Institute for Health and Care Excellence; RCT: Randomised Controlled Trial; RoB: Risk of Bias; ROBIS: risk of bias in systematic reviews; RR: risk ratio; SD: standard deviation

## Appendix B – Literature search strategies

### Literature search strategies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?

#### Clinical

##### **Database(s): EMCare, MEDLINE and Embase (Multifile) – OVID**

EMCare 1995 to December 03, 2019; Embase Classic+Embase 1947 to 2019 December 03; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2019 December 03, 2019

Date of last search: 03 December 2019

*Multifile database codes: emcr=EMCare; emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily*

#	searches
1	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
2	ethosuximide/ use emczd, emcr or ethosuximide/ use ppez or (emeside or ethosuccimid* or ethosucinimid* or ethosuximide or ethylmethysuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sursilep or suksilep or suxilep or suximal or suxinutin or zarondan or zaron-tin).ti,ab.
3	fat intake/ or glycemic index/ or ketogenic diet/ or exp low carbohydrate diet/ or exp triacylglycerol/
4	3 use emczd, emcr
5	exp diet, carbohydrate-restricted/ or exp dietary fats/ or glycemic index/ or exp triglycerides/
6	5 use ppez
7	((adequate adj3 protein*) or atkin* or keto* or kd* or (carbohydrate* adj5 (restrict* or low* or reduc*)) or ((glycemic or glycaemic) adj5 (index or treat* or modulat*)) or (high fat* adj5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or low carb* or lchf or low glyc* index treatment* or lgit or (medium chain adj (tryglyceride* or triglyceride*)) or mct*).ti,ab.
8	or/4,6-7
9	lamotrigine/ use emczd, emcr or lamotrigine/ use ppez or (crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium).ti,ab.
10	levetiracetam/ use emczd, emcr, ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
11	topiramate/ use emczd, emcr, ppez or (epitomax or topamax or topiramate or acomicil or ecuram or epiramat or epitomax or epitoram or erravia or etopro or fagadol or jadix or lusitax or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramos or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi).ti,ab.
12	valproic acid/ use emczd, emcr, ppez or (convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or di n propylacetate or di n propylacetate sodium or di n propylacetic acid or diplexil or dipropyl acetate or dipropyl acetic acid or dipropylacetate or dipropylacetate sodium or dipropylacetetic acid or dipropylacetic acid or diprosin or divalproex or epilam or epilex or epilim chrono or epilim chronosphere or epilim enteric or epilim or episenta or epival cr or ergenyl or ergenyl chrono or ergenyl chronosphere or ergenyl retard or ergenyl or espa valept or everiden or goilim or hexaquin or labazene or leptilan or leptilanol or micropakine or mylproin or myproic acid or n dipropylacetic acid or orfil or orfiril or orlept or petilin or propylisopropylacetic acid or propymal or semisodium valproate or sodium 2 propylpentanoate or sodium 2 propylvalerate or sodium di n propyl acetate or sodium di n propylacetate or sodium dipropyl acetate or sodium dipropylacetate or sodium n dipropylacetate or stavzor or valberg pr or valcote or valepil or valeptol or valerin or valhel pr or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprocura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.

#	searches
13	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonisamid*).ti,ab.
14	clobazam/ use emczd, emcr or clobazam/ use ppez or (chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl).ti,ab.
15	clonazepam/ use emczd, emcr or clonazepam/ use ppez or (aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril).ti,ab.
16	mesuximide/ use emczd, emcr or (alpha methylphensuximide or celontin or methosuximide or celontine or mesuximide or methsuximide or methylsuximide or metsuccimide or petinutin).ti,ab.
17	acetazolamide/ use emczd, emcr or acetazolamide/ use ppez or (acetadiazol or acetamox or acetazolamide or acetazolam or acetazolamid* or acetazolamine or acetazoleamid* or acetozolamine or akzol or akzol or albox or apoacetazolamide or azetazolamide or carbinib or carbonic anhydrase inhibitor or cidamex or dazamide or defiltran or dehydratin or diacarb or diamox or diluran or diomax or diuramid* or diutazol or edemox or eumicton or fonurit or genephamide or glaucomed* or glauconox or glaupax or huma zolamide or humazolamide or ledamox or lediamox or ledimox or natrionex or nephramid or novozolamide or storzolamide or ulcosilvanil or ulcosylvanil).ti,ab.
18	or/2,8-17
19	clinical trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
20	19 use ppez
21	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
22	21 use ppez
23	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
24	23 use emczd, emcr
25	or/20,22,24
26	meta-analysis/
27	meta-analysis as topic/ or systematic reviews as topic/
28	"systematic review"/
29	meta-analysis/
30	(meta analy* or metanaly* or metaanaly*).ti,ab.
31	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
32	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
33	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
34	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
35	(search* adj4 literature).ab.
36	(Medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
37	cochrane.jw.
38	((pool* or combined) adj2 (data or trials or studies or results)).ab.
39	(or/26-27,30,32-38) use ppez
40	(or/28-31,33-38) use emczd, emcr
41	or/39-40
42	or/25,41
43	1 and 18 and 42
44	limit 43 to english language
45	((letter.pt. or letter/ or note.pt. or editorial.pt. or case report/ or case study/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.)
46	45 use emez
47	((letter/ or editorial/ or news/ or exp historical article/ or anecdotes as topic/ or comment/ or case report/ or (letter or comment*).ti.) not (randomized controlled trial/ or random*.ti,ab.)) or ((animals not humans).sh. or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.)

#	searches
48	47 use mesz
49	46 or 48
50	44 not 49

### Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 12 of 12, December 2019; Cochrane Central Register of Controlled Trials, Issue 12 of 12, December 2019

Date of last search 03 December 2019

#	searches
#1	mesh descriptor: [seizures] explode all trees
#2	((absence near/2 (convulsion* or seizure*)) or ((typical or atypical) near/1 absenc*) or "petit mal*" or pyknolepsy or "typical absence*")):ti,ab,kw
#3	#1 or #2
#4	mesh descriptor: [ethosuximide] this term only
#5	((emeside or ethosuccimid* or ethosuccinimid* or ethosuximide or ethylmethysuccimide or ethylsuximide or ethymal or etosuximida or mesentol or pemal or petimid or petinimid* or petnidan or pyknolepsin or pyknolepsinum or ronton or simatin or succinutin or sucsilep or suksilep or suxilep or suximal or suxinutin or zarondan or zarontin)):ti,ab,kw
#6	mesh descriptor: [diet, carbohydrate-restricted] explode all trees
#7	mesh descriptor: [dietary fats] explode all trees
#8	mesh descriptor: [glycemic index] this term only
#9	mesh descriptor: [triglycerides] this term only
#10	((adequate near/3 protein*) or atkin* or keto* or kd* or (carbohydrate* near/5 (restrict* or low* or re-duc*)) or ((glycemic or glycaemic) near/5 (index or treat* or modulac*)) or ("high fat*" near/5 (diet* or plan* or treat*)) or keto or ketogenic or ketogenous or ketotic or "low carb*" or lchf or "low glyc* index treatment*" or lgit or ("medium chain" near/1 (tryglyceride* or triglyceride*)) or mct*)):ti,ab,kw
#11	mesh descriptor: [lamotrigine] this term only
#12	((crisomet or labileno or lametil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium)):ti,ab,kw
#13	mesh descriptor: [levetiracetam] this term only
#14	((elepsia or keppra or kopodex or levetiracetam* or matever or spritam)):ti,ab,kw
#15	mesh descriptor: [topiramate] this term only
#16	((epitomax or topamax or topiramate or acomicil or ecuram or epiamat or epitomax or epitoram or erra-via or etopro or fagadol or jadix or lusitrac or maritop or oritop or piraleps or pirantal or pirepil or qudexy or ramas or sincronil or talopam or tiramat or topaben or topamac or topamax or topepsil or topibrain or topilek or topimark or topimax or topiramat* or topiramato or topiratore or topit or toramat or torlepta or trokendi)):ti,ab,kw
#17	mesh descriptor: [valproic acid] this term only
#18	((convulsofin or delepsine or depacon* or depaken* or depakin* or depakote or depalept or deprakine or "di n propylacetate" or "di n propylacetate sodium" or "di n propylacetic acid" or diplexil or "dipropyl acetate" or "dipropyl acetic acid" or dipropylacetate or "dipropylacetate sodium" or "dipropylacetatic acid" or "dipropylacetic acid" or diprosin or divalproex or epilam or epilex or "epilim chrono" or "epilim chromosphere" or "epilim enteric" or epilim or episenta or "epival cr" or ergenyl or "espa valept" or eve-riden or goilim or hexaquin or labazene or leptilan or leptilanol or micropakine or mylproin or "myproic acid" or "n dipropylacetic acid" or orfil or orfiril or orlept or petilin or "propylisopropylacetic acid" or propymal or "semisodium valproate" or "sodium 2 propylpentanoate" or "sodium 2 propylvalerate" or "sodium di n propyl acetate" or "sodium di n propylacetate" or "sodium dipropyl acetate" or "sodium di-propylacetate" or "sodium n dipropylacetate" or stavzor or "valberg pr" or valcote or valepil or valeptol or valerin or "valhel pr" or valoin or valpakine or valparin or valporal or valprax or valpro or valproate or valprodura or "valproic acid" or valprosid or valprotek or valsup or vupral)):ti,ab,kw
#19	mesh descriptor: [zonisamide] this term only
#20	((excegran or excemid or zonegran or zonisamid*)):ti,ab,kw
#21	mesh descriptor: [clobazam] this term only
#22	((chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urba-dan or urbanil or urbanyl)):ti,ab,kw

#	searches
#23	mesh descriptor: [clonazepam] this term only
#24	((aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril)):ti,ab,kw
#25	((("alpha methylphenisuximide" or celontin or methosuximide or celontine or mesuximide or methsuximide or methylsuximide or metsuccimide or petinutin)):ti,ab,kw
#26	mesh descriptor: [acetazolamide] this term only
#27	((acetadiazol or acetamox or "acetazol amide" or acetazolam or acetazolamid* or acetazolamine or acetazoleamid* or acetozolamine or "ak zol" or akzol or albox or apoacetazolamide or azetazolamide or carbinib or "carbonic anhydrase inhibitor" or cidamex or dazamide or defiltran or dehydratin or diacarb or diamox or diluran or diomax or diuramid* or diutazol or edemox or eumicton or fonurit or genephamide or glaucomed* or glauconox or glaupax or "huma zolamide" or humazolamide or ledamox or lediamox or ledimox or natrionex or nephramid or novozolamide or storzolamide or ulcosilvanil or ulcosylvanil)):ti,ab,kw
#28	{or #4-#27}
#29	#3 and #28

### Database(s): Database of Abstracts of Reviews of Effects - CRD

Cochrane Database of Systematic Reviews, Issue 12 of 12, December 2019; Cochrane Central Register of Controlled Trials, Issue 12 of 12, December 2019

Date of last search 03 December 2019

#	Searches
#1	mesh descriptor seizures explode all trees
#2	((("absence near2 (convulsion* or seizure*)) or ((typical or atypical) near1 absenc*) or "petit mal*" or pyknolepsy or "typical absence*"))
#3	#1 or #2

### Economic

#### Database(s): MEDLINE & Embase (Multifile) - OVID

Embase Classic+Embase 1947 to 2021 March 31; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 31, 2021

Date of last search: 31 March 2021

Multifile database codes: emczd=Embase Classic+Embase; ppez= MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

#	searches
1	exp epilepsy/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(epilep* or seizure* or convuls*).ti,ab. or (continuous spike wave of slow sleep or infant* spasm*).ti,ab.
6	(seizure and absence).sh. use emczd, emcr or seizures/ use ppez or ((absence adj2 (convulsion* or seizure*)) or ((typical or atypical) adj absenc*) or petit mal* or pyknolepsy or typical absence*).ti,ab.
7	(atonic seizure or tonic seizure).sh. use emczd, emcr or exp seizures/ use ppez or ((drop or akinetic or atonic or tonic) adj2 (attack* or epileps* or seizure* or convulsion*)):ti,ab. or brief seizure.ti,ab. or (tonic adj3 atonic adj3 (attack* or epileps* or seizure* or convulsion*)):ti,ab.
8	exp benign childhood epilepsy/ use emczd, emcr or epilepsy, rolandic/ use ppez or (bcects or bects or brec or benign epilepsy or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 epileps*) or (benign adj2 (childhood or neonatal or pediatric or paediatric) adj2 (convulsion* or epileps* or seizure* or spasm*)) or (benign adj3 (convulsion* or epileps*) adj2 centrottemporal adj2 spike*) or cects or ((centralopathic or centrottemporal or temporal-central focal) adj (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) adj2 (convulsion* or epileps* or seizure* or spasm*)):ti,ab.
9	exp generalized epilepsy/ use emczd, emcr or exp epilepsy, generalized/ use ppez

#	searches
10	((((akineti* or atonic or central or diffuse or general or generali?ed or idiopathi* or tonic) adj3 (epilep* or seizure*)) or ((childhood absence or juvenile absence or myoclonic or myoclonia or myoclonic astatic or myoclonus or gtcs) adj2 epilep*) or (epilepsy adj2 eyelid myoclonia) or (ige adj2 phantom absenc*) or impulsive petit mal or (janz adj3 (epilep* or petit mal)) or jeavons syndrome* or ((janz or lafora or lafora body or lundborg or unverricht) adj2 (disease or syndrome)) or ((jme or jmes) and epilep*) or perioral myoclon*).ti,ab.
11	infantile spasm/ use emczd, emcr or spasms, infantile/ use ppez or (((early or infantile) adj2 myoclonic adj2 encephalopath*) or ((early or infantile) adj2 epileptic adj2 encephalopath*) or epileptic spasm* or ((flexor or infantile or neonatal) adj2 (seizure* or spasm*)) or generali?ed flexion epileps* or hypsarrhythmia* or ((jackknife or jack nife or lightening or nodding or salaam) adj (attack* or convulsion* or seizure* or spasm*)) or massive myoclonia or minor motor epilepsy or propulsive petit mal or spasm in*1 flexion or spasmus nutans or west syndrome*).ti,ab.
12	landau kleffner syndrome/ use emczd, emcr, ppez or (dravet or lennox gastaut or lgs or (landau adj2 kleffner) or sme).ti,ab.
13	lennox gastaut syndrome/ use emczd, emcr or lennox gastaut syndrome/ use ppez or generalized epilepsy/ use emczd, emcr or epileptic syndromes/ use ppez
14	(child* epileptic encephalopath* or gastaut or lennox or lgs).ti,ab.
15	myoclonus seizure/ use emczd, emcr or seizures/ use ppez or ((myoclon* adj2 (absence* or epileps* or seizure* or jerk* or progressive familial epilep* or spasm* or convulsion*)) or ((lafora or unverricht) adj2 disease) or muscle jerk).ti,ab.
16	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*).ti,ab.
17	exp epilepsies, partial/ use ppez or exp focal epilepsy/ use emczd, emcr or ((focal or focal onset or local or partial or simple partial) adj3 (epileps* or seizure*).ti,ab.
18	severe myoclonic epilepsy in infancy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez
19	(dravet*1 or (intractable childhood epilepsy adj2 (generalised tonic clonic or gtc)) or icegtc* or (severe adj2 (myoclonic or polymorphic) adj2 epilepsy adj2 infancy) or sme).ti,ab.
20	epilepsy, tonic-clonic/ use ppez or epilepsy, generalized/ use ppez or generalized epilepsy/ use emczd, emcr or grand mal epilepsy/ use emczd, emcr or (((clonic or grand mal or tonic or (tonic adj3 clonic)) adj2 (attack* or contraction* or convuls* or seizure*)) or gtcs or (generali* adj (contraction* or convuls* or insult or seizure*))).ti,ab.
21	or/2,4-20
22	exp budgets/ or exp "costs and cost analysis"/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or economics/ or exp "fees and charges"/ or value of life/
23	22 use ppez
24	budget/ or exp economic evaluation/ or exp fee/ or funding/ or health economics/ or exp health care cost/
25	24 use emczd
26	budget*.ti,ab.
27	cost*.ti.
28	(economic* or pharmaco economic* or pharmacoeconomic*).ti.
29	(price* or pricing*).ti,ab.
30	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*).ab.
31	(financ* or fee or fees).ti,ab.
32	(value adj2 (money or monetary)).ti,ab.
33	or/23,25-32
34	21 and 33
25	limit 34 to english language

**Database(s): NHS Economic Evaluation Database (NHS EED), HTA database – CRD**

Date of last search: 31 March 2021

#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees

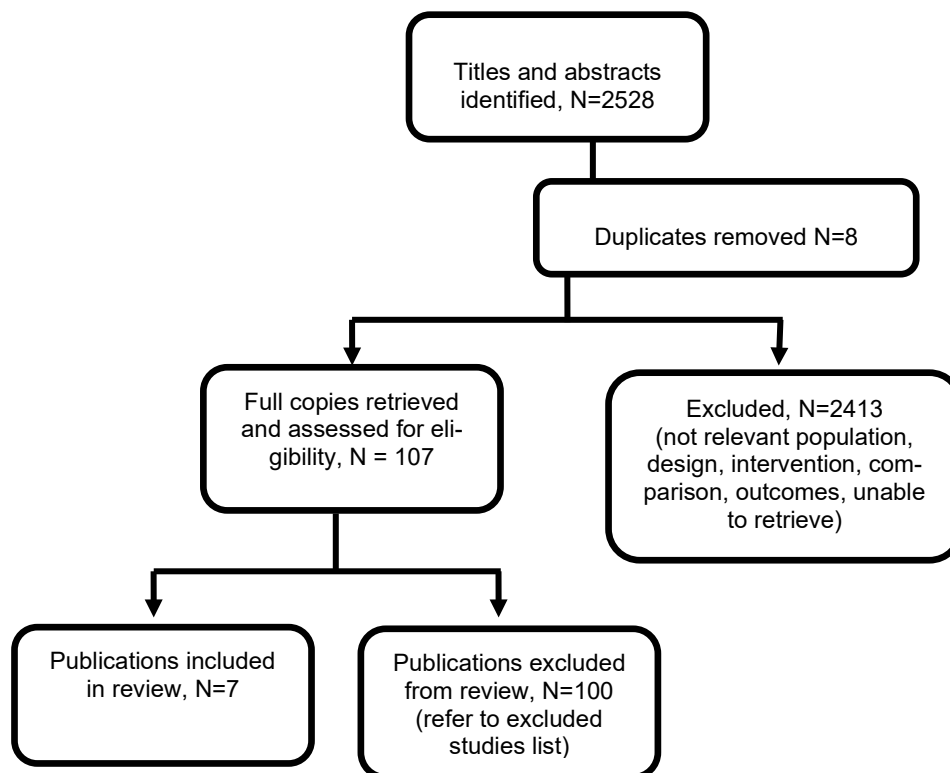


#	searches
5	(epilep* or seizure* or convuls*) or ("continous spike wave of slow sleep" or "infant* spasm*")
6	((absence near2 (convulsion* or seizure*)) or ((typical or atypical) next absenc*) or "petit mal*" or pyknolepsy or "typical absence*")
7	mesh descriptor seizures explode all trees
8	((drop or akinetic or atonic or tonic) near2 (attack* or epileps* or seizure* or convulsion*)) or "brief sei-zure" or (tonic near3 atonic near3 (attack* or epileps* or seizure* or convulsion*))
9	mesh descriptor epilepsy, rolandic this term only
10	(bcects or bects or brec or "benign epilepsy" or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 epileps*) or (benign near2 (childhood or neonatal or pediatric or paediatric) near2 (convul-sion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrottemporal near2 spike*) or cects or ((centralopathic or centrottemporal or "temporal-central focal") near (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epileps* or seizure* or spasm*)))
11	mesh descriptor epilepsy, generalized this term only
12	((((akinetic or atonic or central or diffuse or general or general?ed or idiopathic or tonic) near3 (epilep* or seizure*)) or ((("childhood absence" or "juvenile absence" or myoclonic or myoclonia or "myoclonic astatic" or myoclonus or gtcs) near2 epilep*) or (epilepsy near2 "eyelid myoclonia") or (ige near2 phantom ab-senc*) or "impulsive petit mal" or (janz near3 (epilep* or "petit mal"))) or "jeavons syndrome*" or ((janz or lafora or "lafora body" or lundborg or unverricht) near2 (disease or syndrome)) or ((jme or jmes) and epi-lep*) or "perioral myoclon*")
13	mesh descriptor spasms, infantile this term only
14	((((early or infantile) near2 myoclonic near2 encephalopath*) or ((early or infantile) near2 epileptic near2 encephalopath*) or "epileptic spasm*" or ((flexor or infantile or neonatal) near2 (seizure* or spasm*)) or "general?ed flexion epileps*" or hysarrhythmia* or ((jackknife or "jack nife" or lightening or nodding or sa-laam) next (attack* or convulsion* or seizure* or spasm*)) or "massive myoclonia" or "minor motor epi-lepsy" or "propulsive petit mal" or "spasm in* flexion" or "spasmus nutans" or "west syndrome*")
15	mesh descriptor landau kleffner syndrome this term only
16	(dravet or "lennox gastaut" or lgs or (landau near2 kleffner) or smei)
17	mesh descriptor lennox gastaut syndrome this term only
18	mesh descriptor epileptic syndromes this term only
19	("child* epileptic encephalopath*" or gastaut or lennox or lgs)
20	((myoclon* near2 (absence* or epileps* or seizure* or jerk* or "progressive familial epilep*" or spasm* or convulsion*)) or ((lafora or unverricht) near2 disease) or "muscle jerk")
21	mesh descriptor epilepsies, myoclonic explode all trees
22	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or "doose* syndrome" or mae or "general?ed idiopathic epilepsy") or ((absence or astatic or atonic or tonic or "tonic clonic") near2 (seizure* or spasm*))
23	mesh descriptor epilepsies, partial explode all trees
24	((focal or "focal onset" or local or partial or "simple partial") near3 (epileps* or seizure*))
25	mesh descriptor epilepsies, myoclonic this term only
26	(dravet*1 or ("intractable childhood epilepsy" near2 ("generalised tonic clonic" or gtc)) or icegtc* or (se-vere near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeib or smei)
27	mesh descriptor epilepsy, tonic-clonic this term only
28	mesh descriptor epilepsy, generalized this term only
29	((((clonic or "grand mal" or tonic or (tonic near3 clonic)) near2 (attack* or contraction* or convuls* or sei-zure*)) or gtcs or (general? next (contraction* or convuls* or insult or seizure*)))
30	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

## Appendix C – Clinical evidence study selection

**Clinical study selection for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

**Figure 1: Study selection flow chart**





## Appendix D – Clinical evidence tables

**Clinical evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

**Table 8: Clinical evidence tables**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<b>Full citation</b> Callaghan, N., O'Hare, J., O'Driscoll, D., Comparative study of ethosuximide and sodium valproate in the treatment of typical absence seizures (petit mal), Developmental Medicine and Child Neurology, 24, 830-836, 1982  <b>Ref Id</b> 1080077  <b>Country/ies where the study was carried out</b> Ireland.  <b>Study type</b> RCT.  <b>Aim of the study</b> To compare sodium valproate and ethosuximide in terms of seizure	<b>Sample size</b> Total recruited: N=28 Ethosuximide group: n=14 Sodium valproate group: n=14  <b>Characteristics</b> <u>Age, years, mean (range)</u> Ethosuximide group: 8 (4-14) Sodium valproate group: 9 (5-15)  <u>Gender</u> Ethosuximide group: 8 male; 6 female. Sodium valproate group: 5 male; 9 female.  <u>Age at onset of seizure, years, range</u> Ethosuximide group: 2-5 Sodium valproate group: 3-6  <b>Inclusion criteria</b> Patients with absence attacks associated with three-per-second spike and wave activity in the EEC  <b>Exclusion criteria</b> Not reported	<b>Interventions</b> <u>Ethosuximide:</u> prescribed initially in a dosage of 250mg per day, increased by 250mg increments to a maximum of 1500mg per day. Initially prescribed to be taken at 1 pm, but when the dose was increased to more than 250mg per day it was taken in divided doses at 8 am and 1 pm.  <u>Sodium valproate:</u> prescribed initially in a dosage of 400mg daily, increased by 200mg increments to a maximum of 2400mg daily. Prescribed to be taken at 8 am and 1 pm.	<b>Details</b> Treatment duration: unclear (mean 3 years, range 18 months - 4 years)  Outcome measurement: a 6 hour telemetry was carried out every 6 months, as well as reports from parents and teacher  Follow-up: mean 3 years (range 18 months - 4 years)	<b>Results</b> <u>Primary outcomes</u>  <u>Remission - complete</u> (no longer observed to have attacks during six-hour telemetry at two intervals of six months, and reported to have complete freedom from seizures) Ethosuximide group: n=8/14 Sodium valproate group: n=6/14  <u>Remission - partial</u> (>50% reduction in seizure frequency during six hour telemetry at two intervals of six months, and reported significant reduction in seizure frequency) Ethosuximide group: n=3/14 Sodium valproate group: n=6/14  <u>Remission - none</u> (<50% reduction in seizure frequency during six hour telemetry at two intervals of six months,	<b>Limitations</b> <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u>  <b>Domain 1: Randomisation: Some concerns</b> 1.1: No information, said to be randomised, not further information 1.2: No information 1.3: Probably no, no differences between baseline characteristics in the two groups, but very few baseline characteristics reported  <b>Domain 2: Deviations from intended interventions: Some concerns</b> 2.1: No information 2.2: No information 2.3: No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<p>control and side-effects.</p> <p><b>Study dates</b> Not reported.</p> <p><b>Source of funding</b> Labaz, Warner-Lambert Pharmaceuticals.</p>				<p>and reported slight or no improvement) Ethosuximide group: n=3/14 Sodium valproate group: n=2/14*</p> <p><u>EEG response - normal</u> Ethosuximide group: n=6/14 Sodium valproate group: n=4/14</p> <p><u>Adverse events - any</u> Ethosuximide group: n=1/14 Sodium valproate group: n=2/14</p>	<p>2.4: Probably yes, not all participants had intervention as intended 2.5: Probably yes, four participants crossed over due to poor response to initial drug 2.6: Probably yes</p> <p><b>Domain 3: Missing outcome data: Low risk</b> 3.1: Yes, data was available for nearly all participants</p> <p><b>Domain 4: Measurement of the outcome: Low risk</b> 4.1: Probably no, outcomes were well defined and assessed by telemetry (but not further defined) 4.2: No, outcomes included seizure frequency and adverse events which are unlikely to differ between treatment arms 4.3: Probably yes, not said to be double blind 4.4: Probably no, outcomes are objective</p> <p><b>Domain 5: Selection of the reported result: Some concerns</b> 5.1: No information</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					<p>5.2: No information 5.3: No information</p> <p><b>Domain 6: Overall judgement of bias: Some concerns</b> The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain</p>
<p><b>Full citation</b> Coppola, G., Auricchio, G., Federico, R., Carotenuto, M., Pascotto, A., Lamotrigine versus valproic acid as first-line monotherapy in newly diagnosed typical absence seizures: An open-label, randomized, parallel-group study, <i>Epilepsia</i>, 45, 1049-1053, 2004</p> <p><b>Ref Id</b> 1080163.</p> <p><b>Country/ies where the study was carried out</b> Italy</p> <p><b>Study type</b> RCT</p>	<p><b>Sample size</b> Total recruited: N=38 Intervention group (Lamotrigine): n=19 Control group (Valproic Acid): n=19</p> <p><b>Characteristics</b> <u>Age, years, mean (range)</u> Total sample: 7.5 (3-13)</p> <p><u>Age at seizure onset, years, mean (range)</u> Intervention: 7.5 (4-12) Control: 7.5 (3-13)</p> <p><u>Males, n (%)</u> Intervention: 7 (36.8) Control: 10 (52.6)</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Age from 3 to 13 years</li> <li>• Newly diagnosed typical absence seizures associated with generalized, synchronous 3-Hz (2.5–4 Hz) spike-and-wave activity, lasting &gt;3 s, occurring spontaneously or</li> </ul>	<p><b>Interventions</b> <u>Intervention group</u> 0.5 mg/kg/day for 2 weeks in two divided doses, followed by 1.0 mg/kg/day for an additional 2 weeks. Thereafter, doses were increased in 1-mg/kg/day increments every 5 days until seizures were controlled (as indicated by lack of clinical evidence of absences and no electroclinical seizures in an awake video-EEG with HVEEG and in a 24-h ambulatory EEG), intolerable adverse effects occurred, or a maximum dose of 12 mg/kg/day had been reached. the maximum allowed dose of LTG in patients completing without interruption the</p>	<p><b>Details</b> Duration of treatment: not reported.</p> <p>Outcome measurement: Patients were seen at monthly intervals for ≤12 months, and were questioned about side effects (recorded in a diary), a medical examination and a video EEG recording which included HV-IPS. A 24 hour ambulatory EEG was performed if there was no evidence of absences.</p>	<p><b>Results</b> <i>Primary outcomes</i></p> <p><u>Seizure free, n</u> (no clinical absences reported by external observers for at least the previous month, and no electroclinical seizures detected in awake video-EEG with HV-EEG and in 24-h ambulatory EEG monitoring)</p> <p><u>1 month</u> Intervention group 1/19 Control group 10/19</p> <p><u>3 months</u> Intervention group: n=7/19 Control group: n=12/19</p> <p><u>12 months</u> Intervention group: n=10/19 Control group: n=13/19</p> <p><u>Adverse events - any, n (%)</u> number of participants</p>	<p><b>Limitations</b> <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u></p> <p><b>Domain 1: Randomisation: Low risk</b> 1.1: No information, just said to be randomised 1.2: Probably yes, makes reference to an external investigator 1.3: No, no significant differences between groups at baseline</p> <p><b>Domain 2: Deviations from intended interventions: Low risk</b> 2.1: Yes, open label study 2.2: Yes, open label study</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<p><b>Aim of the study</b> To compare the efficacy of lamotrigine and valproic acid in newly diagnosed children and adolescents with typical absence seizures</p> <p><b>Study dates</b> Not reported (publication date 2004)</p> <p><b>Source of funding</b> Not reported</p>	<p>during one of two trials of 3-min hyperventilation with a 1- to 2-min rest between trials</p> <ul style="list-style-type: none"> <li>Clearly observable clinical signs of typical absence seizures (for example, staring or impairment of consciousness) on the video record</li> <li>Normal clinical, neurologic, and computed tomography (CT)/magnetic resonance imaging (MRI) examination</li> <li>Informed consent by parents or caregivers</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Absences with marked eyelid or perioral myoclonus (eyelid or perioral myoclonia with absences)</li> <li>Absences with marked limb and trunk rhythmic myoclonic jerks (myoclonic absence epilepsy)</li> <li>Absences with single ictal myoclonic jerks of the limbs, trunk, or head</li> <li>Absences with mild or not clinically detectable impairment of consciousness (for example, juvenile myoclonic epilepsy)</li> <li>Other types of epileptic seizures</li> <li>Stimulus-sensitive absences: photosensitive, patternsensitive, self-induced pattern-sensitive</li> <li>Irregular, arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency</li> </ul>	<p>full up titration schedule was reached ~75 days after initiation of treatment.</p> <p><u>Control group</u> Administered as 200-mg enteric-coated non-sustained-release sodium valproate tablets or as liquid formulation (40 mg/ml), started at 10 mg/kg/day and increased by 5 mg/kg/day every 3 days until seizures were controlled or intolerable side effects occurred, up to a maximum of 30 mg/kg/day given in three divided doses.</p>	<p>Data analysed according to intention to treat</p> <p>Follow-up: 12 months (assessments took place at 1 month, 3 months, and 12 months).</p>	<p>experiencing an adverse event Intervention group: n=6/19 Control group: n=2/19</p> <p><u>Treatment cessation due to adverse events</u>, n number of participants withdrawing from treatment due to adverse events Intervention group: n=0/19 Control group: n=0/19</p> <p><u>Withdrawal from study</u> (by 3 months) Intervention group n=6/19 Control group n=3/19.</p> <p><u>Withdrawal from study</u> (by 12 months) Intervention group n=6/19 Control group n=3/19.</p>	<p><b>Domain 3: Missing outcome data: Low risk</b> 3.1: Yes, data was available for all participants randomised</p> <p><b>Domain 4: Measurement of the outcome: Low risk</b> 4.1: No, outcomes were well defined and was assessed using reliable method (EEG) 4.2: No, outcomes included seizure free status and side effects, which are unlikely to differ between treatment arms 4.3: No, said to be unaware of treatment allocation</p> <p><b>Domain 5: Selection of the reported result: Some concerns</b> 5.1: No information, there is no reference to any study protocol 5.2: No information. Trial protocol was not available 5.3: No information. Trial protocol was not available</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<ul style="list-style-type: none"> <li>Central-temporal or occipital focal EEG discharges or abnormal background EEG activity</li> <li>Known or suspected structural brain lesion</li> <li>Progressive neurologic illness</li> <li>Psychiatric disorder requiring medication</li> <li>Chronic cardiovascular, renal, or hepatic disease and, in general, any disease that could interfere with drug absorption, distribution, metabolism, or excretion</li> <li>Long-term comedication with other drugs</li> <li>Suspected poor compliance</li> </ul>				<b>Domain 6: Overall judgment of bias: Some concerns</b> The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain
<b>Full citation</b> Fattore, C., Boniver, C., Capovilla, G., Cerminara, C., Citterio, A., Coppola, G., Costa, P., Darra, F., Vecchi, M., Perucca, E., A multicenter, randomized, placebo-controlled trial of levetiracetam in children and adolescents with newly diagnosed absence epilepsy, <i>Epilepsia</i> , 52, 802-809, 2011  <b>Ref Id</b> 1080326	<b>Sample size</b> Total recruited: N=59 Intervention group (levetiracetam): n=38 Control group (placebo): n=21  <b>Characteristics</b> <u>Age, years, mean (SD, range)</u> Intervention: 8.7 (2.2, 4.9 to 13.0) Control: 7.9 (3.0, 4.0 to 15.0) <u>Males, n</u> Intervention: 15 Control: 12 <u>Syndromic diagnosis, childhood absence epilepsy (n)</u> Intervention: 34 Control: 20 <u>Syndromic diagnosis, juvenile absence epilepsy (n)</u> Intervention: 4	<b>Interventions</b> <u>Intervention group</u> Levetiracetam dosage was 10 mg/kg/day for 3 days (days 1–3), followed by 15 mg/kg/day for the next 4 days (days 4–7). If tolerability was acceptable and clinical seizures occurred at any time between 1 h after the dose increase on day 4 and end of day 7, or if epileptic discharges were detected during the EEG assessment on day 7, dosage was further increased to 20 mg/kg/day on day 8	<b>Details</b> Treatment duration: 14 days.  Outcome measurement: EEG recordings were made on days 7 and 14. Adverse events were assessed at the study visits on days 7 and 14.  Data analysed according to per protocol  Follow-up: 15 days.	<b>Results</b> <u>Primary outcomes</u> <u>Responder status (no clinical seizures on days 13 and 14, and no EEG seizures during the standard EEG on day - ITT analysis)</u>  Levetiracetam n=9/38 Placebo n=1/21  <u>Patients free from clinical and EEG seizures on days 4–7 (this is, first week of treatment when levetiracetam dose could not exceed 15 mg/kg/day)</u> Intervention group: n=4/38 Control group: n=0/21	<b>Limitations</b> <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u>  <b>Domain 1: Randomisation: Low risk</b> 1.1: Yes, randomised using computer-generated random numbers 1.2: Probably yes, makes reference to maintaining blinding for subsequent assignments which were disclosed at study end 1.3: Probably no, some differences for example

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<p><b>Country/ies where the study was carried out</b> Italy</p> <p><b>Study type</b> Multi-centre, randomised, placebo-controlled trial</p> <p><b>Aim of the study</b> To evaluate the potential efficacy of levetiracetam as an antiabsence agent in children and adolescents with newly diagnosed childhood or juvenile absence epilepsy</p> <p><b>Study dates</b> Patient enrolment and treatment: October 2006–November 2008. Last assessment for open label phase: December 2009</p> <p><b>Source of funding</b> Supported by a grant from UCB S.p.A., Pianezza, Italy</p>	<p>Control: 1 <u>Seizure frequency at pretreatment, &gt;10/day</u> Intervention: 26 Control: 18 <u>Seizure frequency at pretreatment, 6–10/day</u> Intervention: 6 Control: 0 <u>Seizure frequency at pretreatment, 1–5/day</u> Intervention: 4 Control: 2 <u>Seizure frequency at pretreatment, 1–6/week</u> Intervention: 2 Control: 1</p> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Age between 4 and 16 years</li> <li>• Recent diagnosis of childhood or juvenile absence epilepsy, as defined by the International League Against Epilepsy (ILAE) criteria (Commission, 1989)</li> <li>• Electroencephalographic (EEG) evidence of regular, synchronous and symmetrical spike-wave paroxysmal discharges with a frequency of about 3 Hz and duration of at least 4 s, occurring spontaneously or during hyperventilation (a 2–3-min hyperventilation test, followed 2 min later by a second hyperventilation if paroxysms were not detected in the first test) or intermittent photic stimulation (IPS; 5 s stimulation at each</li> </ul>	<p>and, if well tolerated, to 30 mg/kg/day on day 11 and maintained until day 14. If no clinical or EEG seizures were detected on days 4–7, but clinical seizures re-emerged during days 8, 9, or 10, dosage was increased to 20 mg/kg/day on the day of seizure emergence and, if well tolerated, increased again after 3 days to 30 mg/kg/day and maintained until day 14. If no clinical or EEG seizures were detected during the double-blind period (or if seizures were detected after day 10 only), the dose was maintained from day 4 to day 14 at 15 mg/kg/day. If a tonic–clonic seizure occurred during the 14-day period, the subject was required to exit the study immediately due to ethical considerations.</p> <p><u>Control group</u> Placebo</p> <p>Depending on age, body weight, and</p>		<p><u>Patients free from clinical and EEG seizures on days 11–14</u> Intervention group: n=7/38 Control group: n=0/21</p> <p><u>50% reduction (vs baseline) in total duration of EEG seizures on day 14</u> Intervention group: n=12/38 Control group: n=3/21</p> <p><u>Adverse events - any</u> Intervention group: n=7/38 Control group: n=3/21</p> <p><u>Adverse events - serious</u> Intervention group n=0/38 Control group n=0/21</p> <p><u>Adverse events - thought to be related to treatment</u> Intervention group: n=3/38 Control group: n=0/21</p> <p><u>Adverse events - leading to discontinuation</u> Intervention group: n=1/38 Control group: n=0/21</p>	<p>gender, but not significant</p> <p><b>Domain 2: Deviations from intended interventions: Low risk</b> 2.1: No, said to be double blind 2.2: No, said to be double blind 2.3: N/A 2.4: Probably no, no mention of deviations from the intervention apart from one withdrawal 2.5: Probably no, nearly all participants received the intervention 2.6: N/A</p> <p><b>Domain 3: Missing outcome data: Low risk</b> 3.1: Yes, data was available for all but 1 participants randomised</p> <p><b>Domain 4: Measurement of the outcome: Low risk</b> 4.1: No, outcomes were well defined and was assessed using reliable method (EEG) 4.2: No, outcomes included seizure free status and side effects, which are unlikely</p>



Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<p>frequency in the 10–30 Hz range, eye closed)</p> <ul style="list-style-type: none"> <li>• A history of clinically evident spontaneously occurring absence seizures impacting on functional abilities</li> <li>• Written informed consent.</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>• A history of generalized tonic clonic seizures</li> <li>• Clinical or EEG findings inconsistent with a diagnosis of childhood or juvenile absence epilepsy</li> <li>• Previous treatment with ASMs (except for earlier treatments for other indications such as febrile seizures, or brief exposures to other ASMs prior to diagnostic assessment)</li> <li>• Intellectual disability</li> <li>• Clinically significant hepatic or renal disorders</li> <li>• History of hypersensitivity reactions to study products or structurally related substances</li> <li>• Any condition that, in the investigator's judgment, was expected to impact negatively on subjects' health or study procedures.</li> </ul>	<p>preference, either a liquid formulation (100 mg/ml solution) or 500 mg tablets were used, with matching placebos.</p> <p>Both treatments were administered in the morning and in the evening in two equally divided doses</p>			<p>to differ between treatment arms</p> <p>4.3: No, randomisation was only broken after outcome measure evaluation</p> <p><b>Domain 5: Selection of the reported result: Some concerns</b></p> <p>5.1: No information, there is no reference to any study protocol</p> <p>5.2: No information. Trial protocol was not available</p> <p>5.3: No information. Trial protocol was not available</p> <p><b>Domain 6: Overall judgement of bias: Some concerns</b></p> <p>The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain</p> <p><b>Other information</b></p> <p>After the 2 week double-blind period, all placebo participants were started on levetiracetam. Some participants in both groups discontinued with levetiracetam and</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					started other drugs, for example, valproate.
<p><b>Full citation</b> Frank, L. M., Enlow, T., Holmes, G. L., Manasco, P., Concannon, S., Chen, C., Womble, G., Casale, E. J., Lamictal (lamotrigine) monotherapy for typical absence seizures in children, <i>Epilepsia</i>, 40, 973-979, 1999</p> <p><b>Ref id</b> 1080361</p> <p><b>Country/ies where the study was carried out</b> USA</p> <p><b>Study type</b> Double blind, placebo controlled study</p> <p><b>Aim of the study</b> To investigate whether lamotrigine is effective and safe for newly diagnosed typical absence seizures in children and adolescents</p>	<p><b>Sample size</b> Total recruited and took part in dose escalation phase: N=45.</p> <p>Total randomised after dose escalation phase: Lamotrigine group: n=15 Placebo group: n=14</p> <p>Total analysed Lamotrigine group: n=14 (1 patient in the lamotrigine, group withdrew consent) Placebo group: n=14 (1 patient failed to meet the 80% compliance standard; however they were included in the analysis on an intent-to-treat basis).</p> <p><b>Characteristics</b> <u>Age, years, mean (SD)</u> Lamotrigine group: 6.9 (2.3) Placebo group: 8.8 (3.1) <u>Gender</u> Lamotrigine group: 36% males, 64% females Placebo group: 36% males, 64% females</p> <p><b>Inclusion criteria</b> • Patients 2-16 years old with newly diagnosed typical absence seizures, as evidenced by the clinical and EEG features of typical</p>	<p><b>Interventions</b> Before randomisation to lamotrigine or placebo, all participants underwent a dose escalation phase to identify the dose at which they would be rendered seizure free.</p> <p><u>Lamotrigine:</u> Initial dose of 0.5mg/kg/day for 2 weeks, followed by 1mg/kg/day for 2 weeks. Following increases by 1mg/kg/day according to response, maximum dose of 15mg/kg/day. Chewable 5mg, 25 and 100mg tablets were provided. Continued at the dose identified during the dose escalation stage for 4 weeks. No adjustment of dose was permitted.</p> <p><u>Placebo:</u> The dose of lamotrigine during the dose escalation phase was tapered to placebo over 2 weeks: patients received 50, 25%, and 0 (this is, 100% placebo) of their</p>	<p><b>Details</b> Duration of treatment: dose escalation study, ≥5 weeks; RCT study, 4 weeks</p> <p>Outcome measurement: Ambulatory 24-hour EEG and hyperventilation test during EEGs were carried out at baseline, end of dose escalation, and end of the RCT phase.</p> <p>Follow-up: 4 weeks (RCT study only).</p>	<p><b>Results</b> <i>Primary outcomes</i></p> <p><u>Remained seizure free at end of placebo controlled phase</u> Lamotrigine group: 9/14 Placebo group: 3/14</p> <p><u>Adverse events - leading to withdrawal from study</u> Lamotrigine group: n=0/14 Placebo group: n=0/14</p>	<p><b>Limitations</b> <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u></p> <p><b>Domain 1: Randomisation: Some concerns</b> 1.1: No information, said to be randomised, not further information 1.2: No information 1.3: No, no significant differences at baseline between groups</p> <p><b>Domain 2: Deviations from intended interventions: Low risk</b> 2.1: No, said to be double blind 2.2: No, said to be double blind 2.3: N/A 2.4: Probably no, no mention of deviations from the intervention 2.5: Probably no, nearly all participants received the intervention apart from one participant who was not compliant 2.6: N/A</p>



Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<p><b>Study dates</b> Not reported</p> <p><b>Source of funding</b> Glaxo Wellcome Inc. (Research Triangle Park, NC)</p>	<p>absence seizures on one of two 3-min hyperventilation tests</p> <ul style="list-style-type: none"> <li>Any woman of reproductive capability was required to use a contraceptive method acceptable to the investigator and to provide a written statement of intent to avoid pregnancy</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>A known or suspected structural lesion</li> <li>A history of poor compliance with medication or abuse of drugs</li> <li>A progressive neurologic illness (defined prospectively as being an unstable pathologic state during the previous 12 months)</li> <li>A psychiatric disorder requiring medication</li> <li>Chronic cardiovascular, renal, or hepatic disease</li> <li>Use of an investigational drug within the previous 12 weeks</li> <li>Any disease thought to interfere with absorption, distribution, metabolism, or excretion of drugs in general</li> <li>With the exception of patients taking methylphenidate, dexamphetamine, or clonidine to treat attention-deficit hyperactivity disorder, patients were not allowed to take psychotropic drugs at any time during the study.</li> </ul>	<p>seizure-free dose during the first, second, and remaining 2 weeks.</p>			<p><b>Domain 3: Missing outcome data: Low risk</b> 3.1: Yes, data was available for all but 1 participants randomised</p> <p><b>Domain 4: Measurement of the outcome: Low risk</b> 4.1: No, outcomes were well defined and was assessed using reliable method (EEG) 4.2: No, outcomes included seizure free status and side effects, which are unlikely to differ between treatment arms 4.3: Probably no, EEG recordings were analysed by an investigator who was unaware of treatments or doses</p> <p><b>Domain 5: Selection of the reported result: Some concerns</b> 5.1: Probably yes, there is a protocol however it is not detailed 5.2: Probably no 5.3: Probably no</p> <p><b>Domain 6: Overall judgement of bias: Some concerns</b> The study is judged to raise some concerns in</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					<p>at least one domain, but not to be at high risk of bias for any domain.</p> <p><b>Other information</b> 28 patients completed double-blind phase (one patient in the LTG, group withdrew consent). Only one patient (in the placebo-treated group) failed to meet the 80% compliance standard; this patient was included in analysis on an intent-to-treat basis.</p>
<p><b>Full citation</b> Glauser, T. A., Cnaan, A., Shinnar, S., Hirtz, D. G., Dlugos, D., Masur, D., Clark, P. O., Capparelli, E. V., Adamson, P. C., Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy, <i>New England Journal of Medicine</i>, 362, 790-799, 2010</p> <p><b>Ref Id</b> 1082357</p>	<p><b>Sample size</b> Total randomised: N=453 Ethosuximide group: n=156 Lamotrigine group: n=149 Valproic acid group: n=148</p> <p><b>Characteristics</b> <u>Age ≥6 years, n (%)</u> Ethosuximide group: 116 (75) Lamotrigine group: 110 (74) Valproic acid group: 113 (77) <u>Male sex, n (%)</u> Ethosuximide group: 65 (42) Lamotrigine group: 57 (38) Valproic acid group: 71 (48)</p> <p>No statistically significant differences seen between the treatment groups</p> <p><b>Inclusion criteria</b></p>	<p><b>Interventions</b> <u>Ethosuximide (Zarontin)</u> 250-mg capsules or 250 mg per 5 ml of syrup. The highest allowable daily dose was 60 mg per kilogram of body weight, to a maximum of 2000 mg/day.</p> <p><u>Lamotrigine (Lamictal)</u> 5-mg and 25-mg chewable tablets or 25-mg tablets. The highest allowable daily dose was 12 mg per kilogram of body weight, to a maximum of 600 mg/day.</p>	<p><b>Details</b> Treatment duration: 12 months.</p> <p>Outcome measurement: seizure status was determined by clinical report, bedside hyperventilation testing, and 1-hour video EEG</p> <p>Data analysed according to intention-to-treat approach</p> <p>Follow-up: 12 months. This paper report</p>	<p><b>Results</b> <i>Primary outcomes</i> <u>Freedom from treatment failure at 16 or 20 weeks</u> (treatment failure defined as persistence of absence seizures, a generalised tonic-clonic seizure at any time, excessive drug-related systemic toxicity of at least 3.0 from baseline, dose-limiting toxicity after a single downward dose modification, and withdrawal initiated by the parent or physician):</p> <p>Ethosuximide: 81/154 Lamotrigine: 43/146 Valproic acid: 85/146</p>	<p><b>Limitations</b> <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u></p> <p><b>Domain 1: Randomisation: Some concerns</b> 1.1: Yes, said to be computer generated 1.2: Probably yes, treatment assignments were performed centrally 1.3: No, no significant differences at baseline between groups</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<p><b>Country/ies where the study was carried out</b> USA</p> <p><b>Study type</b> Multicentre, double-blind, randomised controlled trial</p> <p><b>Aim of the study</b> To assess the efficacy, tolerability, and neuropsychological effect of ethosuximide, valproic acid, and lamotrigine to determine the optimal initial empirical monotherapy for children with childhood absence epilepsy</p> <p><b>Study dates</b> July 2004 to October 2007</p> <p><b>Source of funding</b> Supported by grants from the National Institutes of Health</p>	<ul style="list-style-type: none"> <li>Between 2.5 and 13 years of age</li> <li>Childhood absence epilepsy of new onset that was clinically diagnosed according to the International League Against Epilepsy classification of epilepsy syndromes (including frequent clinical absence seizures and reported normal development)</li> <li>Had bilateral synchronous, symmetric spike waves (2.7 to 5 Hz) on a normal background with at least one electrographically recorded seizure lasting 3 seconds or more on a 1-hour, awake video EEG</li> <li>Weighed 10 kg or more</li> <li>Had a body-mass index below the 99th percentile</li> <li>Had a normal complete blood count and normal levels of serum alanine aminotransferase, serum aspartate aminotransferase, and bilirubin</li> <li>The girls had to be premenarchal</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Had received antiseizure medication for more than 7 days before randomization</li> <li>Had a history of nonfebrile seizures other than absence seizures (for example, afebrile generalized tonic-clonic or myoclonic seizures)</li> <li>Had a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy (for example,</li> </ul>	<p><u>Valproic acid (Depakote)</u> 25-mg capsules or 125-mg dose of sprinkles. The highest allowable daily dose was 60 mg per kilogram of body weight, to a maximum of 3000 mg/day.</p> <p>Doses were increased every 1 to 2 weeks over a 16-week period until either freedom from seizures was attained or side effects limited the dose given</p>	<p>findings at 16 or 20 weeks (primary outcome data based on assessments at week 16 unless the participant had a 5th visit at 20 weeks, in which case data from the 20 week assessment was used. Glauser, 2013 reports 12 months follow-up data.</p>	<p><u>Adverse events - serious (16 or 20 weeks)</u> Ethosuximide: 4/155 Lamotrigine: 2/149 Valproic acid: 2/147</p> <p><u>Intolerable adverse effects (16 or 20 weeks)</u> Ethosuximide: 37/154 Lamotrigine: 25/146 Valproic acid: 35/146</p> <p><u>Study drug discontinued – no reason reported (16 or 20 weeks)</u> Ethosuximide: 0/154 Lamotrigine: 1/146 Valproic acid: 0/146</p> <p><u>Withdrawal from study (16 or 20 weeks)</u> Ethosuximide: 20/154 Lamotrigine: 18/146 Valproic acid: 15/146</p> <p><i>Secondary outcomes</i></p> <p><u>Attentional dysfunction (defined as a Confidence Index of 0.60 or higher on the Conners' Continuous Performance Test, 16 or 20 weeks):</u> Ethosuximide: 35/106 Lamotrigine: 25/104 Valproic acid: 52/106</p>	<p><b>Domain 2: Deviations from intended interventions: Low risk</b> 2.1: Probably no, said to be double blind 2.2: Probably no, said to be double blind 2.3: N/A 2.4: N/A 2.5: N/A 2.6: Yes</p> <p><b>Domain 3: Missing outcome data: Low risk</b> 3.1: Yes, data was available for nearly all participants</p> <p><b>Domain 4: Measurement of the outcome: Low risk</b> 4.1: No, outcomes were well defined and was assessed using reliable method (EEG) 4.2: No, outcomes included seizure free control and side effects, which are unlikely to differ between treatment arms 4.3: No information 4.4: Probably no, outcomes are objective, not subjective</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<p>generalized tonic–clonic or myoclonic seizures)</p> <ul style="list-style-type: none"> <li>• Had a history of a severe dermatologic reaction to any medication</li> <li>• Had a history of major psychiatric disease, autistic-spectrum disorder, or any clinically significant medical condition</li> </ul>				<p><b>Domain 5: Selection of the reported result: Low</b></p> <p>5.1: Probably yes, there is a protocol however it is not detailed</p> <p>5.2: Probably no</p> <p>5.3: Probably no</p> <p><b>Domain 6: Overall judgement of bias: Low</b></p> <p>The study is judged to be at low risk of bias</p>
<p><b>Full citation</b></p> <p>Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC, Childhood Absence Epilepsy Study Team.</p> <p>Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. <i>Epilepsia</i>. 2013 Jan;54(1):141-55.</p>	See Glauser 2010	See Glauser 2010	See Glauser 2010	<p><i>Primary outcomes</i></p> <p><u>Freedom from treatment failure at 12 months</u> (treatment failure defined as persistence of absence seizures, a generalised tonic–clonic seizure at any time, excessive drug-related systemic toxicity of at least 3.0 from baseline, dose-limiting toxicity after a single downward dose modification, and withdrawal initiated by the parent or physician):</p> <p>Ethosuximide: 70/154</p> <p>Lamotrigine: 31/146</p> <p>Valproic acid: 64/146</p> <p><u>Adverse events - serious (12 months)</u></p> <p>Ethosuximide: 4/155</p> <p>Lamotrigine: 2/149</p> <p>Valproic acid: 2/147</p>	See Glauser 2010

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				<u>Intolerable adverse effects (12 months)</u> Ethosuximide: 38/154 Lamotrigine: 29/146 Valproic acid: 48/146  <u>Withdrawal from study (12 months)</u> Ethosuximide: 29/154 Lamotrigine: 18/146 Valproic acid: 21/146  <u>Attentional dysfunction defined as a Confidence Index of 0.60 or higher on the Conners' Continuous Performance Test; 12 months):</u> Ethosuximide: 20/70 Lamotrigine: 8/30 Valproic acid: 34/61	
<b>Full citation</b> Sato, S., White, B. G., Penry, J. K., Valproic acid versus ethosuximide in the treatment of absence seizures, Neurology, 32, 157-163, 1982  <b>Ref Id</b> 1115033  <b>Country/ies where the study was carried out</b> USA	<b>Sample size</b> Total recruited: N=45 Ethosuximide during period I group: n=23 (treatment naïve n=9, refractory n=14) Valproic acid during period I group: n=22 (treatment naïve n=7, refractory n=15)  <b>Characteristics</b> <u>Age (mean, range)</u> 11.7 years, 4-18  <u>Sex</u> 18 male; 27 female.  <b>Inclusion criteria</b>	<b>Interventions</b> <u>Valproic acid and placebo Ethosuximide (followed by Ethosuximide and placebo Valproic acid in period II):</u> For group 1 (first 23 patients enrolled): Daily dosage of Valproic acid started at 15-20 mg per kg and 5 days later increased to a maximum of 30 mg/kg if the 12-hour EEG showed generalised spike wave discharges	<b>Details</b> Duration of treatment: 6 weeks of period I drug, followed by 6 weeks of period II drug  Outcome measurement: assessment of seizure control took place at 6 and 12 weeks of treatment.	<b>Results</b> <u>Primary outcomes</u> <u>Seizure freedom – treatment naïve patients (100% reduction in spike wave bursts on EEG)</u> Ethosuximide in period 1 n=4/9. Valproic acid in period 1: n=6/7  <u>Seizure freedom – refractory patients (80% reduction in spike wave bursts on EEG)</u> Ethosuximide in period 1 n=4/14. Valproic acid in period 1: n=3/15	<b>Limitations</b> <u>Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0)</u>  <b>Domain 1: Randomisation: Some concerns</b> 1.1: No information, said to be randomly assigned, not further information 1.2: No information 1.3: No information, baseline characteristics are reported overall rather than for each group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
<p><b>Study type</b> Double-blind, randomised, response-conditional crossover trial</p> <p><b>Aim of the study</b> To evaluate the efficacy of VPA in treating absence seizures</p> <p><b>Study dates</b> Not reported</p> <p><b>Source of funding</b> The NINCDS</p>	<ul style="list-style-type: none"> <li>Male patients and female patients with no childbearing potential</li> <li>3 to 18 years of age</li> <li>Absence seizures which must have been observed by one of the investigators and must have occurred at least once on the pretreatment 12-hour telemetered EEG. Some patients also had other types of seizures.</li> <li>No evidence of progressive neurologic illness</li> <li>must have been kept on the maximally tolerated daily dosage of ESM for 1 month before the study</li> </ul> <p><b>Exclusion criteria</b> Not reported</p>	<p>For group 2 (the next 22 patients enrolled): Initial daily dosage of 12.5 to 20 mg/kg, with a dosage increase every 2 days for 2 weeks, to a maximum of 60 mg/kg/day</p> <p><u>Ethosuximide and Valproic acid placebo (followed by Valproic acid and Ethosuximide placebo in period II):</u></p> <p>Group 1: Daily dosage ranged from 250 to 1500mg</p> <p>Group 2: Daily dosage was 250 to 1500 mg.</p> <p>For both groups anti-seizure drugs for the treatment of other seizure types were continued throughout the study.</p>	<p>Follow-up: 6 weeks (period 1 only).</p>		<p><b>Domain 2: Deviations from intended interventions: Low risk</b></p> <p>2.1: Probably no, said to be double blind but no details</p> <p>2.2: Probably no, said to be double blind but no details</p> <p>2.3: N/A</p> <p>2.4: Probably no, no mention of deviations from the intervention</p> <p>2.5: Probably no, for period I there were no drop outs. Some participants did not cross over to period II</p> <p>2.6: N/A</p> <p><b>Domain 3: Missing outcome data: Low risk</b></p> <p>3.1: Yes, data was available for nearly all participants for period I</p> <p><b>Domain 4: Measurement of the outcome: Low risk</b></p> <p>4.1: No, outcomes were well defined and was assessed using reliable method (EEG)</p> <p>4.2: No, outcomes included seizure frequency which is unlikely</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					<p>to differ between treatment arms  4.3: No information  4.4: Probably no, outcomes are objective</p> <p><b>Domain 5: Selection of the reported result:</b>  <b>Some concerns</b>  5.1: No information  5.2: No information  5.3: No information  <b>Domain 6: Overall judgement of bias: Some concerns</b>  The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain</p> <p><b>Other information</b>  Both naive and refractory patients were enrolled. Naive patients who had 100% seizure control in the first phase, and refractory patients who had at least 80% seizure control in the first phase were not crossed over to a different drug in phase II, but instead maintained on the same drug. Only those who did not respond or experienced adverse events were</p>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					crossed over in phase II.

*EEG: electroencephalogram; ESM: ethosuximide; LTG: lamotrigine; RCT: randomised controlled trial; SD: standard deviation; VPA: valproic acid*

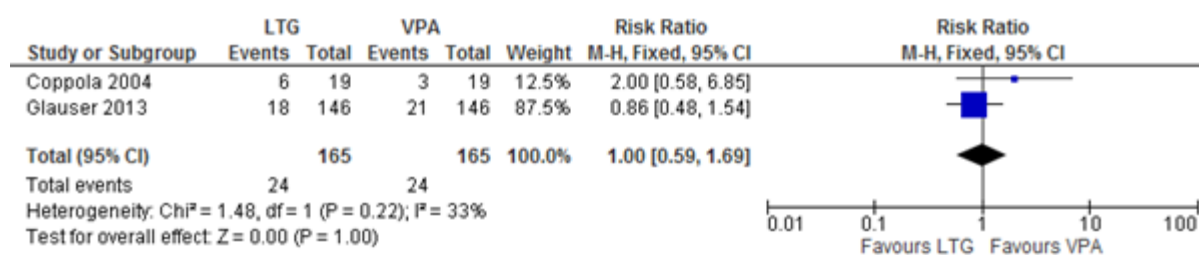


## Appendix E – Forest plots

Forest plots for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?

Comparison 2: lamotrigine versus valproic acid

Figure 2: withdrawal from study (12 months)



## Appendix F – GRADE tables

**GRADE tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

**Table 9: Clinical evidence profile. Comparison 1: ethosuximide versus sodium valproate**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	VPA	Relative (95% CI)	Absolute		
Seizure free at 6 weeks - naive												
1 (Sato 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	4/9 (44.4%)	6/7 (85.7%)	RR 0.52 (0.24 to 1.14)	411 fewer per 1000 (from 651 fewer to 120 more)	⊕⊕⊕⊕ LOW	CRITICAL
Seizure free at 6 weeks - refractory												
1 (Sato 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	4/14 (28.6%)	3/15 (20%)	RR 1.43 (0.39 to 5.28)	86 more per 1000 (from 122 fewer to 856 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
Freedom from treatment failure at 16 or 20 weeks*												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	81/154 (52.6%)	85/146 (58.2%)	RR 0.9 (0.74 to 1.11)	58 fewer per 1000 (from 151 fewer to 64 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Freedom from treatment failure at 12 months*												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	70/154 (45.5%)	64/146 (43.8%)	RR 1.04 (0.81 to 1.33)	18 more per 1000 (from 83 fewer to 145 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Remission - complete (no longer observed to have attacks during six-hour telemetry at two intervals of six months, and reported to have complete freedom from seizures)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	VPA	Relative (95% CI)	Absolute		
1 (Callaghan 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	8/14 (57.1%)	6/14 (42.9%)	RR 1.33 (0.63 to 2.84)	141 more per 1000 (from 159 fewer to 789 more)	⊕○○○ VERY LOW	CRITICAL
<b>Remission - partial (&gt;50% reduction in seizure frequency during six hour telemetry at two intervals of six months, and reported significant reduction in seizure frequency)</b>												
1 (Callaghan 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	3/14 (21.4%)	6/14 (42.9%)	RR 0.5 (0.15 to 1.61)	214 fewer per 1000 (from 364 fewer to 261 more)	⊕○○○ VERY LOW	CRITICAL
<b>Remission - none (&lt;50% reduction in seizure frequency during six hour telemetry at two intervals of six months, and reported slight or no improvement)</b>												
1 (Callaghan 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	3/14 (21.4%)	2/14 (14.3%)	RR 1.5 (0.29 to 7.65)	71 more per 1000 (from 101 fewer to 950 more)	⊕○○○ VERY LOW	CRITICAL
<b>EEG response - normal (follow-up 18 months - 4 years, mean = 3 years)</b>												
1 (Callaghan 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	6/14 (42.9%)	4/14 (28.6%)	RR 1.5 (0.54 to 4.18)	143 more per 1000 (from 131 fewer to 909 more)	⊕○○○ VERY LOW	CRITICAL
<b>Adverse events - any (follow-up 18 months - 4 years, mean = 3 years)</b>												
1 (Callaghan 1982)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	1/14 (7.1%)	2/14 (14.3%)	RR 0.5 (0.05 to 4.9)	71 fewer per 1000 (from 136 fewer to 557 more)	⊕○○○ VERY LOW	CRITICAL
<b>Adverse events - serious (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	4/155 (2.6%)	2/147 (1.4%)	RR 1.9 (0.35 to 10.2)	12 more per 1000 (from	⊕⊕○○ LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	VPA	Relative (95% CI)	Absolute		
										9 fewer to 125 more)		
<b>Adverse events - serious (follow-up 12 months)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	4/155 (2.6%)	2/147 (1.4%)	RR 1.9 (0.35 to 10.2)	12 more per 1000 (from 9 fewer to 125 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Intolerable adverse effects (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	37/154 (24%)	35/146 (24%)	RR 1 (0.67 to 1.5)	0 fewer per 1000 (from 79 fewer to 120 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Intolerable adverse effects (follow-up 12 months)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	38/154 (24.7%)	48/146 (32.9%)	RR 0.75 (0.52 to 1.08)	82 fewer per 1000 (from 158 fewer to 26 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
<b>Study drug discontinued – no reason reported (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	none	0/154 (0%)	0/146 (0%)	RD 0.00 (-0.01 to 0.01)	0 more per 1000 (from 10 fewer to 10 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Withdrawal from study (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	20/154 (13%)	15/146 (10.3%)	RR 1.26 (0.67 to 2.37)	27 more per 1000 (from 34 fewer to 141 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Withdrawal from study (follow-up 12 months)</b>												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	VPA	Relative (95% CI)	Absolute		
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	29/154 (18.8%)	21/146 (14.4%)	RR 1.31 (0.78 to 2.19)	45 more per 1000 (from 32 fewer to 171 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Conners' Continuous Performance Test score &gt; 0.60<sup>*</sup> (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	35/106 (33%)	52/106 (49.1%)	RR 0.67 (0.48 to 0.94)	162 fewer per 1000 (from 29 fewer to 255 fewer)	⊕⊕⊕⊕ MODERATE	IMPORTANT
<b>Conners' Continuous Performance Test score &gt; 0.60<sup>*</sup> (follow-up 12 months)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/70 (28.6%)	34/61 (55.7%)	RR 0.51 (0.33 to 0.79)	273 fewer per 1000 (from 117 fewer to 373 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

\* Treatment failure defined as persistence of absence seizures, a generalised tonic-clonic seizure at any time, excessive drug-related systemic toxicity of at least 3.0 from baseline, dose-limiting toxicity after a single downward dose modification, and withdrawal initiated by the parent or physician.

<sup>\*</sup>An index of 0.60 corresponds to a 60% probability that the child has clinically significant attention deficit disorder

<sup>1</sup> Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

<sup>2</sup> Confidence interval crosses one MID (0.8 or 1.25)

<sup>3</sup> Confidence intervals cross both MIDs (0.8 and 1.25)

<sup>4</sup> Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)

**Table 10: Clinical evidence profile. Comparison 2: lamotrigine versus sodium valproate**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTG	VPA	Relative (95% CI)	Absolute		
Seizure freedom - 1 month												
1 (Copol-pola 2004)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/19 (5.3%)	10/19 (52.6%)	RR 0.1 (0.01 to 0.71)	474 fewer per 1000 (from 153	⊕⊕⊕⊕ MODERATE	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTG	VPA	Relative (95% CI)	Absolute		
										fewer to 521 fewer)		
<b>Seizure freedom - 3 months</b>												
1 (Cop-pola 2004)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	7/19 (36.8%)	12/19 (63.2%)	RR 0.58 (0.3 to 1.15)	265 fewer per 1000 (from 442 fewer to 95 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Seizure freedom - 12 months</b>												
1 (Cop-pola 2004)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	10/19 (52.6%)	13/19 (68.4%)	RR 0.77 (0.46 to 1.3)	157 fewer per 1000 (from 369 fewer to 205 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Freedom from treatment failure at 16 or 20 weeks*</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	43/146 (29.5%)	85/146 (58.2%)	RR 0.51 (0.38 to 0.67)	285 fewer per 1000 (from 192 fewer to 361 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Freedom from treatment failure at 12 months*</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/146 (21.2%)	64/146 (43.8%)	RR 0.48 (0.34 to 0.7)	228 fewer per 1000 (from 132 fewer to 289 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
<b>Adverse events - any (follow-up 12 months)</b>												
1 (Cop-pola 2004)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	6/19 (31.6%)	2/19 (10.5%)	RR 3 (0.69 to 13.03)	211 more per 1000 (from 33 fewer to 1000 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Adverse events - serious (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	2/149 (1.3%)	2/147 (1.4%)	RR 0.99 (0.14 to 6.91)	0 fewer per 1000 (from 12 fewer to 12 more)	⊕⊕⊕⊕ LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTG	VPA	Relative (95% CI)	Absolute		
										fewer to 80 more)		
<b>Adverse events - serious (follow-up 12 months)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	2/149 (1.3%)	2/147 (1.4%)	RR 0.99 (0.14 to 6.91)	0 fewer per 1000 (from 12 fewer to 80 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Treatment cessation due to adverse events (follow-up 12 months)</b>												
1 (Cop-pola 2004)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	none	0/19 (0%)	0/19 (0%)	RD 0.00 (-0.10 to 0.10)	0 fewer per 1000 (from 10 fewer to 10 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
<b>Intolerable adverse effects (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	25/146 (17.1%)	35/146 (24%)	RR 0.71 (0.45 to 1.13)	70 fewer per 1000 (from 132 fewer to 31 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
<b>Intolerable adverse effects (follow-up 12 months)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	29/146 (19.9%)	48/146 (32.9%)	RR 0.6 (0.41 to 0.9)	132 fewer per 1000 (from 33 fewer to 194 fewer)	⊕⊕⊕⊕ MODERATE	CRITICAL
<b>Study drug discontinued – no reason reported (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	1/146 (0.68%)	0/146 (0%)	RR 3 (0.12 to 73.04)	10 more per 1000 (from 10 fewer to 30 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Withdrawal from study (follow-up 3 months)</b>												
1 (Cop-pola 2004)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	6/19 (31.6%)	3/19 (15.8%)	RR 2 (0.58 to 6.85)	158 more per 1000 (from 66	⊕⊕⊕⊕ VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTG	VPA	Relative (95% CI)	Absolute		
										fewer to 924 more)		
<b>Withdrawal from study (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	18/146 (12.3%)	15/146 (10.3%)	RR 1.2 (0.63 to 2.29)	21 more per 1000 (from 38 fewer to 133 more)	⊕⊕⊕⊕ LOW	CRITICAL
<b>Withdrawal from study (12 months)</b>												
2 (Coppola 2004, Glauser 2013)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	24/165 (14.5%)	24/165 (14.5%)	RR 1 (0.59 to 1.69)	0 fewer per 1000 (from 60 fewer to 100 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL
<b>Conners' performance test score &gt; 0.60<sup>4</sup> (follow-up 16 or 20 weeks)</b>												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	25/104 (24%)	52/106 (49.1%)	RR 0.49 (0.33 to 0.73)	250 fewer per 1000 (from 132 fewer to 329 fewer)	⊕⊕⊕⊕ HIGH	IM-PORTANT
<b>Conners' performance test score &gt; 0.60<sup>4</sup> (follow-up 12 months)</b>												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	8/30 (26.7%)	34/61 (55.7%)	RR 0.48 (0.25 to 0.9)	290 fewer per 1000 (from 56 fewer to 418 fewer)	⊕⊕⊕⊕ MODERATE	IM-PORTANT

\* Treatment failure defined as persistence of absence seizures, a generalised tonic-clonic seizure at any time, excessive drug-related systemic toxicity of at least 3.0 from baseline, dose-limiting toxicity after a single downward dose modification, and withdrawal initiated by the parent or physician.

\*An index of 0.60 corresponds to a 60% probability that the child has clinically significant attention deficit disorder

<sup>1</sup> Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

<sup>2</sup> 95% Confidence interval crosses 1 MID (0.8 or 1.25)

<sup>3</sup> 95% Confidence interval crosses both MIDs (0.8 and 1.25)

<sup>4</sup> Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)



**Table 11: Clinical evidence profile. Comparison 3: levetiracetam versus placebo**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	Placebo	Relative (95% CI)	Absolute		
Responder status (free from clinical seizures on days 13 and 14, and no EEG seizures during standard EEG on day 14) – ITT analysis												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	9/38 (23.7%)	1/21 (4.8%)	RR 4.97 (0.68 to 36.61)	189 more per 1000 (from 15 fewer to 1000 more)	⊕○○○ VERY LOW	CRITICAL
Patients free from clinical and EEG seizures - days 4-7 (follow-up 4-7 days)												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	4/38 (10.5%)	0/21 (0%)	POR 5.14 (0.63 to 42.06)	110 more per 1000 (from 10 fewer to 220 more)	⊕○○○ VERY LOW	CRITICAL
Patients free from clinical and EEG seizures - days 11-14 (follow-up 11-14 days)												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>3</sup>	none	7/38 (18.4%)	0/21 (0%)	POR 5.65 (1.1 to 28.96)	180 more per 1000 (from 50 more to 320 more)	⊕⊕○○ LOW	CRITICAL
50% reduction (vs baseline) in total duration of EEG seizures on day 14 (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	12/38 (31.6%)	3/21 (14.3%)	RR 2.21 (0.7 to 6.96)	173 more per 1000 (from 43 fewer to 851 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events - any (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	7/38 (18.4%)	3/21 (14.3%)	RR 1.29 (0.37 to 4.47)	41 more per 1000 (from 90 fewer to 496 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events – serious (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>4</sup>	none	0/38	0/21	RD 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events - thought to be related to treatment (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	3/38 (7.9%)	0/21 (0%)	POR 4.99 (0.45 to 55.33)	80 more per 1000 (from 30 fewer to 190 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events - leading to discontinuation (follow-up mean 14 days)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	Placebo	Relative (95% CI)	Absolute		
1 (Fattore 2011)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>2</sup>	none	1/38 (2.6%)	0/21 (0%)	POR 4.72 (0.08 to 283.20)	30 more per 1000 (from 60 fewer to 110 more)	⊕○○○ VERY LOW	CRITICAL

<sup>1</sup> Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

<sup>2</sup> Confidence intervals cross both MIDs (0.8 and 1.25)

<sup>3</sup> Confidence interval crosses one MID (0.8 or 1.25)

<sup>4</sup> Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)

**Table 12: Clinical evidence profile. Comparison 4: lamotrigine versus placebo**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTG	Placebo	Relative (95% CI)	Absolute		
Remained seizure free at end of placebo controlled phase (follow-up mean 4 weeks)												
1 (Frank 1999)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	9/14 (64.3%)	3/14 (21.4%)	RR 3 (1.02 to 8.8)	429 more per 1000 (from 4 more to 1000 more)	⊕⊕⊕⊕ LOW	CRITICAL
Adverse events - leading to withdrawal from study												
1 (Frank 1999)	RCT	serious <sup>1</sup>	no serious inconsistency	no serious indirectness	very serious <sup>3</sup>	none	0/14 (0%)	0/14 (0%)	RD 0.00 (-0.13 to 0.13)	0 more per 1000 (from 130 fewer to 130 more)	⊕⊕⊕⊕ VERY LOW	CRITICAL

<sup>1</sup> Serious risk of bias in the evidence contributing to the outcomes as per RoB 2

<sup>2</sup> Confidence interval crosses one MID (0.8 or 1.25)

<sup>3</sup> Absolute effect range crosses 2 MIDs (10 more per 1000 and 10 fewer per 1000)

**Table 13: Clinical evidence profile. Comparison 5: ethosuximide versus lamotrigine**

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	LTG	Relative (95% CI)	Absolute		
Freedom from treatment failure at 16 or 20 weeks*												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	LTG	Relative (95% CI)	Absolute		
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/154 (52.6%)	43/146 (29.5%)	RR 1.79 (1.33 to 2.39)	233 more per 1000 (from 97 more to 409 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Freedom from treatment failure at 12 months*												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	70/154 (45.5%)	31/146 (21.2%)	RR 2.14 (1.5 to 3.06)	242 more per 1000 (from 106 more to 437 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events - serious (follow-up 16 or 20 weeks)												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	4/155 (2.6%)	2/149 (1.3%)	RR 1.92 (0.36 to 10.34)	12 more per 1000 (from 9 fewer to 125 more)	⊕⊕⊕⊕ LOW	CRITICAL
Adverse events - serious (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	4/155 (2.6%)	2/149 (1.3%)	RR 1.92 (0.36 to 10.34)	12 more per 1000 (from 9 fewer to 125 more)	⊕⊕⊕⊕ LOW	CRITICAL
Intolerable adverse effects (follow-up 16 or 20 weeks)												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	37/154 (24%)	25/146 (17.1%)	RR 1.4 (0.89 to 2.21)	68 more per 1000 (from 19 fewer to 207 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Intolerable adverse effects (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	38/154 (24.7%)	29/146 (19.9%)	RR 1.24 (0.81 to 1.9)	48 more per 1000 (from 38 fewer to 179 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Study drug discontinued – no reason reported (follow-up 16 or 20 weeks)												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	0/154 (0%)	1/146 (0.68%)	POR 0.13 (0.00 to 6.47)	5 fewer per 1000 (from 7 fewer to 44 more)	⊕⊕⊕⊕ LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	LTG	Relative (95% CI)	Absolute		
Withdrawal from study (follow-up 16 or 20 weeks)												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	20/154 (13%)	18/146 (12.3%)	RR 1.05 (0.58 to 1.91)	6 more per 1000 (from 52 fewer to 112 more)	⊕⊕⊕⊕ LOW	CRITICAL
Withdrawal from study (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	29/154 (18.8%)	18/146 (12.3%)	RR 1.53 (0.89 to 2.63)	65 more per 1000 (from 14 fewer to 201 more)	⊕⊕⊕⊕ MODERATE	CRITICAL
Conners' Continuous Performance Test score > 0.60* (follow-up 16 or 20 weeks)												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious <sup>2</sup>	none	35/106 (33%)	25/104 (24%)	RR 1.37 (0.89 to 2.12)	89 more per 1000 (from 26 fewer to 269 more)	⊕⊕⊕⊕ MODERATE	IMPORTANT
Conners' Continuous Performance Test score > 0.60* (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious <sup>1</sup>	none	20/70 (28.6%)	8/30 (26.7%)	RR 1.07 (0.53 to 2.16)	19 more per 1000 (from 125 fewer to 309 more)	⊕⊕⊕⊕ LOW	CRITICAL

\* Treatment failure defined as persistence of absence seizures, a generalised tonic-clonic seizure at any time, excessive drug-related systemic toxicity of at least 3.0 from baseline, dose-limiting toxicity after a single downward dose modification, and withdrawal initiated by the parent or physician

\*An index of 0.60 corresponds to a 60% probability that the child has clinically significant attention deficit disorder

<sup>1</sup> Confidence intervals cross both MID (0.8 and 1.25)

<sup>2</sup> MID crosses 1 MID (0.8 or 1.25)

## **Appendix G – Economic evidence study selection**

**Economic evidence study selection for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

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

## **Appendix H – Economic evidence tables**

**Economic evidence tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

No evidence was identified which was applicable to this review question.

## **Appendix I – Economic evidence profiles**

**Economic evidence profiles for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

No evidence was identified which was applicable to this review question.

## **Appendix J – Economic analysis**

### **Economic evidence analysis for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

No economic analysis was conducted for this review question.



## Appendix K – Excluded studies

### Excluded clinical and economic studies for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?

#### Clinical studies

**Table 14: Excluded studies and reasons for their exclusion**

Study	Reason for Exclusion
Actrn,, EpiNet-First Trial 2: comparison of efficacy of levetiracetam and sodium valproate in people with previously untreated epilepsy who have generalised seizures, <a href="http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000556549">Http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000556549</a> , 2015	Trial protocol
Actrn, EpiNet-First Trial 5: comparison of efficacy of levetiracetam and lamotrigine in people with previously untreated epilepsy who have unclassified seizures, and for whom sodium valproate is not deemed an acceptable anti-epileptic drug, <a href="http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000641594">Http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000641594</a> , 2015	Trial protocol
Actrn,, EpiNet-First Trial 4: comparison of efficacy of levetiracetam, lamotrigine and sodium valproate in people with previously untreated epilepsy who have unclassified seizures, <a href="http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000640505">Http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000640505</a> , 2015	Trial protocol
Actrn, EpiNet-First Trial 3: comparison of efficacy of levetiracetam and lamotrigine in people with previously untreated epilepsy who have generalised seizures, and for whom sodium valproate is not deemed an acceptable anti-epileptic drug, <a href="http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000639527">Http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000639527</a> , 2015	Trial protocol
Arya, R., Anand, V., Garg, S. K., Michael, B. D., Clobazam monotherapy for partial-onset or generalized-onset seizures, Cochrane Database of Systematic Reviews, 2014 (10) (no pagination), 2014	Systematic review that focuses on people with new-onset focal or generalised seizures and does not report data on people with absence seizures or outcome data relating to this type of seizure
Arya, R., Giridharan, N., Anand, V., Garg, S. K., Clobazam monotherapy for focal or generalized seizures, Cochrane Database of Systematic Reviews, 2018	Systematic review that focuses on people with new-onset focal or generalised seizures and does not report data on people with absence seizures/outcome data relating to this type of seizure
Arzimanoglou, A., Rahbani, A., Zonisamide for the treatment of epilepsy, Expert Review of Neurotherapeutics, 6, 1283-1292, 2006	Drug profile paper
Auvin, S., Advancing pharmacologic treatment options for pharmacologic treatment options for children with epilepsy, Expert Opinion on Pharmacotherapy, 17, 1475-1482, 2016	Narrative review (no methodology reported) that does not report outcome data in sufficient detail for extraction extracted. The studies which are summarised have been checked for inclusion in this review

Study	Reason for Exclusion
Basu, S., Bhattacharyya, K. B., Das, K., Das, D., Comparative study of sodium valproate and lamotrigine as monotherapy in the management of typical absence seizures, <i>Epilepsia</i> , 46, 277, Abstract no: p853, 2005	Conference abstract
Benbadis, S., Klein, P., Schiemann, J., Diaz, A., Elmoufti, S., Whitesides, J., Efficacy, safety, and tolerability of brivaracetam with concomitant lamotrigine or concomitant topiramate in pooled Phase III randomized, double-blind trials: A post-hoc analysis, <i>Epilepsy &amp; Behavior</i> , 80, 129-134, 2018	Pooled analysis from RCTs reporting on interventions that do not meet the criteria specified in the protocol for this review
Beran, R. G., Berkovic, S. F., Dunagan, F. M., Vajda, F. J., Danta, G., Black, A. B., Mackenzie, R., Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy, <i>Epilepsia</i> , 39, 1329-1333, 1998	Mixed epilepsy population without subgroup analysis for people with absence seizures and data are not reported comparatively
Besag, F. M. C., Wallace, S. J., Dulac, O., Alving, J., Spencer, S. C., Hosking, G., Lamotrigine for the treatment of epilepsy in childhood, <i>Journal of Pediatrics</i> , 127, 991-997, 1995	Not comparative
Beydoun, A., D'Souza, J., Treatment of idiopathic generalized epilepsy - A review of the evidence, <i>Expert Opinion on Pharmacotherapy</i> , 13, 1283-1298, 2012	Narrative review (no methodology reported) that does not report outcome data in sufficient detail for extraction extracted. The studies which are summarised have been checked for inclusion in this review
Biton, V., Preliminary open-label experience with topiramate in primary generalized seizures, <i>Epilepsia</i> , 38, S42-S44, 1997	Not comparative
Biton, V., Di Memmo, J., Shukla, R., Lee, Y. Y., Poverenova, I., Demchenko, V., Saiers, J., Adams, B., Hammer, A., Vuong, A., et al., Adjunctive lamotrigine XR for primary generalized tonic-clonic seizures in a randomized, placebo-controlled study, <i>Epilepsy &amp; Behavior</i> , 19, 352-358, 2010	Mixed epilepsy population without subgroup analysis for people with absence seizures
Biton, V., Shneker, B. F., Naritoku, D., Hammer, A. E., Vuong, A., Caldwell, P. T., Messenheimer, J. A., Long-term tolerability and safety of lamotrigine extended-release: Pooled analysis of three clinical trials, <i>Clinical Drug Investigation</i> , 33, 359-364, 2013	Mixed population without subgroup analysis for people with absence seizures
Bonnett, L. J., Tudur Smith, C., Smith, D., Williamson, P. R., Chadwick, D., Marson, A. G., Time to 12-month remission and treatment failure for generalised and unclassified epilepsy, <i>Journal of neurology, neurosurgery, and psychiatry</i> , 85, 603-610, 2014	Describes development of a prognostic model
Brigo, F., Igwe, S. C., Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents, <i>Cochrane Database of Systematic Reviews</i> , 2017 (2) (no pagination), 2017	Systematic review. Included studies were checked for this review
Brigo, F., Igwe, S. C., Bragazzi, N. L., Lattanzi, S., Clonazepam monotherapy for treating people with newly diagnosed epilepsy, <i>Cochrane Database of Systematic Reviews</i> , 2019	Systematic review. Studies/data included in this paper had already been included in the evidence review, those not included were conference abstracts

Study	Reason for Exclusion
Brigo, F., Igwe, S. C., Lattanzi, S., Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents, Cochrane Database of Systematic Reviews, 2019	Systematic review that has been updated – see other studies by same author
Buchanan, N., Lamotrigine in the treatment of absence seizures, Acta Neurologica Scandinavica, 92, 348, 1995	Letter to the editor
Bulau, P., Froscher, W., Schuchardt, V., Kreiten, K., A prospective randomised trial of the effectiveness of clonazepam and diazepam in petit mal epilepsy, Der nervenarzt, 57, 667-671, 1986	Not in English language
Bülau, P., Fröscher, W., Schuchardt, V., Kreiten, K., Prospective randomized study of the effectiveness of clonazepam and diazepam in petit mal status, Der nervenarzt, 57, 667-671, 1986	Not in English language
Buoni, S., Grosso, S., Fois, A., Lamotrigine treatment in childhood drug resistant epilepsy, Journal of Child Neurology, 13, 163-7, 1998	Not comparative
Campos, M. S. A., Ayres, L. R., Morelo, M. R. S., Carizio, F. A. M., Pereira, L. R. L., Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses, International Journal of Clinical Pharmacy, 40, 589-598, 2018	Studies included in this paper (relevant to absence seizures) had already been included in the evidence review
Cao, J., Lin, X. X., Ma, X. M., Liu, H., The efficacy and safety of lamotrigine for absence seizures in children and adolescents: A systematic review and meta-analysis, Journal of Clinical Neuroscience., 2019	Systematic review that does not report outcome data in sufficient detail for extraction. The studies which are summarised have been checked for inclusion in this review
Chadwick, D., Does withdrawal of different antiepileptic drugs have different effects on seizure recurrence? Further results from the MRC Antiepileptic Drug Withdrawal Study, Brain, 122, 441-8, 1999	Mixed population without subgroup analysis for people with absence seizures
Chandra, B., First seizure in adults: to treat or not to treat, Clinical Neurology & Neurosurgery, 94 Suppl, S61-3, 1992	Mixed population without subgroup analysis for people with absence seizures
Cretin, B., Hirsch, E., Adjunctive antiepileptic drugs in adult epilepsy: how the first add-on could be the last, Expert Opinion on Pharmacotherapy, 11, 1053-67, 2010	Narrative review (no methodology reported) that does not report outcome data in sufficient detail for extraction. The studies which are summarised have been checked for inclusion in this review
Cross, J. H., Epilepsy (generalised seizures), BMJ clinical evidence, 2015	Studies/data included in this paper (relevant to absence seizures) had already been included in the evidence review
Curatolo, P., Moavero, R., Lo Castro, A., Cerminara, C., Pharmacotherapy of idiopathic generalized epilepsies, Expert Opinion on Pharmacotherapy, 10, 5-17, 2009	Narrative review (no methodology reported) that does not report outcome data. The studies which are summarised have been checked for inclusion in this review
Duchowny, M., Gilman, J., Messenheimer, J., et al., Long-term tolerability and efficacy of lamotrigine in pediatric patients with epilepsy, Journal of Child Neurology, 17, 278-285, 2002	Not comparative

Study	Reason for Exclusion
Euctr, F. R., Study to investigate the palatability, acceptability, pharmacokinetics, safety and tolerability, and treatment compliance of multidoses of ADV6770 as monotherapy or in combination, in children with childhood absence epilepsy, <a href="http://www.who.int/trialsearch/trial2.aspx?Trialid=euctr2016-002313-22-fr">Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2016-002313-22-fr</a> , 2016	Clinical trials registry entry
Fang, Y., Wu, X., Xu, L., Tang, X., Wang, J., Zhu, G., Hong, Z., Randomized-controlled trials of levetiracetam as an adjunctive therapy in epilepsy of multiple seizure types, <i>Journal of Clinical Neuroscience</i> , 21, 55-62, 2014	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of seizure
French, J. A., Kanner, A. M., Bautista, J., et al, Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society, <i>Neurology</i> , 62, 1252-1260, 2004	Systematic review that does not report outcome data in sufficient detail for extraction. The studies which are summarised have been checked for inclusion in this review
French, J. A., Kanner, A. M., Bautista, J., et al, Efficacy and Tolerability of the New Antiepileptic Drugs, I: Treatment of New-Onset Epilepsy: Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society, <i>Epilepsia</i> , 45, 401-409, 2004	Systematic review that does not report outcome data in sufficient detail for extraction. The studies which are summarised have been checked for inclusion in this review
French, J. A., Kanner, A. M., Bautista, J., et al, Appendix C: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society, <i>CONTINUUM Lifelong Learning in Neurology</i> , 13, 203-211, 2007	Systematic review that does not report outcome data in sufficient detail for extraction. The studies which are summarised have been checked for inclusion in this review
Gamble, C., Williamson, P. R., Chadwick, D. W., Marson, A. G., A meta-analysis of individual patient responses to lamotrigine or carbamazepine monotherapy, <i>Neurology</i> , 66, 1310-1317, 2006	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of seizure
Gasparini, S., Ferlazzo, E., Giussani, G., Italiano, D., Cianci, V., Sueri, C., Spina, E., Beghi, E., Aguglia, U., Rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients with epilepsy (RASLOW) study: a pragmatic multicentre, prospective, randomized, controlled study, <i>Neurological Sciences</i> , 37, 579-583, 2016	Trial protocol
Giorgi, L., Gomez, G., O'Neill, F., Hammer, A. E., Risner, M., The tolerability of lamotrigine in elderly patients with epilepsy, <i>Drugs &amp; Aging</i> , 18, 621-30, 2001	Mixed epilepsy population without subgroup analysis for people with absence seizures
Glauser, T., Ben-Menachem, E., Bourgeois, B., Cnaan, A., Guerreiro, C., Kalviainen, R., Mattson, R., French, J. A., Perucca, E., Tomson, T., Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes, <i>Epilepsia</i> , 54, 551-563, 2013	Systematic review that does not report outcome data in sufficient detail for extraction. The studies which are summarised have been checked for inclusion in this review

Study	Reason for Exclusion
Hemery, C., Ryvlin, P., Rheims, S., Prevention of generalized tonic-clonic seizures in refractory focal epilepsy: A meta-analysis, <i>Epilepsia</i> , 55, 1789-1799, 2014	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of seizure
Hong, Z., Inoue, Y., Liao, W., Meng, H., Wang, X., Wang, W., Zhou, L., Zhang, L., Du, X., Tennigkeit, F., Efficacy and safety of adjunctive lacosamide for the treatment of partial-onset seizures in Chinese and Japanese adults: a randomized, double-blind, placebo-controlled study, <i>Epilepsy research</i> , 127, 267-275, 2016	Mixed epilepsy population without subgroup analysis for people with absence seizures
Houtkooper, M. A., Lammertsma, A., Meyer, J. W., Goedhart, D. M., Meinardi, H., van Oorschot, C. A., Blom, G. F., Hoppener, R. J., Hulsman, J. A., Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine?, <i>Epilepsia</i> , 28, 693-8, 1987	Interventions do not meet the criteria specified in the protocol for this review
Huang, T. S., Zhu, J. L., Li, B., Hu, Y., Chen, L., Liao, J. X., Valproic acid versus lamotrigine as a monotherapy for absence epilepsy in children, <i>Zhongguo dang dai er ke za zhi</i> [Chinese journal of contemporary pediatrics], 11, 653-655, 2009	Not in English language
Kaminow, L., Schimschock, J. R., Hammer, A. E., Vuong, A., Lamotrigine monotherapy compared with carbamazepine, phenytoin, or valproate monotherapy in patients with epilepsy, <i>Epilepsy &amp; Behavior</i> , 4, 659-66, 2003	Mixed epilepsy population without subgroup analysis for people with absence seizures
Kasteleijn-Nolst Trenite, D., Genton, P., Brandt, C., Reed, R. C., The 'Photosensitivity Model' is (also) a model for focal (partial) seizures, <i>Epilepsy Research</i> , 133, 113-120, 2017	Not a treatment study or systematic review of treatment
Kerr, M. P., Baker, G. A., Brodie, M. J., A randomized, double-blind, placebo-controlled trial of topiramate in adults with epilepsy and intellectual disability: Impact on seizures, severity, and quality of life, <i>Epilepsy and Behavior</i> , 7, 472-480, 2005	Mixed epilepsy population without subgroup analysis for people with absence seizures
Krauss, G. L., Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society, <i>Neurology</i> , 64, 172-4; author reply 172-4, 2005	Commentary
Kumar, S., Ramanujam, B., Chandra, P. S., Dash, D., Mehta, S., Anubha, S., Appukutan, R., Rana, M. K., Tripathi, M., Randomized controlled study comparing the efficacy of rapid and slow withdrawal of antiepileptic drugs during long-term video-EEG monitoring, <i>Epilepsia</i> , 59, 460-467, 2018	Mixed epilepsy population without subgroup analysis for people with absence seizures
Marson, A. G., Maguire, M., Ramaratnam, S., Epilepsy, <i>BMJ clinical evidence</i> , 2009	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of seizure
Marson, A., Jacoby, A., Johnson, A., Kim, L., Gamble, C., Chadwick, D., Immediate versus deferred	Systematic review that does not meet the inclusion criteria (evaluates immediate



Study	Reason for Exclusion
antiepileptic drug treatment for early epilepsy and single seizures: A randomised controlled trial, Lancet, 365, 2007-2013, 2005	versus deferred treatment and does not report subgroup analysis for people with absence seizures). Included studies were checked for this review
Mattson, R. H., Cramer, J. A., Collins, J. F., McCutcheon, C. B., Fish, S. L., Mamdani, M. B., Rubino, F. A., Davenport, J., Lubozynski, M. F., Ramsay, R. E., Carter, G. S., Rowan, A. J., Browne, T. R., Ebersole, J. S., Treiman, D. M., Warner, J. J., Wilder, B. J., Salinsky, M., Arroyo, Y., A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults, New England Journal of Medicine, 327, 765-771, 1992	Mixed epilepsy population without subgroup analysis for people with absence seizures
McAuley, C., McShane, T., Ethosuximide was superior to valproate and lamotrigine in controlling absence seizures and minimising side effects, Archives of Disease in Childhood: Education and Practice Edition, 96, 119, 2011	Conference abstract
McDonald, T. J. W., Henry-Barron, B. J., Felton, E. A., Gutierrez, E. G., Barnett, J., Fisher, R., Lwin, M., Jan, A., Vizthum, D., Kossoff, E. H., Cervenka, M. C., Improving compliance in adults with epilepsy on a modified Atkins diet: A randomized trial, Seizure, 60, 132-138, 2018	Interventions do not meet the criteria specified in the protocol for this review
Messenheimer, J. A., Giorgi, L., Risner, M. E., The tolerability of lamotrigine in children, Drug Safety, 22, 303-312, 2000	Systematic review. Studies/data included in this paper had already been included in the evidence review, data not included were taken from a clinical database and insufficient detail is provided to allow extraction of results
Miura, H., Shirai, H., Sunaoshi, W., Effectiveness and plasma levels of clonazepam in the treatment of absence seizures, Journal of the Japan epilepsy society, 5, 41-49, 1987	Not in English language
Moon, K. T., What is the best treatment for childhood absence epilepsy?, American Family Physician, 83, 81-82, 2011	Not primary research or a systematic review
Nadkarni, S., LaJoie, J., Devinsky, O., Current treatments of epilepsy, Neurology, 64, S2-S11, 2005	Narrative review, does not summarise studies in which people with absence seizures were included
Nct., IV Keppra in the Emergency Department for Prevention of Early Recurrent Seizures, <a href="https://clinicaltrials.gov/show/NCT00510783">https://clinicaltrials.gov/show/NCT00510783</a> , 2007	Trial registry entry
Nct., Does Gabapentin and Lamotrigine Have Significantly Fewer Side-Effects While Providing Equal or Better Seizure Control Than the Current Drug Choice, Carbamazepine, for the Treatment of Seizures in the Elderly, <a href="https://clinicaltrials.gov/show/NCT00007670">https://clinicaltrials.gov/show/NCT00007670</a> , 2000	Trial registry entry
Nct., Modified Atkins Diet Plus KetoCal for Adult Epilepsy, <a href="https://clinicaltrials.gov/show/NCT01834482">https://clinicaltrials.gov/show/NCT01834482</a> , 2013	Trial registry entry

Study	Reason for Exclusion
Nevitt, S. J., Sudell, M., Weston, J., Tudur Smith, C., Marson, A. G., Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data, Cochrane Database of Systematic Reviews, 2017	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of seizure
Nevitt, S. J., Sudell, M., Weston, J., Tudur Smith, C., Marson, A. G., Antiepileptic drug monotherapy for epilepsy: A network meta-analysis of individual participant data, Cochrane Database of Systematic Reviews, 2017 (6) (no pagination), 2017	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of seizure
Nieto-Barrera, M., Characteristics and indications of topiramate, Revista de neurologia, 35, S88-S95, 2002	Not in English language
Ohtahara, S., Zonisamide in the management of epilepsy - Japanese experience, Epilepsy Research, 68, S25-S33, 2006	Systematic review which included non-comparative studies (outcomes relating to absence studies based on survey data)
Ormrod, D., McClellan, K., Topiramate: A review of its use in childhood epilepsy, Paediatric Drugs, 3, 293-319, 2001	Mixed epilepsy population without subgroup analysis for people with absence seizures (other than in the context of Lennox Gastaut syndrome)
Pohlmann-Eden, B., Marson, A. G., Noack-Rink, M., et al., Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study, BMC Neurology, 16, 149, 2016	Mixed epilepsy population without subgroup analysis for people with absence seizures
Posner, E., Absence seizures in children, Clinical Evidence, 307-13, 2004	Unavailable from the British Library (checked 18/03/21)
Posner, E., Absence seizures in children, Clinical Evidence, 221-6, 2005	Unavailable from the British Library (checked 18/03/21)
Posner, E., Absence seizures in children, Clinical Evidence, 236-41, 2002	Systematic review that has been updated – see other studies by same author
Posner, E., Absence seizures in children, BMJ clinical evidence, 2008	Systematic review that has been updated – see other studies by same author
Posner, E., Absence seizures in children, Clinical Evidence, 295-300, 2003	Systematic review that does not meet the inclusion criteria. Included studies were checked for this review (checked 18/03/21)
Posner, E., Absence seizures in children, Clinical Evidence (Online), 18, 18, 2013	Systematic review. Studies/data included in this paper had already been included in the evidence review, those not included were conference abstracts
Posner, E. B., Mohamed, K. K., Marson, A. G., Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents, Cochrane Database of Systematic Reviews, 2005 (4) (no pagination), 2005	Systematic review that has been updated – see other studies by same author
Posner, E. B., Mohamed, K., Marson, A. G., A systematic review of treatment of typical absence seizures in children and adolescents with ethosuximide, sodium valproate or lamotrigine, Seizure, 14, 117-122, 2005	Systematic review that has been updated – see other studies by same author

Study	Reason for Exclusion
Posner, E. B., Mohamed, K., Marson, A. G., Ethosuximide, sodium valproate or lamotrigine for absence seizures in children and adolescents, Cochrane database of systematic reviews (Online), CD003032, 2003	Systematic review that has been updated – see other studies by same author
Rosati, A., Ilvento, L., Lucenteforte, E., Pugi, A., Crescioli, G., McGreevy, K. S., Virgili, G., Mugelli, A., De Masi, S., Guerrini, R., Comparative efficacy of antiepileptic drugs in children and adolescents: A network meta-analysis, <i>Epilepsia</i> , 59, 297-314, 2018	Studies/data included in this paper had already been included in the evidence review
Sackellares, J. C., Crosby, C., Tonelson, S., Dreifuss, F. E., Long-term safety and efficacy of valproic acid (VPA) in the treatment of absence seizures, <i>Neurology</i> , 30, 420, 1980	Conference abstract
Sankar, R., Ramsay, E., McKay, A., Hulihan, J., Wiegand, F., Capss- Study Group, A multicenter, outpatient, open-label study to evaluate the dosing, effectiveness, and safety of topiramate as monotherapy in the treatment of epilepsy in clinical practice, <i>Epilepsy &amp; Behavior</i> , 15, 506-12, 2009	Mixed epilepsy population without subgroup analysis for people with absence seizures
Sato, S., Penry, J. K., Driefuss, F. E., Dyken, P. R., Clonazepam in the treatment of absence seizures: a double-blind clinical trial, <i>Neurology</i> , 27, 371, 1977	Conference abstract
Sato, S., Penry, J. K., White, B. G., Driefuss, F. E., Sackellares, J. C., Double-blind crossover study of sodium valproate and ethosuximide in the treatment of absence seizures, <i>Neurology</i> , 29, 603, 1979	Conference abstract
Schmidt, D., Effect of antiepileptic drugs on the postictal state. A critical overview, <i>Epilepsy and Behavior</i> , 19, 176-181, 2010	Not a primary research study or systematic review
Shinnar, S., Pellock, J. M., Conry, J. A., Open-label, long-term safety study of zonisamide administered to children and adolescents with epilepsy, <i>European Journal of Paediatric Neurology</i> , 13, 3-9, 2009	Not randomised
Sogawa, Y., Moshe, S. L., Dlugos, D., Cnaan, A., Shinnar, S., Clark, P., Glauser, T., Occipital intermittent rhythmic delta activity in childhood absence epilepsy; Association with treatment response in the NIH CAE trial, <i>Epilepsy Currents</i> . Conference: 65th Annual Meeting of the American Epilepsy Society, AES. Baltimore, MD United States. Conference Publication:, 12, 2012	Conference abstract
Tabbaa, M., Adjunctive lamotrigine for tonic-clonic seizures in patients with absence seizures, <i>P and T</i> , 32, 111, 2007	Unavailable from the British Library. Last checked 15/03/21
Wallace, S. J., Lamotrigine - A clinical overview, <i>Seizure</i> , 3, 47-51, 1994	Narrative review
Wechsler, R. T., Leroy, R., Van Cott, A., Hammer, A. E., Vuong, A., Huffman, R., VanLandingham, K., Messenheimer, J. A., Lamotrigine extended-release as adjunctive therapy with optional conversion to	Mixed epilepsy population without subgroup analysis for people with absence seizures



Study	Reason for Exclusion
monotherapy in older adults with epilepsy, <i>Epilepsy Research</i> , 108, 1128-36, 2014	
Yuen, A. W. C., Lamotrigine: A review of antiepileptic efficacy, <i>Epilepsia</i> , 35, S33-S36, 1994	Not a primary research study or systematic review
Zhang, L., Liu, Y., Ding, C., Shi, S., Lin, W., Chen, T., Sun, H., Xu, Y., Dong, W., Chen, Q., et al., The efficacy and safety of zonisamide as adjunctive therapy in patients with partial seizure: a multicenter, randomized, double-blinded, placebo-controlled trial, <i>Chinese journal of contemporary neurology and neurosurgery</i> , 11, 408-412, 2011	Not available in English

### Economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

## **Appendix L – Research recommendations**

### **Research recommendations for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of absence seizures?**

No research recommendations were made for this review question.