National Institute for Health and Care Excellence

Draft for consultation

Epilepsies in children, young people and adults

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

NICE guideline number tbc

Evidence reviews underpinning recommendations 5.3.1-5.3.9 in the NICE guideline

November 2021

Draft for Consultation

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

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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)

Population	People with confirmed epilepsy with absence seizures
Intervention	The following treatments and their combinations will be considered: • Acetazolamide • Clobazam • Clonazepam • Ethosuximide • Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures) • Lamotrigine • Levetiracetam • Methsuximide/mesuximide • Sodium Valproate • Topiramate • Zonisamide
Comparison	• Any of the above and their combinations • No treatment/placebo
Outcomes	**Critical** • Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment). • 24 hour EEG seizure freedom

	• Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures)
	• Adverse events, as assessed by:
	  ○ % of patients with reported side effects (trial defined adverse and serious adverse effects)
	  ○ treatment cessation due to adverse event (dichotomous outcome only)
	  ○ mortality
	
	Important
	• Neuropsychological changes (IQ testing, or other validated tools)
	• Health-related quality of life (validated tools only)

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 reportinging 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	N = 28 people with typi-	Ethosuximide n=14	Sodium valproate n=14	• Seizure remission (complete, partial, no

Study	Population	Intervention	Comparison	Outcomes
RCT Ireland	cal absence seizures Mean age: ESM: 8 years (range 4 to14) VPA: 9 years (range 5 to 15)	Initial dose of 250mg/day Dose increased by 250mg/day to a maximum 1500mg/day as required	Initial dose of 400mg/day Dose increased by 200mg/day to a maximum of 2400mg/day	remission) • EEG response - normal • Adverse events - any
Glauser 2010 Multi-centre RCT US Reports 20 week follow-up data	N = 453 people with absence seizures *(three-arm trial)* 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).	• Freedom from treatment failure • Adverse events (serious adverse events; intolerable adverse effects) • Study drug discontinued • Withdrawal from study • Attentional dysfunction (proxy outcome for neuropsychological changes)
Glauser 2013 See Glauser 2010 Reports 12 month follow-up data	See Glauser 2010	See Glauser 2010	See Glauser 2010	• Freedom from treatment failure • Adverse events (serious adverse events; intolerable adverse effects) • Attentional dysfunction (proxy outcome for neuropsychological changes) • Withdrawal from study
Sato 1982 Cross-over RCT; only period 1 was reported and synthesised US	N = 45 people with absence seizures (treatment naive n=16; refractory n=29) First line therapy (naive) and add-on therapy (refractory) Mean age: 11.7 years	<u>Ethosuximide plus placebo</u> n=23 (treatment naïve n=9, refractory n=14) Dosing schedule group 1: Daily dose of 250-1500mg Dosing schedule group 2: Daily dose of 250 to 1500mg Naive patients with 100% seizure control and refractory	<u>Sodium valproate plus placebo</u> n=22 (treatment naïve n=7, refractory n=15) 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.	• Seizure freedom

Study	Population	Intervention	Comparison	Outcomes
	(range 4 to 18)	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.	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. 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.	

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

2 **Table 3: Summary of included studies. Comparison 2: lamotrigine versus sodium**
3 **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 10/mg/kg/day and increased by 5mg/kg/day every 3 days until seizures were under control	• Seizure freedom (1, 3 and 12 months) • Adverse events - any • Treatment cessation due to adverse events • Withdrawal from study

Study	Population	Intervention	Comparison	Outcomes
Glauser 2010 Multi-centre RCT US Reports 20 week follow-up data	N = 453 people with absence seizures *(three-arm trial)* Mean age: not provided	Lamotrigine n=149 5mg and 25mg chewable tablets. Maximum dose of 12 mg/kg up to a maximum of 600mg/day	Sodium valproate n=148 25mg capsules or 125mg dose of sprinkles. Highest allowable daily dose of 60mg/kg (to a maximum of 3000mg).	• Freedom from treatment failure • Adverse events (serious adverse events; intolerable adverse effects) • Study drug discontinued • Withdrawal from study • Attentional dysfunction (proxy outcome for neuropsychological changes)
Glauser 2013 See Glauser 2010 Reports 12 month follow-up data	See Glauser 2010	See Glauser 2010	See Glauser 2010	• Freedom from treatment failure • Adverse events (serious adverse events; intolerable adverse effects) • Attentional dysfunction (proxy outcome for neuropsychological changes) • Withdrawal from study

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 Italy	N = 59 people with absence seizures Mean age LEV: 8.7 years (range 4.9 to 13) Placebo: 7.9 years (range 4 to 15)	Levetiracetam n=38 Initial dosage of 10mg/kg/day for 3 days followed by 15mg/kg/day for 4 days. If accepted and seizures continued dosage increased to 20mg/kg/day and maintained until day 14	Placebo n=21 Equivalent tablet or liquid formulation given.	• Responder status (free from clinical seizures on days 13 and 14; and free from EEG seizures on day 14) • Patients free from clinical and EEG seizures (days 4 – 7; days 11 - 14) • 50% reduction vs baseline in total duration of EEG seizures on day 14 • Adverse events (any; serious; thought to be related to treatment; leading to discontinuation)

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	N=45 people	Lamotrigine	Placebo	• Remained seizure

Study	Population	Intervention	Comparison	Outcomes
RCT US	with absence seizures recruited; n=29 randomised after dose escalation and took part in dose escalation phase. n=28 people with absence seizures analysed (1 patient in lamotrigine group withdrew consent). Mean age: LTG: 6.9 years (SD 2.3) Placebo: 8.8 years (SD 3.1)	n=14 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 tables	n=14 Patients who became seizure free after dose escalation phase were randomised to LTG or placebo – LTG was tapered over 2 weeks. Placebo lasted 4 weeks	free at end of placebo controlled phase • Adverse events - leading to withdrawal from study

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 *(three-arm trial)* 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.	• Freedom from treatment failure • Adverse events (serious adverse events; intolerable adverse effects) • Study drug discontinued • Withdrawal from study • Attentional dysfunction (proxy outcome for neuropsychological changes)
Glauser 2013 See Glauser 2010 Reports 12 month follow-up data	See Glauser 2010	See Glauser 2010	See Glauser 2010	• Freedom from treatment failure • Adverse events (serious adverse events; intolerable adverse effects) • Attentional dysfunction (proxy outcome for neuropsychological changes)

Study	Population	Intervention	Comparison	Outcomes
				• Withdrawal from study

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 ethosuxumide 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 ethosuxumide.

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 an 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. They agreed to include in the recommendation the caveat that sodium valproate should only be offered to girls if they are under the age of 10, noting that girls over this age who are approaching puberty and still experiencing absence seizures are likely to have their diagnosis and treatment reviewed.

There was some evidence which suggested that lamotrigine and levetiracetam were effective in the treatment of absence seizures (including childhood absence epilepsy). The committee decided to recommend these as third-line treatments because ethosuxumide showed to have better outcomes than lamotrigine, including better seizure control. Compared to sodium valproate, lamotrigine showed to be less effective for seizure control, although there were not 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.

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, the committee agreed to recommend the use of these as second-line treatment if first-line is unsuccessful in boys and men with absence seizures and other seizure types, and as first-line treatment in women and girls of childbearing age (given the risks associated with sodium valproate). Lamotrigine and levetiracetam were recommended as second-line treatments because, compared to sodium valproate, lamotrigine showed to be less effective for seizure control, although 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

Based on the evidence identified, lamotrigine and levetiracetam were also recommended as an add-on treatment in boys and men with absence seizures and other seizure types.

As there was evidence for ethosuxumide 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 ethosuxumide 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 5.3.1-5.3.9.

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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	The objective of this review is to determine which antiseizure therapies improve outcomes in people with epilepsy who have absence seizures. This review will determine the effectiveness of antiseizure therapies given alone (monotherapy) or as add-ons (combination therapy).
Searches	The following databases will be searched: • CDSR • CENTRAL • DARE • HTA • MEDLINE & MEDLINE In-Process and Other Non-Indexed Citations • Embase • EMCare Searches will be restricted by:

Field	Content
	• Date: No date limit • English language sutdies • Human studies • RCT and systematic review study design filter
Condition or domain being studied	Epilepsy with absence seizures
Population	Inclusion • People with confirmed epilepsy with absence seizures Exclusion • Newborn babies (under 28 days) with acute symptomatic seizures
Intervention/Exposure/Test	The following antiseizure therapies and their combinations will be considered: • Acetazolamide • Clobazam • Clonazepam • Ethosuximide • Ketogenic diet (included as this is an accepted first or second line treatment for these type of seizures) • Lamotrigine • Levetiracetam • Methsuximide/mesuximide • Sodium Valproate • Topiramate • Zonisamide
Comparator/Reference standard/Confounding factors	• Any of the above and their combinations • No treatment/placebo
Types of study to be included	• Systematic review of RCTs • RCTs

Field	Content
Other exclusion criteria	• 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 • 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. • Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias
Context	Recommendations will apply to those receiving care in any healthcare settings (for example, community, primary, secondary care)
Primary outcomes (critical outcomes)	• Seizure freedom (12 months data and short term, (minimum 3 months with 100% freedom) of starting treatment) *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.* • 24 hour EEG seizure freedom • Time to withdrawal of treatment or change of medication (for example, because of uncontrollable seizures) • Adverse events, as assessed by: ○ % of patients with reported side effects (trial defined adverse and serious adverse effects) ○ treatment cessation due to adverse event (dichotomous outcome only) ○ mortality
Secondary outcomes (important outcomes)	• Neuropsychological changes (IQ testing, or other validated tools)

Field	Content
	• Health-related overall quality of life (measured using validated tools only) Outcomes are in line with those described in the core outcome set for epilepsy http://www.cometinitiative.org/studies/searchresults
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. 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. 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. 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. 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.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Data synthesis

Field	Content
	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 <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. Heterogeneity Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. I^2 values of greater than 50% and 75% will be considered as significant and very significant heterogeneity, respectively. In the presence of heterogeneity, sub-group analysis will be conducted: • according to the risk of bias of individual studies • study location Exact sub-group analysis may vary depending on differences identified within included studies 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. Minimal important differences (MIDs): Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee prespecifies published or other MIDs for specific outcomes • For risk ratios: 0.8 and 1.25. • For continuous outcomes: ○ For one study: the MID is calculated as +/-0.5 times the baseline SD of the control arm. ○ 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. ○ For three or more studies (meta-analysed): the MID is calculated by ranking the studies in or-

Field	Content	
	der of SD in the control arms. The MID is calculated as +/- 0.5 times median SD. ○ For studies that have been pooled using SMD (meta-analysed): +0.5 and -0.5 in the SMD scale are used as MID boundaries. Validity 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: http://www.gradeworkinggroup.org/	
Analysis of sub-groups (stratification)	Stratification If data is available, results will be presented separately by: • Those with and without learning difficulties/disabilities • Age of onset (≤10 years and > 10 years old) • Eyelid myoclonia • Photosensitivity • Typical and atypical absence seizures	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	20 February 2020	
Anticipated completion date	21 April 2021	

Field	Content		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact National Guideline Alliance 5b Named contact e-mail epilepsies@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
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 declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

Field	Content	
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 Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10112	
Other registration details	Not applicable	
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=159420	
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	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	www.nice.org.uk	

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 ethosuccinimid* or ethosuximide or ethylmethylsuccimide 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.
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 fagodol or jadix or lusitrax 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.
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 dipropylacetatic 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 leptilanil 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 valprodura or valproic acid or valprosid or valprotek or valsup or vupral).ti,ab.
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

#	searches
	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 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.
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.)
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

1 Date of last search 03 December 2019
2

#	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 ethylmethylsuccimide 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 reduc*)) or ((glycemic or glycaemic) near/5 (index or treat* or modulat*)) 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 lamepil 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 epiramat or epitomax or epitoram or erravia or etopro or fagodol or jadix or lusitrax 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 everiden or goilim or hexaquin or labazene or leptilan or leptilanil 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 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 urbadan or urbanil or urbanyl)):ti,ab,kw
#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 methylphensuximide” 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 (continous 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 centrotemporal adj2 spike*) or cects or ((centralopathic or centrotemporal 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
10	(((akinetic or atonic or central or diffuse or general or generali?ed or idiopathic 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 ((jacknife 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 smei).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

#	searches
	(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 smeb or smei).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 engish language

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

Date of last search: 31 March 2021

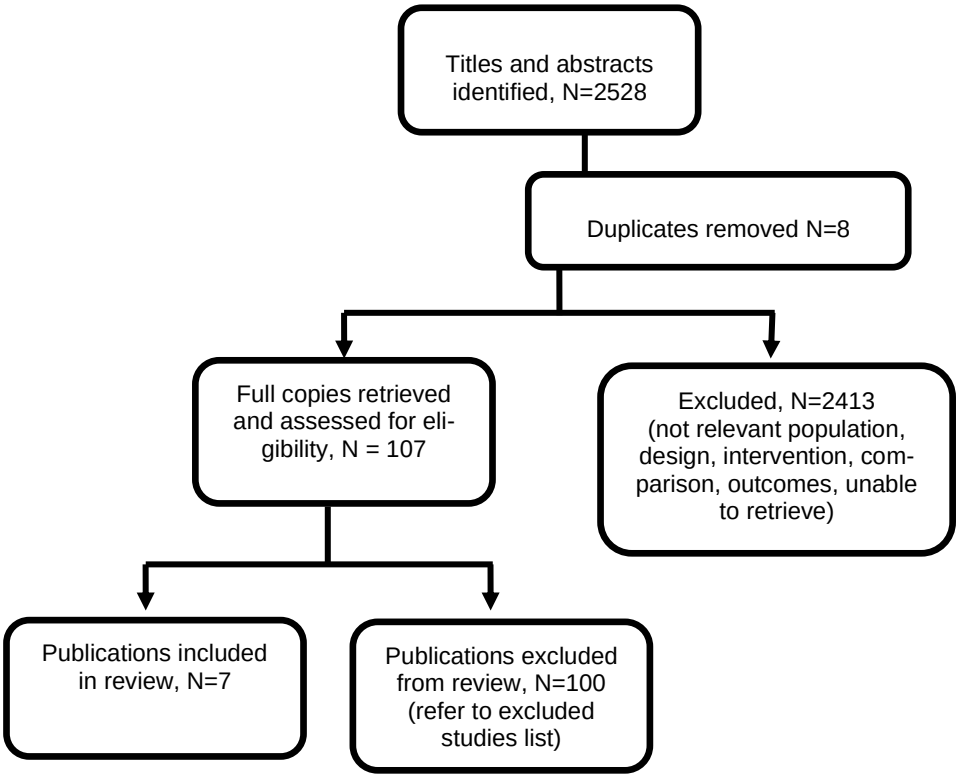
#	searches
1	mesh descriptor epilepsy explode all trees
2	mesh descriptor seizures this term only
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor status epilepticus explode all trees
5	(epilep* or seizure* or convuls*) or (“continous spike wave of slow sleep” or “infant* spasm*”)
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 seizure” 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 (convulsion* or epileps* or seizure* or spasm*)) or (benign near3 (convulsion* or epileps*) near2 centrotemporal near2 spike*) or cects or ((centralopathic or centrotemporal 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 generali?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 absenc*) 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 epilep*) 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 “generali?ed flexion epileps*” or hypsarrhythmia* or ((jacknife or “jack nife” or lightening or nodding or salaam) next (attack* or convulsion* or seizure* or spasm*)) or “massive myoclonia” or “minor motor epi-

#	searches
	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 "generali?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 (severe near2 (myoclonic or polymorphic) near2 epilepsy near2 infancy) or smeb 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 seizure*)) or gtcs or (generali* 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
Full citation 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 **Ref Id** 1080077 **Country/ies where the study was carried out** Ireland. **Study type** RCT. **Aim of the study** To compare sodium valproate and ethosuximide in terms of seizure control and side-	**Sample size** Total recruited: N=28 Ethosuximide group: n=14 Sodium valproate group: n=14 **Characteristics** Age, years, mean (range) Ethosuximide group: 8 (4-14) Sodium valproate group: 9 (5-15) Gender Ethosuximide group: 8 male; 6 female. Sodium valproate group: 5 male; 9 female. Age at onset of seizure, years, range Ethosuximide group: 2-5 Sodium valproate group: 3-6 **Inclusion criteria** Patients with absence attacks associated with three-per-second spike and wave activity in the EEC **Exclusion criteria** Not reported	**Interventions** Ethosuximide: 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. Sodium valproate: 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.	**Details** 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)	**Results** *Primary outcomes* 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) Ethosuximide group: n=8/14 Sodium valproate group: n=6/14 Remission - partial (>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 Remission - none (<50% reduction in seizure frequency during six hour telemetry at two intervals of	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 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 **Domain 2: Deviations from intended interventions: Some concerns** 2.1: No information 2.2: No information 2.3: No information 2.4: Probably yes, not all participants had inter-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
effects. **Study dates** Not reported. **Source of funding** Labaz, Warner-Lambert Pharmaceuticals.				six months, and reported slight or no improvement) Ethosuximide group: n=3/14 Sodium valproate group: n=2/14* <u>EEG response - normal</u> Ethosuximide group: n=6/14 Sodium valproate group: n=4/14 <u>Adverse events - any</u> Ethosuximide group: n=1/14 Sodium valproate group: n=2/14	vention as intended 2.5: Probably yes, four participants crossed over due to poor response to initial drug 2.6: Probably yes **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants **Domain 4: Measurement of the outcome: Low risk** 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 **Domain 5: Selection of the reported result: Some concerns** 5.1: No information 5.2: No information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					5.3: No information **Domain 6: Overall judgement of bias: Some concerns** 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
Full citation 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, Epilepsia, 45, 1049-1053, 2004 **Ref Id** 1080163. **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study**	**Sample size** Total recruited: N=38 Intervention group (Lamotrigine): n=19 Control group (Valproic Acid): n=19 **Characteristics** Age, years, mean (range) Total sample: 7.5 (3-13) Age at seizure onset, years, mean (range) Intervention: 7.5 (4-12) Control: 7.5 (3-13) Males, n (%) Intervention: 7 (36.8) Control: 10 (52.6) **Inclusion criteria** • Age from 3 to 13 years • Newly diagnosed typical absence seizures associated with generalized, synchronous 3-Hz (2.5–4 Hz) spike-and-wave activity, lasting >3 s, occurring spontaneously or during one of two trials of 3-min hyper-	**Interventions** Intervention group 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 full uptitration schedule	**Details** Duration of treatment: not reported. 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. Data analysed according to intention to treat	**Results** *Primary outcomes* Seizure free, n (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) 1 month Intervention group 1/19 Control group 10/19 3 months Intervention group: n=7/19 Control group: n=12/19 12 months Intervention group: n=10/19 Control group: n=13/19 Adverse events - any, n (%) number of participants experiencing an adverse event	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Low risk** 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 **Domain 2: Deviations from intended interventions: Low risk** 2.1: Yes, open label study 2.2: Yes, open label study **Domain 3: Missing outcome data: Low**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the efficacy of lamotrigine and valproic acid in newly diagnosed children and adolescents with typical absence seizures **Study dates** Not reported (publication date 2004) **Source of funding** Not reported	ventilation with a 1- to 2-min rest between trials • Clearly observable clinical signs of typical absence seizures (for example, staring or impairment of consciousness) on the video record • Normal clinical, neurologic, and computed tomography (CT)/magnetic resonance imaging (MRI) examination • Informed consent by parents or caregivers **Exclusion criteria** • Absences with marked eyelid or perioral myoclonus (eyelid or perioral myoclonia with absences) • Absences with marked limb and trunk rhythmic myoclonic jerks (myoclonic absence epilepsy) • Absences with single ictal myoclonic jerks of the limbs, trunk, or head • Absences with mild or not clinically detectable impairment of consciousness (for example, juvenile myoclonic epilepsy) • Other types of epileptic seizures • Stimulus-sensitive absences: photosensitive, patternsensitive, self-induced pattern-sensitive • Irregular, arrhythmic spike/multiple spike and slow-wave EEG discharges with marked variations of discharge frequency • Central-temporal or occipital focal	was reached ~75 days after initiation of treatment. Control group 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.	Follow-up: 12 months (assessements took place at 1 month, 3 months, and 12 months).	Intervention group: n=6/19 Control group: n=2/19 Treatment cessation due to adverse events, n number of participants withdrawing from treatment due to adverse events Intervention group: n=0/19 Control group: n=0/19 Withdrawal from study (by 3 months) Intervention group n=6/19 Control group n=3/19. Withdrawal from study (by 12 months) Intervention group n=6/19 Control group n=3/19.	**risk** 3.1: Yes, data was available for all participants randomised **Domain 4: Measurement of the outcome: Low risk** 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 **Domain 5: Selection of the reported result: Some concerns** 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 **Domain 6: Overall judgment of bias: Some concerns**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	EEG discharges or abnormal background EEG activity • Known or suspected structural brain lesion • Progressive neurologic illness • Psychiatric disorder requiring medication • Chronic cardiovascular, renal, or hepatic disease and, in general, any disease that could interfere with drug absorption, distribution, metabolism, or excretion • Long-term comedication with other drugs • Suspected poor compliance				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
Full citation 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 **Ref Id** 1080326	**Sample size** Total recruited: N=59 Intervention group (levetiracetam): n=38 Control group (placebo): n=21 **Characteristics** Age, years, mean (SD, range) Intervention: 8.7 (2.2, 4.9 to 13.0) Control: 7.9 (3.0, 4.0 to 15.0) Males, n Intervention: 15 Control: 12 Syndromic diagnosis, childhood absence epilepsy (n) Intervention: 34 Control: 20 Syndromic diagnosis, juvenile absence epilepsy (n) Intervention: 4 Control: 1	**Interventions** Intervention group 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 and, if well tolerated, to	**Details** 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.	**Results** *Primary outcomes* Responder status (no clinical seizures on days 13 and 14, and no EEG seizures during the standard EEG on day - ITT analysis Levetiracetam n=9/38 Placebo n=1/21 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) Intervention group: n=4/38 Control group: n=0/21 Patients free from clinical	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Low risk** 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
Country/ies where the study was carried out Italy **Study type** Multi-centre, randomised, placebo-controlled trial **Aim of the study** To evaluate the potential efficacy of levetiracetam as an antiabsence agent in children and adolescents with newly diagnosed childhood or juvenile absence epilepsy **Study dates** Patient enrolment and treatment: October 2006-November 2008. Last assessment for open label phase: December 2009 **Source of funding** Supported by a grant from UCB S.p.A., Pianezza, Italy	<u>Seizure frequency at pretreatment, >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 **Inclusion criteria** • Age between 4 and 16 years • Recent diagnosis of childhood or juvenile absence epilepsy, as defined by the International League Against Epilepsy (ILAE) criteria (Commission, 1989) • 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 hyper-ventilation 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 frequency in the 10–30 Hz	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 the14-day period, the subject was required to exit the study immediately due to ethical considerations. <u>Control group</u> Placebo Depending on age,		<u>and EEG seizures on days 11–14</u> Intervention group: n=7/38 Control group: n=0/21 <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 <u>Adverse events - any</u> Intervention group: n=7/38 Control group: n=3/21 <u>Adverse events - serious</u> Intervention group n=0/38 Control group n=0/21 <u>Adverse events - thought to be related to treatment</u> Intervention group: n=3/38 Control group: n=0/21 <u>Adverse events - leading to discontinuation</u> Intervention group: n=1/38 Control group: n=0/21	gender, but not significant **Domain 2: Deviations from intended interventions: Low risk** 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 **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for all but 1 participants randomised **Domain 4: Measurement of the outcome: Low risk** 4.1: No, outcomes were well defined and was assessed using reliable method (EEG) 4.2: No, outcomes included seizure free status and side ef-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	range, eye closed) • A history of clinically evident spontaneously occurring absence seizures impacting on functional abilities • Written informed consent. **Exclusion criteria** • A history of generalized tonic clonic seizures • Clinical or EEG findings inconsistent with a diagnosis of childhood or juvenile absence epilepsy • 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) • Intellectual disability • Clinically significant hepatic or renal disorders • History of hypersensitivity reactions to study products or structurally related substances • Any condition that, in the investigator's judgment, was expected to impact negatively on subjects' health or study procedures.	body weight, and preference, either a liquid formulation (100 mg/ml solution) or 500 mg tablets were used, with matching placebos. Both treatments were administered in the morning and in the evening in two equally divided doses			fects, which are unlikely to differ between treatment arms 4.3: No, randomisation was only broken after outcome measure evaluation **Domain 5: Selection of the reported result: Some concerns** 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 **Domain 6: Overall judgement of bias: Some concerns** 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 **Other information** After the 2 week double-blind period, all placebo participants were started on levetiracetam. Some participants in both groups discontinued with levetiracetam and start-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					ed other drugs, for example, valproate.
Full citation 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, Epilepsia, 40, 973-979, 1999 **Ref Id** 1080361 **Country/ies where the study was carried out** USA **Study type** Double blind, placebo controlled study **Aim of the study** To investigate whether lamotrigine is effective and safe for newly diagnosed typical absence seizures in children and adolescents	**Sample size** Total recruited and took part in dose escalation phase: N=45. Total randomised after dose escalation phase: Lamotrigine group: n=15 Placebo group: n=14 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). **Characteristics** Age, years, mean (SD) Lamotrigine group: 6.9 (2.3) Placebo group: 8.8 (3.1) Gender Lamotrigine group: 36% males, 64% females Placebo group: 36% males, 64% females **Inclusion criteria** • Patients 2-16 years old with newly diagnosed typical absence seizures, as evidenced by the clinical and EEG features of typical absence seizures on one of two 3-min hyperventilation tests	**Interventions** 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. Lamotrigine: 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 tables were provided. Continued at the dose identified during the dose escalation stage for 4 weeks. No adjustment of dose was permitted. Placebo: 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	**Details** Duration of treatment: dose escalation study, ≥5 weeks; RCT study, 4 weeks 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. Follow-up: 4 weeks (RCT study only).	**Results** *Primary outcomes* Remained seizure free at end of placebo controlled phase Lamotrigine group: 9/14 Placebo group: 3/14 Adverse events - leading to withdrawal from study Lamotrigine group: n=0/14 Placebo group: n=0/14	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 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 **Domain 2: Deviations from intended interventions: Low risk** 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 **Domain 3: Missing**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Glaxo Wellcome Inc. (Research Triangle Park, NC)	• 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 **Exclusion criteria** • A known or suspected structural lesion • A history of poor compliance with medication or abuse of drugs • A progressive neurologic illness (defined prospectively as being an unstable pathologic state during the previous 12 months) • A psychiatric disorder requiring medication • Chronic cardiovascular, renal, or hepatic disease • Use of an investigational drug within the previous 12 weeks • Any disease thought to interfere with absorption, distribution, metabolism, or excretion of drugs in general • 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.	seizure-free dose during the first, second, and remaining 2 weeks.			**outcome data: Low risk** 3.1: Yes, data was available for all but 1 participants randomised **Domain 4: Measurement of the outcome: Low risk** 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 **Domain 5: Selection of the reported result: Some concerns** 5.1: Probably yes, there is a protocol however it is not detailed 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgement of bias: Some concerns** The study is judged to raise some concerns in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					at least one domain, but not to be at high risk of bias for any domain. **Other information** 28 patients completed double-blind phase 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.
Full citation 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, New England Journal of Medicine, 362, 790-799, 2010 **Ref Id** 1082357 **Country/ies where the study was car-**	**Sample size** Total randomised: N=453 Ethosuximide group: n=156 Lamotrigine group: n=149 Valproic acid group: n=148 **Characteristics** Age ≥6 years, n (%) Ethosuximide group: 116 (75) Lamotrigine group: 110 (74) Valproic acid group: 113 (77) Male sex, n (%) Ethosuximide group: 65 (42) Lamotrigine group: 57 (38) Valproic acid group: 71 (48) No statistically significant differences seen between the treatment groups **Inclusion criteria** • Between 2.5 and 13 years of age	**Interventions** Ethosuximide (Zarontin) 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. Lamotrigine (Lamictal) 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.	**Details** Treatment duration: 12 months. Outcome measurement: seizure status was determined by clinical report, bedside hyperventilation testing, and 1-hour video EEG Data analysed according to intention-to-treat approach Follow-up: 12 months. This	**Results** *Primary outcomes* Freedom from treatment failure at 16 or 20 weeks (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): Ethosuximide: 81/154 Lamotrigine: 43/146 Valproic acid: 85/146	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 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 **Domain 2: Deviations from intended inter-**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ried out USA **Study type** Multicentre, double-blind, randomised controlled trial **Aim of the study** 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 **Study dates** July 2004 to October 2007 **Source of funding** Supported by grants from the National Institutes of Health	• 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) • 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 • Weighed 10 kg or more • Had a body-mass index below the 99th percentile • Had a normal complete blood count and normal levels of serum alanine aminotransferase, serum aspartate aminotransferase, and bilirubin • The girls had to be premenarchal **Exclusion criteria** • Had received antiseizure medication for more than 7 days before randomization • Had a history of nonfebrile seizures other than absence seizures (for example, afebrile generalized tonic–clonic or myoclonic seizures) • Had a history consistent with juvenile absence epilepsy or juvenile myoclonic epilepsy (for example, generalized tonic–clonic or myoclonic seizures)	Valproic acid (Depakote) 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. 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	paper report findings at 16 or 20 weeks (primary outcome data based on assessments at week 16 unless 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.	Adverse events - serious (16 or 20 weeks) Ethosuximide: 4/155 Lamotrigine: 2/149 Valproic acid: 2/147 Intolerable adverse effects (16 or 20 weeks) Ethosuximide: 37/154 Lamotrigine: 25/146 Valproic acid: 35/146 Study drug discontinued – no reason reported (16 or 20 weeks) Ethosuximide: 0/154 Lamotrigine: 1/146 Valproic acid: 0/146 Withdrawal from study (16 or 20 weeks) Ethosuximide: 20/154 Lamotrigine: 18/146 Valproic acid: 15/146 *Secondary outcomes* Attentional dysfunction (defined as a Confidence Index of 0.60 or higher on the Conners' Continuous Performance Test, 16 or 20 weeks): Ethosuximide: 35/106 Lamotrigine: 25/104 Valproic acid: 52/106	**ventions: Low risk** 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 **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants **Domain 4: Measurement of the outcome: Low risk** 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 **Domain 5: Selection of the reported result: Low**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Had a history of a severe dermatologic reaction to any medication • Had a history of major psychiatric disease, autistic-spectrum disorder, or any clinically significant medical condition				5.1: Probably yes, there is a protocol however it is not detailed 5.2: Probably no 5.3: Probably no **Domain 6: Overall judgement of bias: Low** The study is judged to be at low risk of bia
Full citation Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC, Childhood Absence Epilepsy Study Team. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia. 2013 Jan;54(1):141-55.	See Glauser 2010	See Glauser 2010	See Glauser 2010	*Primary outcomes* Freedom from treatment failure at 12 months (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): Ethosuximide: 70/154 Lamotrigine: 31/146 Valproic acid: 64/146 Adverse events - serious (12 months) Ethosuximide: 4/155 Lamotrigine: 2/149 Valproic acid: 2/147 Intolerable adverse effects (12 months) Ethosuximide: 38/154 Lamotrigine: 29/146	See Glauser 2010

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Valproic acid: 48/146 Withdrawal from study (12 months) Ethosuximide: 29/154 Lamotrigine: 18/146 Valproic acid: 21/146 Attentional dysfunction defined as a Confidence Index of 0.60 or higher on the Conners' Continuous Performance Test; 12 months): Ethosuximide: 20/70 Lamotrigine: 8/30 Valproic acid: 34/61	
Full citation Sato, S., White, B. G., Penry, J. K., Valproic acid versus ethosuximide in the treatment of absence seizures, Neurology, 32, 157-163, 1982 **Ref Id** 1115033 **Country/ies where the study was carried out** USA **Study type** Double-blind, randomised, response-conditional crosso-	**Sample size** 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) **Characteristics** Age (mean, range) 11.7 years, 4-18 Sex 18 male; 27 female. **Inclusion criteria** • Male patients and female patients with no childbearing potential • 3 to 18 years of age • Absence seizures which must have	**Interventions** Valproic acid and placebo Ethosuximide (followed by Ethosuximide and placebo Valproic acid in period II): 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 For group 2 (the next 22 patients enrolled): Initial daily dosage of 12.5 to 20 mg/kg, with a dosage increase	**Details** 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. Follow-up: 6 weeks (period 1 only).	**Results** *Primary outcomes* Seizure freedom – treatment naive patients (100% reduction in spike wave bursts on EEG) Ethosuximide in period 1 n=4/9. Valproic acid in period 1: n=6/7 Seizure freedom – refractory patients (80% reduction in spike wave bursts on EEG) Ethosuximide in period 1 n=4/14. Valproic acid in period 1: n=3/15	**Limitations** Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 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 **Domain 2: Deviations from intended interventions: Low risk**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ver trial **Aim of the study** To evaluate the efficacy of VPA in treating absence seizures **Study dates** Not reported **Source of funding** The NINCDS	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. • No evidence of progressive neurologic illness • must have been kept on the maximally tolerated daily dosage of ESM for 1 month before the study **Exclusion criteria** Not reported	every 2 days for 2 weeks, to a maximum of 60 mg/kg/day <u>Ethosuximide and Valproic acid placebo (followed by Valproic acid and Ethosuximide placebo in period II):</u> Group 1: Daily dosage ranged from 250 to 1500mg Group 2: Daily dosage was 250 to 1500 mg. For both groups antiseizure drugs for the treatment of other seizure types were continued throughout the study.			2.1: Probably no, said to be double blind but no details 2.2: Probably no, said to be double blind but no details 2.3: N/A 2.4: Probably no, no mention of deviations from the intervention 2.5: Probably no, for period I there were no drop outs. Some participants did not cross over to period II 2.6: N/A **Domain 3: Missing outcome data: Low risk** 3.1: Yes, data was available for nearly all participants for period I **Domain 4: Measurement of the outcome: Low risk** 4.1: No, outcomes were well defined and was assessed using reliable method (EEG) 4.2: No, outcomes included seizure frequency which is unlikely to differ between treatment arms 4.3: No information 4.4: Probably no, out-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					comes are objective **Domain 5: Selection of the reported result: Some concerns** 5.1: No information 5.2: No information 5.3: No information **Domain 6: Overall judgement of bias: Some concerns** 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 **Other information** 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 crossed over in phase II.

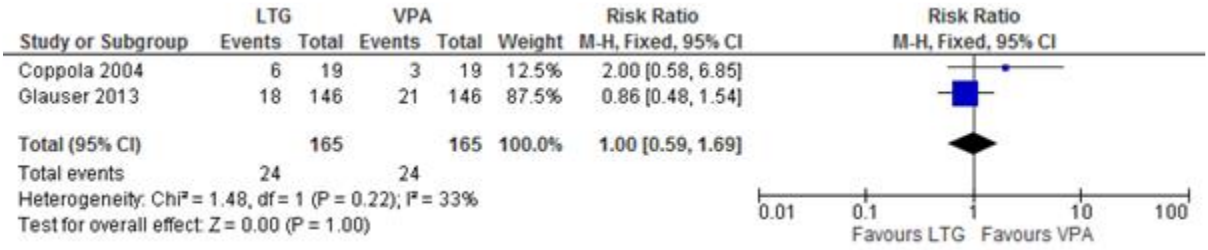
1 *EEG: electroencephalograml; ESM: ethosuximide; LTG: lamotrigine; RCT: randomised controlled trial;SD: standard deviation; VPA: valproic acid*

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)



1 Appendix F – GRADE tables

2 GRADE tables for review question: What antiseizure therapies (monotherapy or add-on) are effective in the treatment of 3 absence seizures?

4 **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[1]	no serious inconsistency	no serious indirectness	serious[2]	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)	⊕⊕OO LOW	CRITICAL
Seizure free at 6 weeks - refractory												
1 (Sato 1982)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO 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[2]	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)	⊕⊕⊕O 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[2]	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)	⊕⊕⊕O 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[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	CRITICAL
Remission - partial (>50% reduction in seizure frequency during six hour telemetry at two intervals of six months, and reported significant reduction in seizure frequency)												
1 (Callaghan 1982)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	CRITICAL
Remission - none (<50% reduction in seizure frequency during six hour telemetry at two intervals of six months, and reported slight or no improvement)												
1 (Callaghan 1982)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	CRITICAL
EEG response - normal (follow-up 18 months - 4 years, mean = 3 years)												
1 (Callaghan 1982)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	CRITICAL
Adverse events - any (follow-up 18 months - 4 years, mean = 3 years)												
1 (Callaghan 1982)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	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[3]	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	⊕⊕OO 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		
										125 more)		
Adverse events - serious (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕⊕OO 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	very serious[3]	none	37/154 (24%)	35/146 (24%)	RR 1 (0.67 to 1.5)	0 fewer per 1000 (from 79 fewer to 120 more)	⊕⊕OO LOW	CRITICAL
Intolerable adverse effects (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	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)	⊕⊕⊕O 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[4]	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)	⊕⊕OO LOW	CRITICAL
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[3]	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)	⊕⊕OO LOW	CRITICAL
Withdrawal from study (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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	⊕⊕OO 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		
										171 more)		
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[2]	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)	⊕⊕⊕O 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	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.*
¥An index of 0.60 corresponds to a 60% probability that the child has clinically significant attention deficit disorder
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Confidence interval crosses one MID (0.8 or 1.25)
[3] Confidence intervals cross both MIDs (0.8 and 1.25)
[4] 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 (Coppo-la 2004)	RCT	serious[1]	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 fewer to 521 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Seizure freedom - 3 months												

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		
1 (Coppola 2004)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	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)	⊕⊕OO LOW	CRITICAL
Seizure freedom - 12 months												
1 (Coppola 2004)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕⊕OO LOW	CRITICAL
Freedom from treatment failure at 16 or 20 weeks*												
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
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	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
Adverse events - any (follow-up 12 months)												
1 (Coppola 2004)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕⊕OO LOW	CRITICAL
Adverse events - serious (follow-up 16 or 20 weeks)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕⊕OO LOW	CRITICAL
Adverse events - serious (follow-up 12 months)												

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		
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕⊕OO LOW	CRITICAL
Treatment cessation due to adverse events (follow-up 12 months)												
1 (Coppo-la 2004)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	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)	⊕OOO VERY 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[2]	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)	⊕⊕⊕O 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[2]	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)	⊕⊕⊕O 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[3]	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)	⊕⊕OO LOW	CRITICAL
Withdrawal from study (follow-up 3 months)												
1 (Coppo-la 2004)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/19 (31.6%)	3/19 (15.8%)	RR 2 (0.58 to 6.85)	158 more per 1000 (from 66 fewer to 924 more)	⊕OOO VERY LOW	CRITICAL
Withdrawal from study (follow-up 16 or 20 weeks)												

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**		
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕⊕OO LOW	CRITICAL
Withdrawal from study (12 months)												
2 (Coppo-la 2004, Glauser 2013)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	CRITICAL
Conners' 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	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
Conners' performance test score > 0.60[¥] (follow-up 12 months)												
1 (Glauser 2013)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	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)	⊕⊕⊕O 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
1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% Confidence interval crosses 1 MID (0.8 or 1.25)
[3] 95% Confidence interval crosses both MIDs (0.8 and 1.25)
[4] 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**		

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	Placebo	Relative (95% CI)	Absolute	Quality	Importance
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[1]	no serious inconsistency	no serious indirectness	very serious[2]	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)	⊕OOO VERY LOW	CRITICAL
Patients free from clinical and EEG seizures - days 4-7 (follow-up 4-7 days)												
1 (Fattore 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	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)	⊕OOO VERY LOW	CRITICAL
Patients free from clinical and EEG seizures - days 11-14 (follow-up 11-14 days)												
1 (Fattore 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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)	⊕⊕OO 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[1]	no serious inconsistency	no serious indirectness	very serious[2]	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)	⊕OOO VERY LOW	CRITICAL
Adverse events - any (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	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)	⊕OOO VERY LOW	CRITICAL
Adverse events – serious (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/38	0/21	RD 0.00 (-0.07 to 0.07)	0 more per 1000 (from 70 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - thought to be related to treatment (follow-up mean 14 days)												
1 (Fattore 2011)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	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)	⊕OOO VERY LOW	CRITICAL
Adverse events - leading to discontinuation (follow-up mean 14 days)												
1 (Fattore	RCT	serious[1]	no serious	no serious	very serious[2]	none	1/38	0/21	POR 4.72	30 more per	⊕OOO	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LEV	Placebo	Relative (95% CI)	Absolute	Quality	Importance
2011)			inconsistency	indirectness			(2.6%)	(0%)	(0.08 to 283.20)	1000 (from 60 fewer to 110 more)	VERY LOW	

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Confidence intervals cross both MIDs (0.8 and 1.25)*
[3] *Confidence interval crosses one MID (0.8 or 1.25)*
[4] *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			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LTG	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Remained seizure free at end of placebo controlled phase (follow-up mean 4 weeks)												
1 (Frank 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	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)	⊕⊕OO LOW	CRITICAL
Adverse events - leading to withdrawal from study												
1 (Frank 1999)	RCT	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	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)	⊕OOO VERY LOW	CRITICAL

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*
[2] *Confidence interval crosses one MID (0.8 or 1.25)*
[3] *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			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	LTG	Relative (95% CI)	Absolute	Quality	Importance
Freedom from treatment failure at 16 or 20 weeks*												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	LTG	Relative (95% CI)	Absolute	Quality	Importance
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[1]	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)	⊕⊕OO 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[1]	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)	⊕⊕OO 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[2]	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)	⊕⊕⊕O 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[2]	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)	⊕⊕⊕O MODERATE	CRITICAL
Study drug discontinued – no reason reporte (follow-up 16 or 20 weeks)												
1 (Glauser 2010)	RCT	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	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)	⊕⊕OO LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ETH	LTG	Relative (95% CI)	Absolute	Quality	Importance
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[1]	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)	⊕⊕OO 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[2]	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)	⊕⊕⊕O 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[2]	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)	⊕⊕⊕O 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[1]	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)	⊕⊕OO 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

[1] Confidence intervals cross both MIDs (0.8 and 1.25)

[2] 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, Http://www.who.int/trialsearch/trial2.aspx?Trialid=actrn12615000556549, 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 valporate is not deemed an acceptable anti-epileptic drug, Http://www.who.int/trialsearch/trial2.aspx? Trialid=actrn12615000641594, 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, Http://www.who.int/trialsearch/trial2.aspx? Trialid=actrn12615000640505, 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 valporate is not deemed an acceptable anti-epileptic drug, Http://www.who.int/trialsearch/trial2.aspx? Trialid=actrn12615000639527, 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
Basu, S., Bhattacharyya, K. B., Das, K., Das, D., Comparative study of sodium valproate and lamotrigi-	Conference abstract

Study	Reason for Exclusion
ne as monotherapy in the management of typical absence seizures, Epilepsia, 46, 277, Abstract no: p853, 2005	
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, Epilepsy & Behavior, 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, Epilepsia, 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, Journal of Pediatrics, 127, 991-997, 1995	Not comparative
Beydoun, A., D'Souza, J., Treatment of idiopathic generalized epilepsy - A review of the evidence, Expert Opinion on Pharmacotherapy, 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, Epilepsia, 38, S42-S44, 1997	Not comparative
Biton, V., Di Memmo, J., Shukla, R., Lee, Y. Y., Poverennova, 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, Epilepsy & Behavior, 19, 352â€• 358, 2010	Mixed epilespy 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, Clinical Drug Investigation, 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, Journal of neurology, neurosurgery, and psychiatry, 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, Cochrane Database of Systematic Reviews, 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, Cochrane Database of Systematic Reviews, 2019	Systematic review. Studies/data included in this paper had already been included in the evidence review, those not included were conference abstracts
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,	Letter to the editor

Study	Reason for Exclusion
1995	
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, 667â€• 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, 667â€• 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 extracted. 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 pediatic patients with epilepsy, Journal of Child Neurology, 17, 278-285, 2002	Not comparative
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, Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2016-002313-22-fr, 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	Systematic review that does not report data on people with absence seizures/outcome data relating to this type of

Study	Reason for Exclusion
seizure types, Journal of Clinical Neuroscience, 21, 55-62, 2014	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, Neurology, 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, Epilepsia, 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, CONTINUUM Lifelong Learning in Neurology, 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, Neurology, 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, Neurological Sciences, 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, Drugs & Aging, 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, Epilepsia, 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
Hemery, C., Ryvlin, P., Rheims, S., Prevention of generalized tonic-clonic seizures in refractory focal epilepsy: A meta-analysis, Epilepsia, 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, Epilepsy research, 127, 267â€• 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., Ox-	Interventions do not meet the criteria specified in the protocol for this review

Study	Reason for Exclusion
carbazepine (GP 47.680): a possible alternative to carbamazepine?, Epilepsia, 28, 693-8, 1987	
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, Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics], 11, 653â€• 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, Epilepsy & Behavior, 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, Epilepsy Research, 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, Epilepsy and Behavior, 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, Neurology, 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, Epilepsia, 59, 460-467, 2018	Mixed epilepsy population without subgroup analysis for people with absence seizures
Marson, A. G., Maguire, M., Ramaratnam, S., Epilepsy, BMJ clinical evidence, 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 antiepileptic drug treatment for early epilepsy and single seizures: A randomised controlled trial, Lancet, 365, 2007-2013, 2005	Systematic review that does not meet the inclusion criteria (evaluates immediate 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 Dis-	Conference abstract

Study	Reason for Exclusion
ease in Childhood: Education and Practice Edition, 96, 119, 2011	
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, 41â€• 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, https://clinicaltrials.gov/show/NCT00510783, 2007	Trial registry entry
Nct,, Does Gabapentin and Lamotriginel 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, https://clinicaltrials.gov/show/NCT00007670, 2000	Trial registry entry
Nct,, Modified Atkins Diet Plus KetoCal for Adult Epilepsy, https://clinicaltrials.gov/show/NCT01834482, 2013	Trial registry entry
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	Mixed epilepsy population without sub-

Study	Reason for Exclusion
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	group 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
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, Epilepsia, 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, Neurology, 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, Epilepsy & Behavior, 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, Neurology, 27, 371, 1977	Conference abstract
Sato, S., Penry, J. K., White, B. G., Driefuss, F. E., Sackellares, J. C., Double-blind crossover study of	Conference abstract

Study	Reason for Exclusion
sodium valproate and ethosuximide in the treatment of absence seizures, Neurology, 29, 603, 1979	
Schmidt, D., Effect of antiepileptic drugs on the postictal state. A critical overview, Epilepsy and Behavior, 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, European Journal of Paediatric Neurology, 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, Epilepsy Currents. 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, P and T, 32, 111, 2007	Unavailable from the British Library. Last checked 15/03/21
Wallace, S. J., Lamotrigine - A clinical overview, Seizure, 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 monotherapy in older adults with epilepsy, Epilepsy Research, 108, 1128-36, 2014	Mixed epilepsy population without subgroup analysis for people with absence seizures
Yuen, A. W. C., Lamotrigine: A review of antiepileptic efficacy, Epilepsia, 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, Chinese journal of contemporary neurology and neurosurgery, 11, 408â€• 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.