National Institute for Health and Care Excellence

Final

Epilepsies in children, young people and adults

[M] Discontinuation of pharmacological treatment

NICE guideline NG217

Evidence reviews underpinning recommendations 4.6.1 to 4.6.7 in NICE guideline

April 2022

Final

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

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ISBN: 978-1-4731-4513-9

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Evidence review for discontinuation of pharmacological treatment

Review question

What are the criteria for stopping antiseizure medications in people with epilepsy?

Introduction

When an individual is commenced on antiseizure medication this does not mean that it has to be continued for life; equally however there may be certain circumstances where the prognosis is such that medication should continue. Appropriate decisions need to be made based on personal circumstance as to whether antiseizure medication should be discontinued. The aim of this review is to identify what criteria should be used to guide when to discontinue antiseizure medication.

Summary of the protocol

See **Error! Reference source not found.** for a summary of the Population, Presence or absence of a prognostic risk or predictive factor, and Outcome (PPO) characteristics of this review.

Table 1:Summary of the protocol (PPO table)

Population	**Inclusion:** • children, young people or/and adults with epilepsy who are currently taking ASMs **Exclusion:** • newborn babies (under 28 days) with acute symptomatic seizures
Presence or absence of a prognostic, risk or predictive factor	Suggestive criteria may include: • Length of seizure freedom • Type of epilepsy (history of status, severity, number of seizures before remission, • EEG (abnormal versus normal) • Cause of epilepsy (acute symptomatic seizures) • Age of onset • Sex • Number of ASMs • Other prescribed medication • Side effects of ASMs • Lifestyle factors (sleep deprivation, work factors, driving, recreational drugs, alcohol intake, pregnancy) *Note: studies must make adjustment for confounding factors in their analysis*
Outcome	**Critical** • Time to recurrence of seizure • Reinitiating ASMs **Important** • Reduction in side effects *As measured using odds ratio (OR), or hazard ratio (HR) adjusted from regression analysis.*

ASMs: antiseizure medications; EEG; electroencephalogram; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR; hazard ratio; OR: odds ratio

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

Seventeen studies were included for this review; 1 systematic review and individual participant data (IPD) meta-analysis (Lamberink 2017), 1 randomised controlled trial (RCT)

(Lossius 2008), 4 prospective observational studies (Berg 2006, Dooley 1996, Rathore 2011 and Su 2013), and 11 retrospective observational studies (Altunbasak 1999, Braathen 1997, Boshuisen 2012, Caviedes 1998, Karalok 2020, Lachhwani 2008, Menon 2012, Ohta 2004, Ou 2018, Park 2010 and Tang 2017). Lossius 2008 was not captured in the IPD meta-analysis by Lamberink 2017 because study authors were not able to obtain the data from the Lossius 2008 study on time.

The RCT compared a group randomised to withdraw from antiseizure medications (ASMs) with a group randomised to continue on ASMs (Lossius 2008) and reported the odds of remaining seizure free according to different potential risk factors. The study compared the prior use of carbamazepine (CBZ) with other ASMs in assessing the risk of remaining seizure free after withdrawal of ASM. Of the other 16 studies, 14 examined potential risk factors associated with seizure recurrence (Berg 2006, Boshuisen 2012, Caviedes 1998, Dooley 1996, Karalok 2020, Lachhwani 2008, Lamberink 2017, Menon 2012, Ohta 2004, Ou 2018, Park 2010, Rathore 2011, Su 2013, and Tang 2017), 1 examined potential risk factors for seizure recurrence rate (Braathen 1997) and 1 study examined potential risk factors for seizure recurrence rate and time (Altunbasak 1999).

Ten studies included a population of people with onset of epilepsy during childhood (<18 years of age) (Altunbasak 1999, Braathen 1997, Boshuisen 2012, Caviedes 1998, Dooley 1996, Karalok 2020, Lachhwani 2008, Menon 2012, Ohta 2004 and Rathore 2011), 6 studies included both people with onset of epilepsy during childhood and adulthood (Berg 2006, Lamberink 2017, Lossius 2008, Ou 2018, Su 2013, and Tang 2017), and 1 study did not report the age of onset of the people included (Park 2010).

Eleven studies examined people who were medically treated for epilepsy (Altunbasak 1999, Braathen 1997, Caviedes 1998, Dooley 1996, Karalok 2020, Lamberink 2017, Lossius 2008, Ohta 2004, Ou 2018, Su 2013 and Tang 2017) (referred to as 'medically treated' hereafter), and 6 studies examined people who had undergone surgery for epilepsy (Berg 2006, Boshuisen 2012, Lachhwani 2008, Menon 2012, Park 2010 and Rathore 2011) (referred to as 'surgically treated' hereafter).

All of the studies adjusted for confounding factors as specified in the protocol. However, the confounding factors adjusted for varied across studies.

The included studies are summarised in Table 1 and Table 2.

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

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 1 and Table 2.

Table 1: Summary of included studies for those who were medically treated

Study	Population	Potential risk factors examined	Outcomes
Altunbasak 1999 Retrospective cohort study	N=97 children with epilepsy Age at seizure onset ranged from 2 months to 12 years;	• Duration of ASM withdrawal <6 months • Age of seizure onset >2 years	• Seizure relapse rate • Seizure relapse time

Study	Population	Potential risk factors examined	Outcomes
Turkey	mean (SD) = 4.5 years (3.3 years) Follow-up range: 2 to 4 years		
Braathen 1997 Retrospective cohort study Sweden	N = 161 children with epilepsy Age and gender were not reported Follow-up, mean = 5.8 years	• Duration of treatment • Age at seizure onset • History of febrile convulsions • Diagnostic class • Irregular spike-wave • 3-Hz spike wave activity on EEG after 6 months of treatment	• Seizure recurrence
Caviedes 1998 Retrospective cohort study Spain	N = 226 children with epilepsy Age at seizure onset, mean (SD) = 53.25 months (35.35 months) Follow-up, mean (SD): 5.85 years (3.87 years)	• Type of epilepsy • Abnormal neurological examination • Location of paroxystic activity • Seizure type • Drug administered • Poor school progress • Age at onset of withdrawal	• Seizure recurrence
Dooley 1996 Prospective cohort study Canada	N = 97 children with epilepsy Age at seizure onset, mean (SD) = 65.9 months (45.89 months) Follow-up range: between 12 to 57 months; mean (SD) = 32.4 months (13.1) months	• Female sex • Age at seizure onset • Seizure type • Neurological abnormalities	• Seizure recurrence
Karalok 2020 Retrospective cohort study Turkey	N= 284 children with epilepsy Age at onset: < 6 years, n (%) = 114 (40.1) > 6 years, n (%) = 170 (59.9) Follow-up, mean (range) = 8.3 years (3-17) years	• Electro-clinical classification • Seizure-free time	• Seizure recurrence
Lamberink 2017 Systematic review and individual participant data (IPD) meta-analysis of prognostic	N = 1769 children and adults with epilepsy Age at onset 0 to 10 years, n (%): 1087 (61)	• History of febrile seizures • ≥10 seizures before remission • Self-limiting epilepsy syndrome • Developmental delay	• Seizure recurrence

Study	Population	Potential risk factors examined	Outcomes
studies – prospective, retrospective and RCTs The IPD meta-analysis was conducted in The Netherlands. Individual studies were conducted in Brazil, The Netherlands, UK, Servia, Spain, Italy, US	11 to 17 years, n (%): 387 (22) ≥18 years, n (%): 295 (17) Maximum follow-up after start of antiepileptic drug withdrawal was 23 years (median 5.3 years, IQR 3.0 to 10.0 years)	• Epileptiform abnormality	
Lossius 2008 Randomised-controlled study Norway	N=150 children and adults with epilepsy Age at seizure onset ranged from 0 to 60 years Follow-up: median = 47 months (41 months for patients off medication)	• Prior use of CBZ when compared with other ASMs • Normal neurological examination	• Seizure freedom
Ohta 2004 Retrospective cohort study Japan	N = 82 children with epilepsy Age at seizure onset: Mean = 3 years 10 months Range = 7 months to 14 years 2 months Follow-up: Average follow-up period from start of ASM discontinuation to last visit = 4 years 7 months Average follow-up period from complete discontinuation of ASM to last visit = 2 years 9 months	• Age at seizure onset ≥ 6 years • Time from start of ASM before seizure control ≥ 5 years • Number of seizures before seizure control ≥ 5 • Number of ASMs before seizure control ≥ 2 • Complex partial seizure	• Seizure recurrence
Ou 2018 Retrospective cohort study China	N = 161 children and adults with epilepsy Age at onset 0 to 18 years n=111 >18 years n = 50 Follow-up, mean (SD; range): 41.97 (31.19; 0.5-156) months	• Multiple co-occurring seizure types • Perinatal injury • Seizures not controlled in first 6 months of treatment • Combination of ASMs	• Seizure recurrence

Study	Population	Potential risk factors examined	Outcomes
Su 2013 Prospective cohort study China	N = 99 children and adults with epilepsy Early ASM withdrawal group n = 44 (51.2%) Delayed ASM withdrawal group n = 42 (48.8%) Age at seizure onset, median (range): 18 years (6-67 years) Follow-up, mean (SD) = 2.1 (1.5) years	• Epileptiform abnormalities after withdrawal • Early withdrawal after 2 to 3 years seizure free	• Seizure recurrence
Tang 2017 Retrospective cohort study China	N = 195 children and adults with epilepsy Age at onset, mean (SD): 18.23 (13.63) Follow-up, Median (P_{25} - P_{75}) Non-relapse group = 25 (19.8) Relapse group = 15.91 (2.71)	• Received more than one ASM • Course of epilepsy (longer than 6 months) prior to initiation of ASM treatment	• Seizure recurrence

ASM: antiseizure medication; CBZ: carbamazepine; IPD: individual participant data; IQR: inter-quartile range; RCT: randomised controlled trial; SD: standard deviation

Table 2: Summary of included studies for those who were surgically treated

Study	Population	Potential risk factors examined	Outcomes
Berg 2006 Prospective cohort study US	N=291 children and adults with epilepsy Age at onset ranged between <5 years old and more than 40 years old Follow-up: not reported; patients were assessed every 3 months after discharge from hospital	• Delayed remission • Continued auras	• Seizure recurrence
Boshuisen 2012 Retrospective cohort study Multicentre (Europe)	N = 766 children with epilepsy; of which n=444 had ASM discontinuation No information on age Follow-up, mean (SD) = 61.6 (29.7) months	• Time interval to ASM reduction • Multifocal MRI lesions • Epilepsy etiology • Number of ASMs used at time of surgery • Type of surgery • Immediate postoperative seizure freedom	• Seizure recurrence in those with ASM reduction and with ASM discontinuation after surgery

Study	Population	Potential risk factors examined	Outcomes
		• Previous surgery • Postoperative EEG findings • Epileptic abnormalities • No EEG performed • Resection of the anatomical lesion • Proven incomplete resection of the anatomical lesion	
Lachhwani 2008 Retrospective cohort study US	N=97 children with epilepsy Age at epilepsy onset: Birth to 13 years Follow-up: 24 months after surgery	• Post-operative ASM use	• Seizure recurrence
Menon 2012 Retrospective cohort study India	N = 94 children with epilepsy Age at onset, mean (SD): Non-recurrence group = 7.4 years (5 years) Recurrence group = 7.2 years (6.4 years) Follow-up not reported. Patients assessed at 3 months, 1 year and then yearly after surgery	• Duration of epilepsy • Interictal epileptiform discharges	• Seizure recurrence
Park 2010 Retrospective cohort study Korea	N = 223 children and adults with epilepsy Follow-up: mean (range) = 72.6 months (12 to 138 months)	• Time to ASM reduction • Normal MRI results • Seizure recurrence before reduction • Epilepsy duration • Cortical dysplasia • Preoperative number of ASMs • Incomplete resection	• Seizure recurrence
Rathore 2011 Prospective cohort study India	N = 258 children with epilepsy Seizure recurrence n = 64 Seizure-free n = 194 Age at epilepsy onset: Seizure group, mean (SD) = 9.13 (7.85)	• Absence of definitive hippocampal sclerosis • Interictal epileptiform discharges • Seizure recurrence before attempted ASM withdrawal • Age at anterior temporal lobectomy	• Seizure recurrence

Study	Population	Potential risk factors examined	Outcomes
	Seizure-free group, mean (SD) = 9.39 (6.69) Follow-up, mean (SD) = 8 (2) years	• Epilepsy duration ≥20 years	

ASM: antiepileptic medication; EEG: electroencephalogram; MRI: magnetic resonance imaging; SD: standard deviation

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of studies included in the evidence review

See the evidence profiles in appendix F.

Summary of the evidence

Potential risk factors examined were reported separately for those who were medically treated only and those who were surgically treated as these are considered 2 very distinct populations. An increased risk of seizure recurrence was reported when adjusted relative estimates and 95% confidence intervals (CIs) were >1. A decreased risk of seizure recurrence was reported when adjusted relative estimates and 95% CIs were <1. No meta-analyses were conducted, therefore all factors reported are from single studies.

Medically treated population

The following factors were associated with an increased risk of seizure recurrence in those who were medically treated and whose age at epilepsy onset was mixed:

- ≥10 seizures before remission (low quality evidence)
- History of febrile seizures (low quality evidence)
- Seizures that were not controlled in the first 6 months of treatment (low quality evidence)
- Perinatal injury (moderate quality evidence)
- Course of epilepsy (longer than 6 months) prior to initiation of ASM treatment (low quality evidence)
- Epileptiform electroencephalogram (EEG) abnormalities before withdrawal (moderate quality evidence)
- Epileptiform EEG abnormalities after withdrawal (moderate quality evidence)
- Received > 1 ASM (low quality evidence)
- Developmental delay (low quality evidence)
- Normal neurological examination (low quality evidence)

The following factors were associated with a decreased risk of seizure recurrence in those who were medically treated and whose age at epilepsy onset was mixed:

- Use of carbamazepine compared with other ASMs (remaining seizure free for 1 year; low quality evidence)
- Use of carbamazepine compared with other ASMs (remaining seizure free for 41 months; moderate quality evidence)

The following factors were associated with a decreased risk of seizure recurrence in those who were medically treated and whose age at epilepsy onset was mixed:

- Self-limiting epilepsy syndrome (formerly called "benign course", for example: absence epilepsy, benign epilepsy with centrotemporal spikes (rolandic epilepsy), Panayiotopoulos syndrome (moderate quality evidence)

The following factors showed no association with risk of seizure recurrence in those who were medically treated and whose age at epilepsy onset was mixed:

- Multiple co-occurring seizure types (very low quality evidence)
- Early withdrawal of ASMs (after 2-3 years seizure free) (moderate quality evidence)
- Combination of ASMs (very low quality evidence)

The following factors were associated with an increased risk of seizure recurrence in those who were medically treated and were children at epilepsy onset:

- Seizure type: simple partial (low quality evidence)
- Seizure type: generalised (moderate quality evidence)
- Seizure type: partial (moderate quality evidence)
- Electroclinical classification (genetic/structural-metabolic and unknown) (low quality evidence)
- Seizure-free time (<3 years) (low quality evidence)
- Time from start of ASM treatment to seizure control ≥ 5 years (moderate quality evidence)
- Irregular spike-wave after 1 year of treatment (low quality evidence)
- 3-Hz spike wave activity on EEG after 6 months of treatment (low quality evidence)
- Location of paroxystic activity: frontal (all patients and in patients with focal epilepsy specifically; low quality evidence)
- Location of paroxystic activity: parietal (low quality evidence)
- The following diagnosis: benign partial epilepsy with centrotemporal [rolandic] spikes (BECT) and simple partial seizures (SPS); primarily generalised tonic-clonic seizures (GTCS), GTCS during the night, autoimmune epilepsy, and GTCS as the only ictal manifestation in children with rolandic spikes (low quality evidence)
- Focal epilepsy (moderate quality evidence)
- Sodium valproate (moderate quality evidence)
- Age at seizure onset >2 years (low quality evidence)
- Age >5 years at onset of withdrawal (low quality evidence)
- Female sex (moderate quality evidence)
- Age at seizure onset over 10 years (low quality evidence)
- Age at onset of epilepsy ≥ 6 years (moderate quality evidence)
- Abnormal neurological examination (all patients and in patients with focal epilepsy specifically low quality evidence)
- Poor school progress (all patients and in patients with generalised epilepsy specifically; low quality evidence)
- Neurological abnormalities (moderate quality evidence)
- Interval between seizures < 1 month at disease onset (patients with focal epilepsy only; low quality evidence)Pathological neonatal period (patients with generalised epilepsy only; low quality evidence)
- Generalised groups of irregular spike-wave in EEG in patients with generalised epilepsy (patients with generalised epilepsy only; low quality evidence)

The following factors were associated with a decreased risk of seizure recurrence in those who were medically treated and were children at epilepsy onset:

- Seizure type: absences/spasms (low quality evidence)
- Duration of ASM withdrawal < 6 months (low quality evidence)
- Duration of treatment < 1 year (low quality evidence)
- Mean duration of seizures < 1 minute (patients with generalised epilepsy only; low quality evidence)

The following factors showed no association with risk of seizure recurrence in those who were medically treated and were children at epilepsy onset:

- History of febrile convulsions in children with complex partial seizures (very low quality evidence)
- Number of seizures before seizure control (low quality evidence)
- Complex partial seizures (low quality evidence)
- Favourable age at seizure onset (defined as: >10 years for children with rolandic epilepsies and <10 years for children with other seizure types; low quality evidence)
- Abnormal EEG prior to withdrawal (patients with focal epilepsy only; low quality evidence)

Surgically treated population

The following factors were associated with an increased risk of seizure recurrence in those who were surgically treated and whose age at epilepsy onset was mixed or not reported:

- Delayed remission (low quality evidence)
- Continued auras (after adjustment for delayed remission; low quality evidence)
- Seizure recurrence before ASM reduction (moderate quality evidence)
- Epilepsy duration (>11 years; low quality evidence)
- Normal magnetic resonance imaging (MRI) results (low quality evidence)
- Time to ASM reduction <9 months (moderate quality evidence)

The following factors showed no association with risk of seizure recurrence in those who were surgically treated and whose age at epilepsy onset was mixed or not reported:

- Preoperative number of ASMs (low quality evidence)
- Incomplete resection (low quality evidence)

The following factors were associated with an increased risk of seizure recurrence in those who were surgically treated and were children at epilepsy onset:

- Epileptic abnormalities on postoperative EEG findings (in those with ASM reduction; moderate quality evidence))
- Proven incomplete resection of the anatomical lesion (in those with ASM reduction; high quality evidence)
- Absence of definitive hippocampal sclerosis (HS) on pathology (moderate quality evidence)
- Longer preoperative duration of epilepsy (high quality evidence)
- Multifocal MRI lesions (moderate quality evidence)
- Interictal epileptiform discharges on 1-year postoperative EEG (moderate quality evidence)

- Interictal epileptiform discharges (IEDs) on 1-year anterior temporal lobectomy (ATL) EEG
- ASMs discontinued ≤ 6 months after surgery (moderate quality evidence)
- Type of surgery: hemispherectomy (in those with ASM reduction; moderate quality evidence)
- Proven incomplete resection of the anatomical lesion (in those with ASM reduction; high quality evidence)
- Proven incomplete resection of the anatomical lesion (in those with ASM discontinuation; high quality evidence)
- Previous surgery (in those with ASM reduction; moderate quality evidence))

The following factors were associated with a decreased risk of seizure recurrence in those who were surgically treated and were children at epilepsy onset:

- Shorter time interval from surgery to start of ASM reduction, per 3 months (high quality evidence)
- Shorter time interval from surgery to complete ASM discontinuation (moderate quality evidence)

The following factors showed no association with risk of seizure recurrence in those who were surgically treated and were children at epilepsy onset:

- Immediate postoperative seizure freedom (in those with ASM reduction; moderate quality evidence)
- Immediate postoperative seizure freedom (in those with ASM discontinuation; low quality evidence)
- Epileptic abnormalities on postoperative EEG findings (in those with ASM discontinuation; low quality evidence)
- Seizure recurrence before attempted ASM withdrawal (moderate quality evidence)
- Epilepsy aetiology (in those with ASM reduction; focal cortical dysplasia was used as the reference category to compare it with tumour, vascular pathology, hippocampal sclerosis, Rasmussen's encephalitis, other; high quality evidence)
- Epilepsy aetiology: (in those with ASM discontinuation; focal cortical dysplasia was used as the reference category to compare it with tumour, vascular pathology, hippocampal sclerosis, Rasmussen's encephalitis, other; moderate quality evidence)
- Epilepsy duration ≥ 20 years (moderate quality evidence)
- Postoperative EEG findings (in those with ASM reduction; low quality evidence)
- No EEG performed (in those with ASM reduction; low quality evidence)
- Postoperative EEG findings (in those with ASM discontinuation; moderate quality evidence)
- No EEG performed (in those with ASM discontinuation; low quality evidence)
- Number of ASMs used at time of surgery (in those with ASM reduction; low quality evidence)
- Number of ASMs used at time of surgery (in those with ASM discontinuation; moderate quality evidence)
- ASMs discontinued ≤ 12 months after surgery (moderate quality evidence)
- ASMs discontinued ≤ 24 months after surgery (low quality evidence)
- Type of surgery (in those with ASM reduction; moderate quality evidence)
- Type of surgery: multilobar resection (in those with ASM reduction; moderate quality evidence)

- Resection of the anatomical lesion (in those with ASM reduction; moderate quality evidence)
- Type of surgery (in those with ASM discontinuation; low quality evidence)
- Type of surgery: hemispherectomy (in those with ASM discontinuation; low quality evidence)
- Type of surgery: multilobar resection (in those with ASM discontinuation; low quality evidence)
- Resection of the anatomical lesion (in those with ASM discontinuation; moderate quality evidence)
- Age at anterior temporal lobectomy ≥ 30 years (low quality evidence)
- Previous surgery (in those with ASM discontinuation; low quality evidence)

No evidence was found for the outcomes of reinitiating ASMs and reduction in side effects. No subgroup analyses could be carried out for adults (>18 years old) or those with or without learning disabilities only.

Economic evidence

Included studies

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

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

Excluded studies

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

Summary of studies included in the economic evidence review

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.

Summary of the economic evidence

No evidence was identified which was applicable to this review question

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The aim of this review was to identify which factors or criteria should be met to help determine when it is most likely safe and appropriate for a person with epilepsy to discontinue antiseizure medications. The committee agreed on 2 critical outcomes: time to recurrence of

seizure, and reinitiating ASMs. These outcomes were selected as the most direct indicators of the safety of discontinuation of ASMs.

The committee also identified 1 important outcome: reduction in side effects. The committee agreed that this would be a good indicator of having successfully stopped or titrated ASMs, provided patients remained seizure-free.

The quality of the evidence

The quality of the evidence was assessed with an adapted GRADE approach and was rated as high to very low quality, indicating uncertainties in some of the domains.

The risk of bias in studies contributing to the evidence was assessed using the Quality in Prognostic Studies (QUIPS) checklist. Common issues with the low quality evidence studies included varied methods for evaluating confounders across study sites; not reporting the characteristics of the population included in adequate detail and reporting bias as, for some studies, parents were asked to provide retrospective information about the prognostic variables under study.

Outcomes were mostly downgraded due to imprecision in the data. Outcomes were also downgraded due to risk of bias that arose from potential bias in study participation, prognostic factor measurement and confounding factors measurement.

Benefits and harms

The committee discussed the findings of the review, and considered whether the evidence was of sufficient strength to highlight any individual factors for seizure recurrence following antiseizure medication discontinuation in the recommendations. Overall, the committee agreed that indicating individual factors was not appropriate as it could imply that using single factors (as opposed to overall clinical impression) was sufficient to guide decision- making. The committee noted that the individual factors shown as part of the evidence review require an appropriate context in order to be useful in clinical practice. For instance, the factor ‘epileptiform abnormalities on EEG’ could be perceived as a widely accepted indicator of seizure recurrence in those whose antiseizure medication has been discontinued, however the committee noted that this would depend on the type of medication the person was taking, the type of epilepsy as well as other individual factors which should be carefully considered. For these reasons, the committee considered that individual factors for seizure recurrence do not provide definitive answers and based the recommendations on its experience and expertise.

The committee agreed that, once the person with epilepsy has been started on antiseizure medication, there should be an ongoing assessment of the benefits and risks of continuing antiseizure medication. This assessment should be done with the person with epilepsy at any appointment or review and could also involve the person’s family and carers if necessary. The committee emphasised that information should be available in an accessible format and be adapted to the needs of each person.

The committee agreed that, after the person has been seizure free for 2 years, an individualised risk assessment of the risk of seizure recurrence should be conducted. The committee agreed that 2 years of seizure freedom is widely accepted in clinical practice and that it is an important point at which to consider discontinuation as a means of reducing the risks associated with unnecessary treatment that may go on indefinitely. The committee agreed that discussions to discontinue antiseizure medication could take place with the person’s healthcare professional but recommended that, where there is uncertainty about the benefit of continuing antiseizure medications or concerns regarding the risk of seizure recurrence when discontinuing medication, advice from an epilepsy specialist should be sought. However, the committee also agreed that for people who have had epilepsy surgery, discontinuation of treatment must include input from the relevant epilepsy surgery centre due to the variety of surgical techniques used and the complex nature of epilepsy surgery.

The committee noted that when discussing whether to discontinue antiseizure medication, there are a number of factors that should be considered. For example, remission is unlikely to be achieved in a number of circumstances, such as in people with juvenile onset idiopathic generalised epilepsy, or people with epilepsies associated with structural abnormalities, neurodegenerative conditions or neurological conditions, including intellectual disabilities. In addition, the committee agreed that the risk of sudden unexpected death in epilepsy (SUDEP) should also be considered. Preferences and lifestyle, such as driving, concerns about medication side effects, work status, stigma attached to antiseizure medication or the implications of seizure recurrence are the most common variables people with epilepsy consider when balancing the benefits and risks of discontinuing antiseizure medication.

Once an individual has entered a seizure-free period and the decision to discontinue medication has been made a plan, based on the individual's risk and preferences, should be agreed with the person with epilepsy and their parents or carers, if appropriate. Based on the committee's experience, full discontinuation should take place over a minimum of 3 months. For people who are discontinuing treatment with benzodiazepines and barbiturates, discontinuation should take place over 6 months or longer if possible due to the possibility of withdrawal symptoms.

The committee agreed that for people who are taking multiple medications, discontinuation should take place 1 at a time. They also agreed to recommend that if seizures recur during or after discontinuation of treatment, the last dose reduction should be reversed and advice sought from a specialist in line with an agreed plan.

Cost effectiveness and resource use

Recommendations are in line with current practice, although the committee discussed that there may be an increase in referrals to specialist services for cases when is not clear whether a person should be withdrawn or not. As referral to specialist services is already widely undertaken in such circumstances it is thought that this increase would be small and any increase will be offset by decreased healthcare contacts from improved care.

Recommendations supported by this evidence review

This evidence review supports recommendations 4.6.1 to 4.6.7.

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Appendices

Appendix A – Review protocol

Review protocol for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

Table 3: Review protocol for discontinuation of pharmacological treatment

Field	Content
PROSPERO registration number	CRD42020178587
Review title	Stopping antiseizure medications
Review question	What are the criteria for stopping antiseizure medications in people with epilepsy?
Objective	To identify factors or criteria which should be met to help determine when it is most likely safe and appropriate for a person with epilepsy to stop taking their anti-epileptic medication. The aim is to provide guidance when it should be considered that ASMs can be withdrawn.
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: • Date: no date limit • English language studies • Human studies
Condition or domain being studied	Children, young people and adults with epilepsy who are taking ASMs

Field	Content
Population	Inclusion • children, young people or adults with epilepsy who are currently taking ASMs Exclusion • newborn babies (under 28 days) with acute symptomatic seizures
Presence or absence of a prognostic, risk or predictive factor	Suggestive criteria may include: • Length of seizure freedom • Type of epilepsy (history of status, severity, number of seizures before remission, • EEG (abnormal versus normal) • Cause of epilepsy (acute symptomatic seizures) • Age of onset • Sex • Number of ASMs • Other prescribed medication • Side effects of ASMs • Lifestyle factors (sleep deprivation, work factors, driving, recreational drugs, alcohol intake, pregnancy)
Confounding factors	Any of those listed above *Note: studies must make adjustment for confounding factors in their analysis, and this will be accounted for in the GRADE analysis*
Types of study to be included	• Systematic reviews of observational cohort studies • Prospective or retrospective cohort studies • If cohort studies are unavailable to inform decision making, then case-control studies of at least 50 people in each arm will be considered for inclusion • Prospective study designs will be prioritised over retrospective study designs • Population-based studies and multicentre studies will be prioritised Univariate studies will only be included if no studies with multivariate analysis are identified Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.

Field	Content
	Conference abstracts will not be included because these do not typically provide sufficient information to fully assess the risk of bias.
Other exclusion criteria	• Studies with a mixed population (that is including children, young people and adults with epilepsy and others with a condition different to epilepsy) will be excluded, unless subgroup analysis for epilepsy has been reported. Conference abstracts will not be included because these do not typically provide sufficient information to fully assess the risk of bias
Context	Recommendations will apply to those receiving care in healthcare settings (for example community, primary, secondary care).
Primary outcomes (critical outcomes)	• Time to recurrence of seizure • Reinitiating ASMs As measured using odds ratio (OR), or hazard ratio (HR) adjusted from regression analysis.
Secondary outcomes (important outcomes)	Reduction in side effects NB: 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. Titles and abstracts of the retrieved citations will be screened. The full text of potentially eligible studies will be retrieved and will be assessed in line with the inclusion criteria outlined in the review protocol. 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 reason for its exclusion. Draft included and excluded study lists will be circulated to the committee for their comments, resolution of any disputes will be by discussion between the senior reviewer, topic advisor and chair. Duplicate screening will not be undertaken for this question. A standardised form will be used to extract data from studies and will include: study setting; study design; study aim; study dates; funding; sample size; participant demographics and baseline characteristics; inclusion and exclusion crite-

Field	Content
	ria; details of factors measured within the study, the confounding factors, and those adjusted for in multivariable analysis, study methodology; recruitment and study completion rates; outcomes and times of measurement; and information for assessment of risk of bias. All data extraction will be quality assured by a senior reviewer. For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • ROBINS-I for non-randomised studies • QUIPS checklist for prognostic factor studies 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. <u>Data synthesis</u> Where possible meta-analysis to combine the effect estimates across studies for an independent prognostic factor will be conducted only if there is sufficient number of studies, a consistent measure to assess this factor is used, and each study has adjusted for similar sets of confounders. We will assess the confounders which have been included in the multiple regression of included studies, and make a decision regarding levels of similarity in adjustment, unless sufficiently similar, data will not be pooled. We will extract either OR or HR; however we will conduct separate meta-analysis for those studies reporting OR and those reporting HR, as it is inappropriate to pool OR and HR. If no meta-analysis is conducted a narrative summary of the available results for each factor will be provided. <u>Heterogeneity</u> Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 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

Field	Content	
	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. 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)	If data is available, results will be presented separately by: • Adults and children • Those with or without learning difficulties	
Type and method of review	☐	Intervention
	☐	Diagnostic
	☒	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	01 June 2020	
Anticipated completion date	07 April 2021	
Named contact	**5a. Named contact** National Guideline Alliance **5b. Named contact e-mail** epilepsies@nice.org.uk **5c. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance	

Field	Content	
Review team members	• National Guideline Alliance (NGA) 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.	
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/gid-ng10112/documents/committee-member-list	
Other registration details	Not applicable	
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020178587	
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, withdrawal, ASMs	
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	

Field	Content
Details of final publication	www.nice.org.uk

ASM: antiseizure medication; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; EEG: electroencephalogram; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HR: hazard ratio; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; OR: odds ratio; QUIPS: Quality in Prognostic Studies; ROBINS-I: Risk of Bias in Non-randomised Studies of Interventions; ROBIS: Risk of Bias in Systematic Review

Appendix B – Literature search strategies

Literature search strategies for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

Clinical

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

EMCare 1995 to January 22, 2021; Embase Classic+Embase 1947 to 2021 January 22; Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 2021 January 22, 2021
Date of last search: 22 January 2021

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	exp epilepsy/ or landau kleffner syndrome/ or exp seizure/ or "seizure, epilepsy and convulsion"/
2	1 use emczd, emcr
3	exp epilepsy/ or seizures/ or seizures, febrile/ or exp status epilepticus/
4	3 use ppez
5	(convulsion* or dravet syndrome or epilep* or continous spike wave of slow sleep or landau kleffner syndrome or lennox gastaut syndrome or infant* spasm* or seizure* or west syndrome).ti,ab.
6	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.
7	myoclonic astatic epilepsy/ use emczd, emcr or exp epilepsies, myoclonic/ use ppez or ((myoclonic adj2 (astatic or atonic)) or (myoclonic adj3 (seizure* or spasm*)) or doose* syndrome or mae or generali?ed idiopathic epilepsy).ti,ab. or ((absence or astatic or atonic or tonic or tonic clonic) adj2 (seizure* or spasm*)).ti,ab.
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	or/2,4-8
10	anticonvulsive agent/ use emczd, emcr or exp anticonvulsants/ use ppez
11	carbamazepine/ use emczd, emcr or exp carbamazepine/ use ppez or carbamazepin*.sh. or (amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol).ti,ab.
12	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.
13	clonazepam/ use emczd, emcr or clonazepam/ use ppez or (aklonil or antelepsin or clonazepam or clonex or clonopam or clonopin or clonotril or coquan or iktorivil or kenoket or klonazepam or klonopin or kriadex or landsen or lonazep or paxam or povanil or ravotril or rivatril or rivotril).ti,ab.

#	searches
14	corticotropin/ use emczd, emcr or exp adrenocorticotropic hormone/ use ppez or adrenocorticotropic hormone*.sh. or (acethropan or acetophran or acortan or acorto or acth or acthar or acthelea or acthon or acton or actonar or actrope or adactan or (adrenal cortex adj (trophic or tropic) adj hormone) or adrenocorticaltrophormon or adrenocorticotrop* or adrenocorticotrop* or adrenocorticotrophin or adrenocorticotropic hormone or adrenocorticotropin* or adrenomone or adrenotropin or cibacthen or corticotrophin* or corticotropic or corticotropin* or cortigel or cortilin or cortiphyson or cortosyn or cortrophin * or cortropin or cortrosyn or cosyntropin* or cotrophin* or exactin or hp acthar gel or humacthid or humactid or porcine acth or porcine corticotropin or procortan or reacthin or s cortophin or solacthyl or synacthen retard or tetracosactide or tetracosactrin or tetracosapeptide).ti,ab.
15	ethosuximide/ use emczd, emcr or ethosuximide/ 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.
16	gabapentin/ use emczd, emcr or gabapentin/ use ppez or gabapentin*.sh. or (apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin).ti,ab.
17	hydrocortisone*.hw. use emczd, emcr or hydrocortisone/ use ppez or (17 hydroxycorticosterone or acticort or aeroseb hc or ala-cort or ala-scalp or alfacort or algicortis or alkindi or alpha derm or alphaderm or anucort-hc or anumed-hc or anutone-hc or aquanil hc or balneol-hc or barseb hc or beta-hc or biacort or cetacort or cobadex or colocort or compound f or cordicare lotion or coripen or cort dome or cortef or cortenema or cortibel or corticorenol or cortifair or cortifan or cortiphate or cortisol or cortisole or cortispray or cortoderm or cortril or cotacort or covocort or cremicort-h or cutaderm or dermacrin hc lotion or dermaid or derm-aid cream or dermaid soft cream or dermocare or dermocortal or dermolate or dioderm or eczacort or ef cortelan or efcortelan or egocort or eksalb or eldecort or emo-cort or epicort or epicortisol or ficortril or filocot or flexicort or glycort or gly-cort or h-cort or hebcort or hemorrhoidal hc or hemril-30 or hemril-hc uniserts or hi-cor or hidrotisona or hycor or hycort or hydracort or hydrasson or hydro ricortex or hydrocort or hydrocorticosteroid or hydrocortisate or hydrocortisone or hydrocortisone or hydrocortisonum or hydrocortisyl or hydrocortone or hydrogalen or hydrokort or hydrokortison or hydro-rx or hydrotopic or hysone or hytisone or hytone or incortin h or instacort 10 or kyypakkaus or lacticare hc or lemnis fatty cream hc or lenirit or medihaler cort or medihaler duo or medrocil or mildison or mitocortyl demangeaisons or munitren or nogenic hc or novohydrocort or nutracort or optef or otosone f or penecort or plenadren or prepcort or prevex h or pro cort or procort or proctocort or procto-kit or proctosol-hc or proctosone or proctozone or procutan or rectasol-hc or rectocort or rederm or sanatison or scalp-aid or schericur or scherosone or sistral hydrocort or skincalm or stie-cort or substance m or synacort or texacort or triburon-hc or unicort or vasocort).ti,ab.
18	lacosamide/ use emczd, emcr or lacosamide/ use ppez or (erlosamide or harkoseride or lacosamide or vimpat).ti,ab.
19	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.
20	levetiracetam/ use emczd, emcr,ppez or (elepsia or keppra or kopodex or levetiracetam* or matever or spritam).ti,ab.
21	nitrazepam/ use emczd, emcr,ppez or (apodorm or atempol or benzalin or dormalon or dormo-puren or dumolid or eatan or eunoctin or hypnotex or imadorm or imeson or insomin or mogadan or nelbon or nirven or nitra zepam or nitrados or nitravet or nitrazadon or nitrazep or nitrazepam or nitrodiazepam or novanox or pacisyn or radedorm or remnos or restorem or rhoxal nitrazepam or rhoxal-nitrazepam or sedamon or serenade or somnased or somnibel n or somnite).ti,ab.
22	oxcarbazepine/ use emczd, emcr or oxcarbazepine/ use ppez or oxcarbazepin*.sh. or (apydan or carbamazepine or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin).ti,ab.
23	prednisolone*.hw. use emczd, emcr or exp prednisolone/ use ppez or (adelcort or antisolon* or aprednislon* or benisolon* or berisolon* or caberdelta or capsoid or co hydeltra or codelcortone or compresolon or cortadelton* or cortalone or cortelinter or cortisolone or cotolone or dacortin or decaprednil or decortril or dehydro cortex or dehydro hydrocortison* or dehydrocortex or dehydrocortisol* or dehydrohydrocortison* or delcortol or delta cortef or delta cortril or delta ef cortelan or delta f or delta hycortol or delta hydrocortison* or delta ophticor or delta stab or delta1 dehydrocortisol or delta1 dehydrohydrocortisone or delta1 hydrocortisone or deltacortef or delta-cortef or deltacortenolo or deltacortil or deltacortoil or deltacortril or deltaderm or deltaglycortril or deltahycortol or deltahydrocortison* or deltaophticor or deltasolone or deltastab or deltidrosol or deltisolon* or deltisolone or deltolasson or deltolassone or

#	searches
	deltosona or deltosone or depo-predate or dermosolon or dhasolone or di adreson* or diadreson* or diadresonf or di-adreson-f or dicortol or domucortone or encortelon* or encortolon* or equisolon or fernisolone-p or glistelone or hefasolon or hostacortin or hydeltra or hydeltrone or hydrelta or hydrocortancyl or hydrocortidelt or hydrodeltalone or hydrodeltisone or hydroretrocortin* or inflanefran or insolone or keteocort h or key-pred or lenisolone or leocortol or liquipred or lygal or kopftinktur n or mediasolone or meprisolon* or metacortalon* or metacortandralon* or metacortelone or meti derm or meticortelone or metiderm or meti-derm or morlone or mydrapred or neo delta or nisolon or nisolone or opredsone or panafcortelone or panafcortolone or panafort or paracortol or phlogex or pre cortisyl or preconin or precortalon or precortancyl or precortisyl or predacort 50 or predaject-50 or predalone 50 or predartrin* or predate or predeltilone or predisole or predisyr or pred-ject-50 or predne dome or prednecort or prednedome or prednelan or predni coelin or predni h tablinen or prednicoelin or prednicort * or prednifor drops or predni-helvacort or predniment or predniretard or prednis or prednisil or prednisolon* or prednivet or prednorsolon* or predonine or predorgasolon* or prelon or prelone or prenilone or prenin or prenolone or preventan or prezolon or rubycort or scherisolon* or serilone or solondo or solone or solupren* or spiricort or spolotane or sterane or sterolone or supercortisol or taracortelone or walesolone or wysolone).ti,ab.
24	prednisone/ use emczd, emcr or prednisone/ use ppez or (ancortone or biocortone or colisone or cortan or cortancyl or cortidelt or cortiprex or cutason or dacorten or dacortin or de cortisyl or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or dellacort a or delta 1 dehydrocortisone or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or deltacorten* or deltacortisone or delta-cortisone or deltacortone or delta-dome or deltasone or deltison or deltisona or deltra or di adreson or diadreson or drazone or encorton* or enkortolon or enkorton or fernisone or hostacortin or insone or kortancyl or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or orasone or orisane or panafcort or panasol or paracort or pehacort or precort or precortal or predni tablinen or prednicen-m or prednicorm or prednicot or prednidib or predniment or prednison* or prednisone or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or sone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.
25	pyridoxine/ use emczd, emcr,ppez or pyridoxine*.sh. or (adermine or becilan or beesix or benadon or bexivit or bonadon or bonasanit or campoviton 6 or esa b or gravidox or hexa betalin or hexabetalin or hexabione or hexavibex or hexermin or hexobion or pabroxin or piridoxin* or pyridipca or pyridosine or pyridoxin* or pyridoxin* or pyridoxinium or pyridoxol or pyrivel or pyroxin or rodex or uvimag b6 or viderma or vitamin* b6).ti,ab.
26	rufinamide/ use emczd, emcr or rufinamide*.sh. or (banzel or inovelon or rufinamid* or xilep).ti,ab.
27	exp steroid/ use emczd, emcr or steroids/ use ppez or steroid*.sh. or steroid*.ti,ab.
28	sultiame/ use emczd, emcr or (conadil or contravul or elisal or ospolot or riker or sulphenytame or sulthiame or sultiam* or trolone).ti,ab.
29	tetracosactide/ use emczd, emcr or cosyntropin/ use ppez or (acth or actholain or adrenocorticotropin or corticotropin or cortosyn or cortrosinta depot or cortrosyn or cosyntropin or depot tetracosactrin or nuvacthen or synacten or synacthen* or synacthin* or synathen or synthetic acth or tetracosactid* or tetracosactin* or tetracosapeptide).ti,ab.
30	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.
31	vagus nerve stimulation/ use emczd, emcr or vagus nerve stimulation/ use ppez or ((vagal or vagus) adj2 (activity or stimulat*)).ti,ab.
32	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

#	searches
	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.
33	vigabatrin/ use emczd, emcr,ppez or (4 vinyl 4 aminobutyric acid or 4 vinylaminobutyric acid or 4 vinyl-gaba or gamma vinyl 4 aminobutyric acid or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid or gamma vinylgaba or n vinyl 4 aminobutyric acid or n vinyl gaba or n vinyl gamma aminobutyric acid or sabril sabrilex or vigadrone or sabril or sabrilex or vigabatrin or gamma vinyl gaba or gamma vinyl gamma aminobutyric acid).ti,ab.
34	zonisamide/ use emczd, emcr or zonisamide/ use ppez or (excegran or excemid or zonegran or zonis-amid*).ti,ab.
35	bromide/ use emczd, emcr or exp bromides/ use ppez or (bromid* or hydrobromide*).ti,ab.
36	midazolam/ use emczd, emcr,ppez or (buccolam or dalam or doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or midacum or midazo or midazol or midazolam or midolam or miloz or versed).ti,ab.
37	cannabidiol/ use emczd, emcr,ppez or (cannabidiol or epidiolex or nabidiolex).ti,ab.
38	diazepam/ use emczd, emcr,ppez or (alboral or aliseum or alupram or amiprol or ansiolin or antenex or anxionil or apaurin* or apozepam or armonil or arzepam or assival or atensine or audium or azedipamin or benzopin or betapam or bialzepam or bialzepan or calmpose or caudel or cercin* or cersine or chlor-diazepam or compaz or desconet or diaceplex or dialag or dialar or diano or diapam or diapanil or dia-pax or diapin or diapine or diapo or diaquel or diastat or diazelium or diazem or diazemuls or diazepa* or diazepin or diazidem or dipaz or dipezona or dizac or doval or drenian or ducene or dupin or duxen or elcion or eridan or euphorin or eurosan or evacalm or fanstan or faustan or gewacalm or gubex or kratium or lamra or lembrol or lipodiazepam or lorinon or lovium or melode or mentalium or methyldiaz-epinon or methyldiazepinone or morosan or neocalme or neurolytril or nivalen or noan or novazam or ortopsique or paceum or pacitran or paxum or placidox or plidan or propam or psychopax or q-pam or radizepam or relanium or reliver or reposepan or saromet or sedapam or seduxen or serendin or setonil or sibazon or simasedan or sipam or sonacon or stesolid or stesolin or tanquo tablinen or tensium or tranimul or tranquirit or tranquo puren or trazepam or umbrium or valaxona or valiquid or valium or valpam or valrelease or vanconin or vatran or vazen or vival or vivol or zetran).ti,ab.
39	fenfluramine/ use emczd, emcr or (adipomin or fenflurami* or fenured or kataline or minifage or moderex or obedrex or pesos or phenfluoramine or phenylethylamine or ponderal or ponderax or pon-derex or pondimin or ponflural or rotondin).ti,ab.
40	stiripentol/ use emczd, emcr or (stiripentol* or diacomit).ti,ab.
41	acetazolamide/ use emczd, emcr or acetazolamide/ use ppez
42	(acetadiazol or acetamox or acetazol amide or acetazolam or acetazolamid* or acetazolamine or aceta-zoleamid* or acetozolamine or ak zol or akzol or albox or apoacetazolamide or azetazolamide or car-binib or carbonic anhydrase inhibitor or cidamex or dazamide or defiltran or dehydratin or diacarb or di-amox 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.
43	(corpus callosotomy or felbamate or rufinamide).ti,ab,sh.
44	mesuximide/ use emczd, emcr
45	(alpha methylphensuximide or celontin or methosuximide or celontine or mesuximide or methsuximide or methylsuximide or metsuccimide or petinutin).ti,ab.
46	phenobarbital/ use emczd, emcr or exp phenobarbital/ use ppez
47	(adonal or aephenal or agrypnal or alepsal or amylofene or andral or aparoxal or aphenylbarbit or aphenyletten or atrofen or austrominal or barbapil or barbellen or barbenyl or barbilettae or barbilixir or barbinal or barbiphen or barbiphenyl or barbivis or barbonal or barbonalett or barbophen or bardorm or bartol or bialminal or calmetten or calminal or carbronal or cardenal or cemalonal or codibarbital or cor-onaletta or cratecil or damoral or dezibarbitur or dormina or dormiral or dromural or ensobarb or en-sodorm or epanal or epidorm or epilol or episedal or epsylone or eskabarb or etilfen or euneryl or fenbital or fenemal or fenobarbital or fenolbarbital or fenosed or fenylettae or gardenal* or gardepanyl or glysoletten or haplopan or haplos or helional or hennoletten or hypnaletten or hypno tablinetten or hypnogen fragner or hypnolone or hypno-tablinetten or hypnotal or hypnotalon or hysteps or hysteps or

#	searches
	lefebar or leonal or leonal leo or lephebar or lepinal or lethyl or linasen or liquital or lixophen or lubergal or lubrokal or lumesettes or lumesyn or luminal or luminale or luminaletas or luminalette or luminaletten or luminalettes or luminalum or lumofridetten or luphenil or luramin or menobarb or molinal or monosodium salt or neurobarb or nirvonal or noptil or nova pheno or nunol or parkotal or pharmetten or phen bar or phenaemal or phenemal or phenethylbarbital sodium or phenobal or phenobarb or phenobarbital or phenobarbitol or phenobarbiton or phenobarbitone or phenobarbitural or phenobarbyl or phenonyl or phenotal or phenoturic or phenoyl or phenyl ethyl barbituric acid or phenylbarbital or phenylethyl barbituric acid or phenylethylbarbituric acid or phenylethylmalonyl urea or phenylethylmalonylurea or phenyletten or phenyral or polcominal or promptonal or seda tablinen or sedabar or sedicat or sedizorin or sedlyn or sedofen or sedonal or sedonettes or seneval or sevenal or sombutol mcclung or somnolens or somnoletten or somnosan or somonal or spasepilin or starifen or starilettae or stental or teolaxin or theolaxin or triabarb or tridezibarbitur or uni-feno or versomnal or wakobital or zadoletten or zadonal).ti,ab.
48	primidone/ use ppez or primidone/ use emczd, emcr
49	(apo-primidone or cyral or desoxyphenobarbital or desoxyphenobarbitone or hexadiona or lepsiral or liskantin or liskantin or majsolin or midone or misodine or mizodin or mutigan or mylepsin or mylepsinum or mysolin or mysoline or neurosyn or primaclone or primaclone or primadone or primidon* or prysoline or pyrimidone or resimatil or sertan).ti,ab.
50	phenytoin/ use emczd, emcr or phenytoin/ use ppez
51	(alepsin or aleviatin or antilepsin or antisacer or cansoin or citrullamon or comital or cumatil or danten or dantoin or denyl or di hydan or difenin or difetoin or differenin or difhydan or dihydan or di-hydan or dilantin or dilantin or dintoin or dintoina or diphantoin* or diphedal or diphedan or di-phen or diphenin* or diphentoin or diphenyl hydantoin or diphenylan or diphenyldantoin or diphenylhydantoin* or diphenytoin or ditoin or ditomed or ekko or epamin or epanutin or epelin or epilan or epilantin or eptal or eptoin or felantin or fenantoin or fenatoin or fenidantoin or fenitoin or fenytoin* or hidanil or hidantal or hydantin or hydantinal or hydantoinal or hydantol or idantoin or lehydan or lepitoin or minetoin or neosidantoina or phenhydan or phenhydane or phenilep or phentytoin or phenybin or phenydan or phenydantin or phenytek or phenytex or phenytoin* or pyoredol or sanepil or sodantoin or sodanton or solantoin or solantyl or tacosal or vasilcon or zentropil).ti,ab.
52	perampanel/ use emczd, emcr
53	(fycompa or perampanel).ti,ab.
54	brivaracetam/ use emczd, emcr
55	(brivaracetam or brivlera or nubriveo or rikelta).ti,ab.
56	exp eslicarbazepine/ use emczd, emcr
57	(eslicarbazepin* or aptiom or zebinix).ti,ab.
58	stiripentol/ use emczd, emcr or (stiripentol* or diacomit).ti,ab.
59	or/10-58
60	59 and (abstain* or abstinen* or stop* or withdraw*).ti,ab,hw.
61	((drug*1 or polydrug* or substance*) adj3 (abstain* or abstinen* or stop* or withdraw*)).ti,ab.
62	9 and or/60-61
63	limit 62 to english language
64	((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.)
65	64 use emez

#	searches
66	((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.)
67	66 use mesz
68	65 or 67
69	63 not 68

Database(s): Cochrane Library

Cochrane Database of Systematic Reviews, Issue 01 of 12, January 2021; Cochrane Central Register of Controlled Trials, Issue 1 of 12, January 2021
Date of last search: 22 January 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	(convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”):ti,ab
6	(((early or infantile) near/2 myoclonic near/2 encephalopath*) or ((early or infantile) near/2 epileptic near/2 encephalopath*) or “epileptic spasm*” or ((flexor or infantile or neonatal) near/2 (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 epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”):ti,ab
7	((myoclonic near/2 (astatic or atonic)) or (myoclonic near/3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”):ti,ab ((absence or astatic or atonic or tonic or “tonic clonic”) near/2 (seizure* or spasm*)):ti,ab
8	(bcects or bects or brec or “benign epilepsy” or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 epileps*) or (benign near/2 (childhood or neonatal or pediatric or paediatric) near/2 (convulsion* or epileps* or seizure* or spasm*)) or (benign near/3 (convulsion* or epileps*) near/2 centrotemporal near/2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near/2 (convulsion* or epileps* or seizure* or spasm*))):ti,ab
9	{or #1-#8}
10	mesh descriptor: [anticonvulsants] explode all trees
11	mesh descriptor: [carbamazepine] explode all trees
12	(amizepine or carbamazepin* or carbazepin or epitol or finlepsin or neurotol or tegretol):ti,ab
13	mesh descriptor: [clobazam] this term only
14	(chlorepin or chlorepine or clobazam or clobazepam or clorepin or frisium or noiafren or onfi or urbadan or urbanil or urbanyl):ti,ab
15	mesh descriptor: [clonazepam] this term only
16	(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
17	mesh descriptor: [adrenocorticotropic hormone] explode all trees
18	(acethropan or acetophran or acortan or acorto or acth or acthar or acthelea or acthon or acton or actonar or actrope or adactan or (“adrenal cortex” next (trophic or tropic) next hormone) or adrenocorticaltrophormon or adrenocorticotrop* or adrenocorticotrop* or adrenocorticotrophin or “adrenocorticotropic hormone” or adrenocorticotropin* or adrenomone or adrenotropin or cibacthen or corticotrophin* or corticotropic or corticotropin* or cortigel or cortilin or cortiphyson or cortosyn or cortrophin * or cortropin or cortrosyn or cosyntropin* or cotrophin* or exactin or “hp acthar gel” or humacthid or humactid or “porcine acth” or “porcine corticotropin” or procortan or reacthin or “s cortophin” or solacthyl or “synacthen retard” or tetracosactide or tetracosactrin or tetracosapeptide):ti,ab
19	mesh descriptor: [ethosuximide] this term only
20	(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

#	searches
	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
21	mesh descriptor: [gabapentin] this term only
22	(apogabapentin or convalis or dineurin or gabalept or gabaliquid or geriasan or gabapentin* or gabatin or gantin or gralise or kaptin or keneil or neurontin or neurotonin or novogabapentin or nupentin):ti,ab
23	mesh descriptor: [hydrocortisone] explode all trees
24	(hydroxycorticosterone or acticort or “aeroseb hc” or “ala-cort” or “ala-scalp” or alfacort or algicortis or alkindi or “alpha derm” or alphaderm or “anucort-hc” or “anumed-hc” or “anutone-hc” or “aquanil hc” or “balneol-hc” or “barseb hc” or “beta-hc” or biacort or cetacort or cobadex or colocort or “compound f” or “cordicare lotion” or coripen or “cort dome” or cortef or cortenema or cortibel or corticorenol or cortifair or cortifan or cortiphate or cortisol or cortisole or cortispray or cortoderm or cortril or cotacort or covocort or “cremicort-h” or cutaderm or “dermacrin hc lotion” or dermaid or “derm-aid cream” or “dermaid soft cream” or dermocare or dermocortal or dermolate or dioderm or eczacort or “ef cortelan” or efcortelan or egocort or eksalb or eldecort or “emo-cort” or epicort or epicortisol or ficortril or filocot or flexicort or glycort or “gly-cort” or “h-cort” or hebcort or “hemorrhoidal hc” or “hemril-30” or “hemril-hc uniserts” or “hi-cor” or hidrotisona or hycor or hycort or hydracort or hydrasson or “hydro ricortex” or hydrocort or hydrocorticosteroid or hydrocortisate or hydrocortisone or hydrocortisone or hydrocortisonum or hydrocortisyl or hydrocortone or hydrogalen or hydrokort or hydrokortison or “hydro-rx” or hydrotopic or hysone or hytisone or hytone or “incortin h” or “instacort 10” or kyypakkaus or “lacticare hc” or “lemnis fatty cream hc” or lenirit or “medihaler cort” or “medihaler duo” or medrocil or mildison or “mitocortyl demangeaisons” or munitren or “nogenic hc” or novohydrocort or nutracort or optef or “otosone f” or penecort or plenadren or prepcort or “prevex h” or “pro cort” or procort or proctocort or “procto-kit” or “proctosol-hc” or proctosone or proctozone or procutan or “rectasol-hc” or rectocort or rederm or sanatison or “scalp-aid” or schericur or scherosone or “sistral hydrocort” or skincalm or “stie-cort” or “substance m” or synacort or texacort or triburon-hc or unicort or vasocort):ti,ab
25	mesh descriptor: [lacosamide] this term only
26	(erlosamide or harkoseride or lacosamide or vimpat):ti,ab
27	mesh descriptor: [lamotrigine] this term only
28	(crisomet or labileno or lamepil or lamictal or lamictin or lamiktal or lamodex or lamogine or lamotrigin* or lamotrix or neurium):ti,ab
29	mesh descriptor: [levetiracetam] this term only
30	(elepsia or keppra or kopodex or levetiracetam* or matever or spritam):ti,ab
31	mesh descriptor: [nitrazepam] this term only
32	(apodorm or atempol or benzalin or dormalon or “dormo-puren” or dumolid or eatan or eunoctin or hypnotex or imadorm or imeson or insomin or mogadan or nelbon or nirven or “nitra zepam” or nitrados or nitravet or nitrazadon or nitrazep or nitrazepam or nitrodiazepam or novanox or pacisyn or radedorm or remnos or restorem or “rhoxal nitrazepam” or “rhoxal-nitrazepam” or sedamon or serenade or somnased or “somnibel n” or somnite):ti,ab
33	mesh descriptor: [oxcarbazepine] this term only
34	(apydan or oxcarbazepin* or oxocarbazepine or oxrate or oxtellar or timox or trileptal or trileptin):ti,ab
35	mesh descriptor: [prednisolone] explode all trees
36	(adelcort or antisolon* or aprednislon* or benisolon* or berisolon* or caberdelta or capsoid or “co hydeltra” or codelcortone or compresolon or cortadelton* or cortalone or cortelinter or cortisolone or cotolone or dacortin or decaprednil or decortril or “dehydro cortex” or “dehydro hydrocortison*” or dehydrocortex or dehydrocortisol* or dehydrohydrocortison* or delcortol or “delta cortef” or “delta cortril” or “delta ef cortelan” or “delta f” or “delta hycortol” or “delta hydrocortison*” or “delta ophticor” or “delta stab” or “delta1 dehydrocortisol” or “delta1 dehydrohydrocortisone” or “delta1 hydrocortisone” or deltacortef or “delta-cortef” or deltacortenolo or deltacortil or deltacortoil or deltacortril or deltaderm or deltaglycortril or deltahycortol or deltahydrocortison* or deltaophticor or deltasolone or deltastab or deltidrosol or deltisolon* or deltisolone or deltolasson or deltolassone or deltosona or deltosone or “depo-predate” or dermosolon or dhasolone or “di adreson*” or diadreson* or diadresonf or “di-adreson-f” or dicortol or domucortone or encortelon* or encortolon* or equisolon or “fernisolone-p” or glistelone or hefasolon or hostacortin or hydeltra or hydeltrone or hydrelta or hydrocortancyl or hydrocortidelt or hydrodeltalone or hydrodeltisone or hydroretrocortin* or inflanefran or insolone or “keteocort h” or “key-pred” or lenisolone or leocortol or liquipred or lygal or “kopftinktur n” or mediasolone or meprisolon* or metacortalon* or metacortandralon* or metacortelone or “meti derm” or meticortelone or metiderm or “meti-derm” or morlone or mydrapred or “neo delta” or nisolon or nisolone or opredsone or panafcortelone or panafcortolone or panafort or paracortol or phlogex or “pre cortisyl” or preconin or precortalon or precortancyl or precortisyl or “predacort 50” or “predaject-50” or “predalone 50” or predartrin* or predate or predeltilone or predisole or predisyr or “pred-ject-50” or “predne dome” or prednecort or prednedome or prednelan or “predni coelin” or “predni h tablinen” or prednicoelin or prednicort * or “prednifor drops” or “prednihelvacort” or predniment or predniretard or prednis or prednisil or prednisolon* or prednivet or prednorsolon* or predonine or predorgasolon* or prelon or prelone or prenilone or prenin or prenolone or preventan or prezolon or rubycort or scherisolon* or serilone or solondo or solone or solupren* or spiricort or spolotane or sterane or sterolone or supercortisol or taracortelone or walesolone or wysolone):ti,ab

#	searches
37	mesh descriptor: [prednisone] this term only
38	(ancortone or biocortone or colisone or cortan or cortancyl or cortidelt or cortiprex or cutason or da-corten or dacortin or “de cortisyl” or decortancyl or decortin* or decortisyl or dihydrocortisone or dekortin or delitisone or “dellacort a” or “delta 1 dehydrocortisone” or “delta cortelan” or “delta cortisone” or “delta dome” or “delta e” or “delta prenovis” or deltacorten* or deltacortisone or “delta-cortisone” or del-tacortone or “delta-dome” or deltasone or deltison or deltisona or deltra or “di adreson” or diadreson or drazone or encorton* or enkortolon or enkorton or fernisone or hostacortin or insone or kortancyl or “liq-uid pred” or lodotra or “me-korti” or meprison or metacortandracin or meticorten or meticortine or nisona or orasone or orisane or panafcort or panasol or paracort or pehacort or precort or precortal or “predni tablinen” or “prednicen-m” or prednicorm or prednicot or prednidib or predniment or prednison* or pred-nisone or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servi-sone or sone or steerometz or sterapred or ultracorten or urtilone or winpred):ti,ab
39	mesh descriptor: [pyridoxine] this term only
40	(adermine or becilan or beesix or benadon or bexivit or bonadon or bonasanit or “campoviton 6” or “esa b” or gravidox or “hexa betalin” or hexabetalin or hexabione or hexavibex or hexermin or hexobion or pabroxin or piridoxin* or pyridipca or pyridosine or pyridoxin* or pyridoxin* or pyridoxinium or pyridoxol or pyrivel or pyroxin or rodex or uvimag b6 or viderma or “vitamin* b6”):ti,ab
41	(banzel or inovelon or rufinamid* or xilep):ti,ab
42	mesh descriptor: [steroids] this term only
43	steroid*:ti,ab
44	(conadil or contravul or elisal or ospolot or riker or sulphenytame or sulthiame or sultiam* or tro-lone):ti,ab
45	mesh descriptor: [cosyntropin] this term only
46	(acth or actholain or adrenocorticotropin or corticotropin or cortosyn or “cortrosinta depot” or cortrosyn or cosyntropin or “depot tetracosactrin” or nuvacthen or synacten or synacthen* or synacthin* or synathen or “synthetic acth” or tetracosactid* or tetracosactin* or tetracosapeptide):ti,ab
47	mesh descriptor: [topiramate] this term only
48	(epitomax or topamax or topiramat* or acomicil or ecuram or epiramat or epitomax or epitoram or erra-via 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
49	mesh descriptor: [vagus nerve stimulation] this term only
50	((vagal or vagus) near/2 (activity or stimulat*)):ti,ab
51	mesh descriptor: [valproic acid] this term only
52	(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 ace-tate” 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 chrono-sphere” 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 laba-zene 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
53	mesh descriptor: [vigabatrin] this term only
54	(“4 vinyl 4 aminobutyric acid” or “4 vinylaminobutyric acid” or “4 vinylgaba” or “gamma vinyl 4 aminobu-tyric acid” or “gamma vinyl gaba” or “gamma vinyl gamma aminobutyric acid” or “gamma vinylgaba” or “n vinyl 4 aminobutyric acid” or “n vinyl gaba” or “n vinyl gamma aminobutyric acid” or “sabril sabrilex” or vigadrone or sabril or sabrilex or vigabatrin or “gamma vinyl gaba” or “gamma vinyl gamma aminobu-tyric acid”):ti,ab
55	mesh descriptor: [zonisamide] this term only
56	(excegran or excemid or zonegran or zonisamid*):ti,ab
57	mesh descriptor: [bromides] explode all trees
58	(bromid* or hydrobromide*):ti,ab
59	mesh descriptor: [midazolam] this term only
60	(buccolam or dalam or doricum or dormicum or dormonid or fortanest or fulsed or hypnoval or hypnovel or hypnoyvel or ipnovel or midacum or midazo or midazol or midazolam or midolam or miloz or versed):ti,ab
61	mesh descriptor: [cannabidiol] this term only
62	(cannabidiol or epidiolex or nabidiolex):ti,ab
63	mesh descriptor: [diazepam] explode all trees

#	searches
64	(alboral or aliseum or alupram or amiprol or ansiolin or antenex or anxionil or apaurin* or apozepam or armonil or arzepam or assival or atensine or audium or azedipamin or benzopin or betapam or bialzepam or bialzepan or calmpose or caudel or cercin* or cersine or chlordiazepam or compaz or desconet or diaceplex or dialag or dialar or diano or diapam or diapanil or diapax or diapin or diapine or diapo or diaquel or diastat or diazelium or diazem or diazemuls or diazepa* or diazepin or diazidem or dipaz or dipezona or dizac or doval or drenian or ducene or dupin or duxen or elcion or eridan or euphorin or eurosan or evacalm or fanstan or faustan or gewacalm or gubex or kratium or lamra or lembrol or lipodiazepam or lorinon or lovium or melode or mentalium or methyldiazepinon or methyldiazepinone or morosan or neocalme or neurolytril or nivalen or noan or novazam or ortopsique or paceum or pacitran or paxum or placidox or plidan or propam or psychopax or “q-pam” or radizepam or relanium or reliver or reposepan or saromet or sedapam or seduxen or serendin or setonil or sibazon or simasedan or sipam or sonacon or stesolid or stesolin or “tanquo tablinen” or tensium or tranimul or tranquirit or “tranquo puren” or trazepam or umbrium or valaxona or valiquid or valium or valpam or valrelease or vanconin or vatran or vazen or vival or vivol or zetran):ti,ab
65	mesh descriptor: [fenfluramine] explode all trees
66	(adipomin or fenflurami* or fenured or kataline or minifage or moderex or obedrex or pesos or phenfluoramine or phenylethylamine or ponderal or ponderax or ponderex or pondimin or ponflural or rotondin):ti,ab
67	(stiripentol* or diacomit):ti,ab
68	(conadil or contravul or elisal or ospolot or riker or sulphenytame or sulthiame or sultiam* or trolone):ti,ab
69	mesh descriptor: [acetazolamide] this term only
70	(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
71	(“corpus callosotomy” or felbamate or rufinamide).ti,ab,kw.
72	(“alpha methylphensuximide” or celontin or methosuximide or celontine or mesuximide or methsuximide or methylsuximide or metsuccimide or petinutin):ti,ab
73	mesh descriptor: [phenobarbital] this term only
74	(adonal or aephenal or agrypnal or alepsal or amylofene or andral or aparoxal or aphenylbarbit or aphenyletten or atrofen or austrominal or barbapil or barbellen or barbenyl or barbilettae or barbilixir or barbinal or barbiphen or barbiphenyl or barbivis or barbonal or barbonalett or barbophen or bardorm or bartol or bialminal or calmetten or calminal or carbronal or cardenal or cemalonal or codibarbital or coronaletta or cratecil or damoral or dezibarbitur or dormina or dormiral or dromural or ensobarb or ensodorm or epanal or epidorm or epilol or episedal or epsylone or eskabarb or etilfen or euneryl or fenbital or fenemal or fenobarbital or fenolbarbital or fenosed or fenylettae or gardenal* or gardepanyl or glysoletten or haplopan or haplos or helional or hennoletten or hypnaletten or “hypno tablinetten” or “hypnogen fragner” or hypnolone or “hypno-tablinetten” or hypnotal or hypnotalon or hysteps or hysteps or lefebar or leonal or leonal leo or lephebar or lepinal or lethyl or linasen or liquital or lixophen or lubergal or lubrokal or lumesettes or lumesyn or luminal or luminale or luminaletas or luminalette or luminaletten or luminalettes or luminalum or lumofridetten or luphenil or luramin or menobarb or molinal or “monosodium salt” or neurobarb or nirvonal or noptil or “nova pheno” or nunol or parkotal or pharmetten or “phen bar” or phenaemal or phenemal or “phenethylbarbital sodium” or phenobal or phenobarb or phenobarbital or phenobarbitol or phenobarbiton or phenobarbitone or phenobarbitural or phenobarbyl or phenonyl or phenotal or phenoturic or phenoyl or pentobarbital or “phenyl ethyl barbituric acid” or phenylbarbital or “phenylethyl barbituric acid” or “phenylethylbarbituric acid” or “phenylethylmalonyl urea” or phenylethylmalonylurea or phenyletten or phenyral or polcominal or promptonal or “seda tablinen” or sedabar or sedicat or sedizorin or sedlyn or sedofen or sedonal or sedonettes or seneval or sevenal or “sombutol mcclung” or somnolens or somnoletten or somnosan or somonal or spasepilin or starifen or starilettae or stental or teolaxin or theolaxin or triabarb or tridezibarbitur or uni-feno or versomnal or wakobital or zadoletten or zadonal):ti,ab
75	mesh descriptor: [primidone] this term only
76	(“apo-primidone” or cyral or desoxyphenobarbital or desoxyphenobarbitone or hexadiona or lepsiral or liskantin or liskantin or majsolin or midone or misodine or mizodin or mutigan or mylepsin or mylepsinum or mysolin or mysoline or neurosyn or primaclone or primaclone or primadone or primidon* or prysoline or pyrimidone or resimatil or sertan):ti,ab
77	mesh descriptor: [phenytoin] this term only
78	(alepsin or aleviatin or antilepsin or antisacer or cansoin or citrullamon or comital or cumatil or danten or dantoin or denyl or “di hydan” or difenin or difetoin or differenin or difhydan or dihydan or “di-hydan” or dilantin or dilantin or dintoin or dintoina or diphantoin* or diphedal or diphedan or “di-phen” or diphenin* or diphentoin or “diphenyl hydantoin” or diphenylan or diphenyldantoin or diphenylhydantoin* or diphenytoin or ditoin or ditomed or ekko or epamin or epanutin or epelin or epilan or epilantin or eptal or

#	searches
	eptoin or felantin or fenantoin or fenatoin or fenidantoin or fenitoin or fenytoin* or hidanil or hidantal or hydantin or hydantinal or hydantoinal or hydantol or idantoin or lehydan or lepitoin or minetoin or ne-osidantoina or phenhydan or phenhydane or phenilep or phentytoin or phenybin or phenydan or phenydantin or phenytek or phenytex or phenytoin* or pyoredol or sanepil or sodantoin or sodanton or solantoin or solantyl or tacosal or vasilcon or zentropil):ti,ab
79	(fycompa or perampanel):ti,ab
80	(brivaracetam or brivlera or nubriveo or rikelta):ti,ab
81	(eslicarbazepin* or aptiom or zebinix):ti,ab
82	(stiripentol* or diacomit):ti,ab
83	{or #10-#82}
84	#83 and (abstain* or abstinen* or stop or stopping or withdraw*).ti,ab,kw.
85	((drug* or polydrug* or substance*) near/3 (abstain* or abstinen* or withdraw*)):ti,ab
86	#9 and (#84 or #85)

Database(s): DARE; HTA database - CRD Date of last search: 22 January 2021

#	searches
1	mesh descriptor seizures this term only
2	mesh descriptor epilepsy explode all trees
3	mesh descriptor seizures, febrile this term only
4	mesh descriptor: [status epilepticus] explode all trees
5	(convulsion* or “dravet syndrome” or epilep* or “continous spike wave of slow sleep” or “landau kleffner syndrome” or “lennox gastaut syndrome” or “infant* spasm*” or seizure* or “west syndrome”)
6	(((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 epilepsy” or “propulsive petit mal” or “spasm in* flexion” or “spasmus nutans” or “west syndrome*”)
7	((myoclonic near2 (astatic or atonic)) or (myoclonic near3 (seizure* or spasm*)) or “doose* syndrome” or mae or “generali?ed idiopathic epilepsy”) ((absence or astatic or atonic or tonic or “tonic clonic”) near2 (seizure* or spasm*))
8	(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 cen-trotemporal near2 spike*) or cects or ((centralopathic or centrotemporal or “temporal-central focal”) next (convulsion* or epileps* or seizure*)) or ((osylvian or postrolandic or roland*) near2 (convulsion* or epi-leps* or seizure* or spasm*)))
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

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 sei-zure*)) 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.

#	searches
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 (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

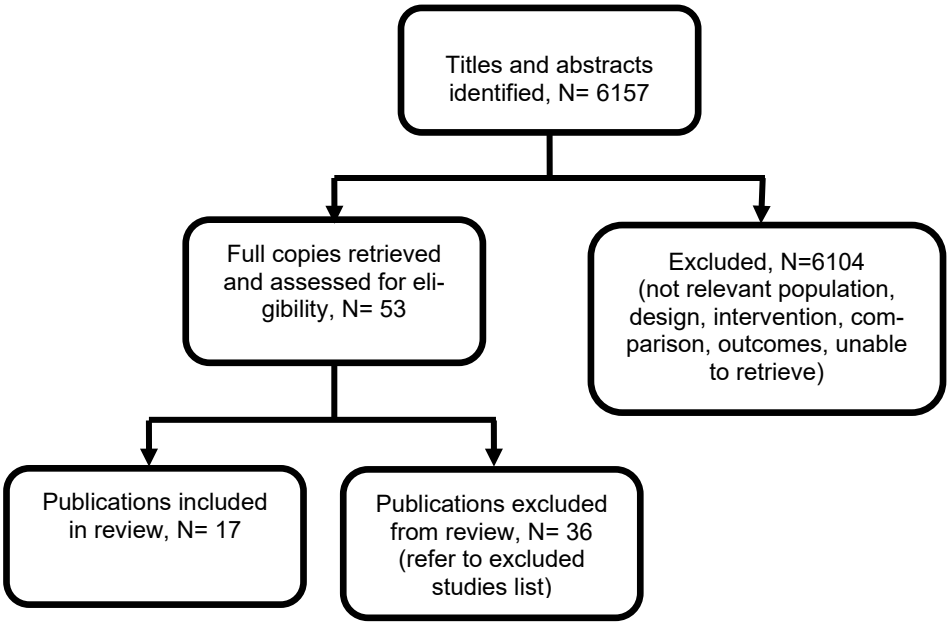
#	searches
1	mesh descriptor epilepsy explode all trees

#	searches
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 epilepsy" 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

Study selection for: What are the criteria for stopping antiseizure medications in people with epilepsy?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Evidence tables for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

Table 4: Evidence tables

Study details	Participants	Methods	Results	Comments
Full citation Altunbasak, S., Artar, O., Burgut, R., Yildiztas, D., Relapse risk analysis after drug withdrawal in epileptic children with uncomplicated seizures, Seizure, 8, 384-389, 1999 **Ref Id** 1245521 **Country/ies where the study was carried out** Turkey **Study type** Retrospective cohort study **Study dates** Recruitment: 1991 - 1995 **Funding** Supported by The Research Fund of Çukurova University	**Number** **Total** N=97 **Characteristics** Gender, n (%) Boys = 58 (60) Girls = 39 (40) Age at onset of first seizure, Mean (SD), range 4.5 years (3.3 years), 2 months to 12 years <24 months, n (%) = 38(39) >24 months, n (%) = 59(61) Age during the study period, Mean (SD), range, years 12.5 (3.6), 4 to 20 years Seizure classification, n (%) Generalised seizures = 25 (26) Partial seizures = 72 (74) Period between onset of seizures and onset of ASM therapy, n 0-3 months = 59 (61) 4-6 months = 14 (14) 7-12 months = 8 (8) >12 months = 16 (24)	**Follow-up duration** Follow-up duration for patients without seizure recurrence, range, years 2 to 4 **Statistical analysis** Univariate associations were assessed using chi-squared test or Fisher's exact test. Multivariate analyses of factors that may have an effect: • on relapse rate was carried out using Multivariate logistic regression and • on relapse time was carried out using Cox proportional hazard models **No details on adjustment for confounders are reported.**	**Results** Potential risk factors for relapse rate (reference category), aRR (95% CI), p-value Duration of ASM withdrawal < 6 months (duration of ASM withdrawal > 6 months) = 0.218 (0.0496 to 0.957), 0.04 Age of seizure onset > 2 years (age of seizure onset < 2 years) = 7.41 (1.30 to 42.2), 0.008 Risk factors for shorter relapse time (reference category), aRR (95% CI), p-value Duration of ASM withdrawal < 6 months (duration of ASM withdrawal > 6 months) = 0.270 (0.077 to 0.929), 0.037 Age of seizure onset > 2 years (age of seizure onset < 2 years) = 6.82 (1.41 to 33), 0.04	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Moderate risk (source and method used to identify population were not clearly defined, likely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (no definition of prognostic factors, unclear if measurement is valid and reliable for all participants and unclear if method and setting of measurement is the same for all participants; may likely introduce substantial bias). **Outcome Measurement**: Low risk (unsure if the method and setting of outcome measure-

Study details	Participants	Methods	Results	Comments
	Number of seizures before ASM therapy, n (%) <10 seizures =73 (75) >10 seizures = 24 (25) Period between onset of ASM and seizure control, n (%) 0-3 months = 60 (62) 4-6 months =16 (6) 7-12 months = 8 (7) >12 months = 24 (25) Number of seizures after starting ASM, n (%) <10 seizures = 81 (83) >10 seizures = 16 (17) Period between seizure control and starting ASM withdrawal, n (%) <2 years = 10 (10) 2-3 years = 25 (26) >3 years - 62 (64) EEG at diagnosis, n (%) No EEG = 3 (3) Normal EEG = 11 (11) EEG with paroxysmal slow waves = 52 (54) EEG with sharp waves, spike-and waves, polyspike-and waves = 31 (32) The duration of withdrawal, n (%) 1-5 months = 18 (19) >5 months = 79 (81)			ment is the same for all participants, but unlikely to introduce substantial bias) **Study Confounding**: Moderate risk (partial definition of confounders, and unsure if confounders were measured in the same setting for all participants) **Statistical Analysis and Reporting**: Low risk (only statistically significant results were reported, but unlikely to introduce substantial bias) **Overall Quality: Moderate**

Study details	Participants	Methods	Results	Comments
	Aetiology, n(%) Idiopathic = 72 (74) Remote symptomatic = 25 (26) Family history of epilepsy, n(%) Positive = 10 (11) Negative = 87 (89) History of previous febrile convulsion, n(%) Positive = 38 (39) Negative = 59 (61) **Inclusion criteria** • Patients with at least 2 afrebrile seizures before 12 years, which were not due to metabolic or infectious disease of the central nervous system **Exclusion criteria** Patients with: • neonatal convulsions • central nervous system disorders • any inborn error of metabolism or febrile convulsion			
Full citation Berg, A. T., Vickrey, B. G., Langfitt, J. T., Sperling, M. R., Shinnar, S., Bazil, C., Walczak, T., Spencer, S. S., Reduction of ASMs in postsurgical patients who	**Number** Total surgical patients recruited, N = 396 Patients with temporal lobe resections, n = 348	**Follow-up duration** Not reported. Patients were followed up every 3 months after discharge from hospital. **Statistical analysis**	**Results** Potential predictors of relapse (reference category), aRR (95% CI), p-value	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (unclear whether there was adequate participation by eligible

Study details	Participants	Methods	Results	Comments
attain remission, Epilepsia, 47, 64-71, 2006 **Ref Id** 1216723 **Country/ies where the study was carried out** US **Study type** Prospective cohort study **Study dates** Recruitment: June 1996 to January 2001 **Funding** Received grant from the National Institute of Neurological Disorders and Stroke.	Total patients included in analysis N = 291 patients who had achieved a 1 year remission. Reasons for exclusion: 95 patients did not attain 1 year remission and 10 patients had not attained 1 year remission at the time of last ASM withdrawal. Continued >/= 2 ASMs group, n (%) 162 (56%) Reduced ASMs (2 to 1 or 1 to 0) group, n (%) 129 (44%) Reduced from 2 to 1 ASM, n = 88 Reduced from 1 to 0 ASM, n = 41 **Characteristics** **Age at onset of epilepsy, n (%)** Continued >/= 2 ASMs <5 years = 39 (57) 5-9 years = 22 (49) 10-19 years = 51 (50) 20 -29 years = 24 (73) 30 -39 years = 13 (57) 40+ years = 6 (55) Reduced ASMs <5 years = 29 (43) 5-9 years = 23 (51) 10-19 years = 51 (50)	Results of impact of ASM reduction on relapse rate are displayed as Kaplan-Meier curves. Analyses were adjusted for: age at onset; age at time of surgery; history of febrile seizures; use of intracranial monitoring and anteromedial temporal lobectomy with hippocampectomy (medial temporal) versus neocortical surgery, and specific pathologic findings in the tissue; whether seizures occurred during immediate postsurgical recovery with or without auras (subjective sensory or psychic events). A relapse was considered the occurrence of a seizure after a patient had attained remission. period (before discharge from hospital), whether remission was immediate or delayed (i.e., the patient had one or more seizures after hospital discharge before attaining remission), and the persistence of auras after attaining remission from clinical seizures. ASM reduction dates were treated as time- dependent	Delayed remission after hospital discharge (immediate remission) = 2.26 (1.15 to 4.48), 0.02. Continued auras, after adjustment for delayed remission (no persistent auras) = 2.06 (0.95 to 4.49), 0.07	individuals, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unsure if measurement is valid and reliable for all participants and unclear if method and setting of measurement is the same for all participants; may likely introduce substantial bias) **Outcome Measurement**: Moderate risk (duration of follow-up not indicated, may likely introduce substantial bias) **Study Confounding**: High risk (no definition of confounders, evaluation varied across sites hence method of measurement for confounders likely to be varied) **Statistical Analysis and Reporting**: Low risk (only reported adjusted variables that were considered significant, unlikely to introduce substantial bias) **Overall Quality: Moderate**

Study details	Participants	Methods	Results	Comments
	20 -29 years = 9 (27) 30 -39 years = 10 (43) 40+ years = 5 (45) **History of febrile seizures, n (%)** <u>Continued ASMs</u> No = 114 (57) Yes = 48 (52) <u>Reduced ASMs</u> No = 85 (43) Yes = 44 (48) **Generalised tonic-clonic seizures, n(%)** <u>Continued ASMs</u> No = 35 (49) Yes = 127 (58) <u>Reduced ASMs</u> No = 37 (51) Yes = 92 (42) **Duration of epilepsy, n (%)** <u>Continued ASMs</u> <5 years = 11 (61) 5-9 years = 15(48) 10 -14 years = 19 (51) 15 - 19 years = 27 (68) 20+ years = 90 (55) <u>Reduced ASMs</u> <5 years = 7(39) 5-9 years = 16(52) 10 -14 years = 18 (49) 15 - 19 years = 13(32) 20+ years = 75 (45)	covariates in a Cox proportional hazards model and reported as rate ratios. Remission was defined as at least 1 year seizure free		**Other information** Assessed potential difference between patients reducing from 2 to 1 ASM and from 1 to 0 ASM but no difference was found. So treated both situations as the same unless otherwise stated. <u>Probability of remaining seizure free after reducing ASMs, RR (95% CI)</u> At 6 months = 0.93 (0.88 to 0.97) At 1 year = 0.84 (0.77 to 0.90) At 2 years = 0.74 (0.66 to 0.82)

Study details	Participants	Methods	Results	Comments
	Duration of intractable epilepsy, n (%) Continued ASMs <5 years = 45 (64) 5-9 years = 20 (56) 10 -14 years = 21 (50) 15 - 19 years = 24 (59) 20+ years = 25 (43) Reduced ASMs <5 years = 25 (36) 5-9 years = 16 (44) 10 -14 years = 21 (50) 15 - 19 years = 17 (41) 20+ years = 33 (57) **Age at surgical evaluation, n (%)** Continued ASMs <20 years = 9 (45) 20 -29 years = 31 (56) 30 -39 years = 56 (54) 40 -49 years = 43(57) 50+ years = 23(62) Reduced ASMs <20 years = 11 (55) 20 -29 years = 24 (44) 30 -39 years = 47 (46) 40 -49 years = 33 (43) 50+ years = 14 (38) **Presurgical seizure frequency, n (%)** Continued ASMs 1 month = 13 (76) 2- 4 months = 54 (59) 5 - 10 months = 42 (53) 11 - 30 months = 33 (51)			

Study details	Participants	Methods	Results	Comments
	>30 months = 20 (54) Reduced ASMs 1 month = 4 (24) 2- 4 months = 38 (41) 5 - 10 months = 38 (47) 11 - 30 months = 32 (49) >30 months = 17 (46) **Intracranial monitoring during evaluation, n (%)** Continued ASMs No = 104 (58) Yes = 58 (52) Reduced ASMs No = 75 (42) Yes = 54 (48) **Type of surgery, n (%)** Continued ASMs Neocortical = 16 (59) Medial-temporal = 146 (55) Reduced ASMs Neocortical = 11 (41) Medial-temporal = 118 (45) **Pathology, n (%)** Continued ASMs MTS = 121 (56) Malignant tumor = 8 (53) Developmental tumor = 4 (67) Vascuar = 2 (29) Disorder of cortical development = 34 (50) Other[a] = 76 (60) Reduced ASMs			

Study details	Participants	Methods	Results	Comments
	MTS = 94 (44) Malignant tumor = 7 (47) Developmental tumor = 1 (33) Vascuar = 5 (71) Disorder of cortical development = 34 (50) Other[a] = 51 (40) [a]Other includes gliosis, evidence of inflammation, and normal **Seizures during immediate postoperative period (before hospital discharge), n(%)** Continued ASMs No = 152 (55) Yes = 10 (77) Reduced ASMs No = 126 (45) Yes = 3 (23) **Delayed remission after discharge from hospital, n (%)** Continued ASMs No = 87 (46) Yes = 75 (74) Reduced ASMs No = 103 (54) Yes = 26 (26) **Persistent auras after remission of clinical seizures, n (%)** Continued ASMs No = 126(53) Yes = 36 (65)			

Study details	Participants	Methods	Results	Comments
	Reduced ASMs No = 110 (47) Yes = 19 (35) **Inclusion criteria** • Patients ≥12 years old at time of initial presentation for surgical evaluation • Have at least 2 failed first-line antiepileptic drugs • have a minimum of 20 partial or secondarily generalised seizures during the previous 2 years as documented by history obtained from patients and medical records **Exclusion criteria** • Patients who did not meet the basic eligibility criteria • Patients who had only non-epileptic seizures or generalised epilepsy • Patients whose intellectual functioning was too impaired to complete study forms • Patients who had previous epilepsy surgery (but not necessarily previous neurosurgery for other reasons)			
Full citation Boshuisen, K., Arzimanoglou, A., Cross, J. H., Uiterwaal, C. S. P. M.,	**Number** N=766 children; of which n=444 had ASM discontinuation	**Follow-up duration** Mean (SD): 61.6 (29.7) months **Statistical analysis**	**Results** Multivariable Cox regression model (TTR): seizure recurrences during/after ASM withdrawal, aHR (95%CI), p-value	**Limitations** Methodological limitations assessed using the QUIPS Checklist

Study details	Participants	Methods	Results	Comments
Polster, T., Van Nieuwenhuizen, O., Braun, K. P. J., Timing of antiepileptic drug withdrawal and long-term seizure outcome after pASMiatric epilepsy surgery (TimeToStop): A retrospective observational study, The Lancet Neurology, 11, 784-791, 2012 **Ref Id** 1082302 **Country/ies where the study was carried out** Multicentre (Europe) **Study type** Retrospective cohort **Study dates** April 13 and December 19, 2009 **Funding** Dutch National Epilepsy Fund	**Characteristics** Multifocal MRI lesion, n (%): 66 (8.8) Immediate postoperative seizure freedom, n (%): 700 (92.4) Age, sex, and presence/ absence of LDs was not reported. All patients underwent surgery **Inclusion criteria** • Those who received surgery between Jan 1 2000 to Oct 1 2008 • < 18 years old • 1 year post-operative follow-up • ASM withdrawal started post-operatively **Exclusion criteria** • Those who had their ASMs tapered despite continued post-operative seizures, including auras	Previously identified predictors of seizure recurrence were tabulated against start and completion of ASM withdrawal by Cox proportional hazard regression models to assess which factors were associated with the timing of ASM withdrawal and could be considered potential confounders of the relation between timing and seizure outcome. The crude associations between time to recurrence and time to discontinuation were analysed by Cox proportional hazard regression models and adjusted for the earlier identified possible confounders. Missing data were collected through telephone interviews with study participants, if possible.	Shorter time interval from surgery to start of ASM reduction, per 3 months (longer time from surgery to start of ASM discontinuation) 0.94 (0.89 to 1), 0.05 Multifocal MRI lesions (no evidence of multifocal MRI lesions) 2.27 (1.23 to 4.20), 0.01 Epilepsy aetiology (malformations of cortical development) 0.97 (0.81 to 1.15), 0.71 Number of ASMs used at time of surgery (reference category unclear) 0.98 (0.75 to 1.27), 0.87 Type of surgery (reference category unclear) 1.16 (0.85 to 1.60), 0.35 Hemispherectomy (lobar resection) 2.28 (1.03 to 5.04), 0.04 Multilobar resection (lobar resection) 1.70 (0.85 to 3.43), 0.14 Immediate postoperative seizure freedom (delayed seizure freedom) 0.58 (0.29 to 1.14), 0.12 Previous surgery (no previous surgery) 2.28 (1.02 to 5.10), 0.04	**Study Participation**: Low risk (all eligible participants who had surgery within a specified period of time were included) **Study Attrition**: Low risk (adequate description of participants lost to follow-up) **Prognostic Factor Measurement**: Low risk (factors measured by the same study investigators, unlikely to introduce bias) **Outcome Measurement**: Low risk (outcome measurement was valid and reliable) **Study Confounding**: Low risk (possible confounders, as reported in previous studies, were included) **Statistical Analysis and Reporting**: Low risk (multivariate regression model) **Overall Quality: High**

Study details	Participants	Methods	Results	Comments
			Postoperative EEG findings (reference category unclear) 1.04 (0.78 to 1.39), 0.77 Epileptic abnormalities on postoperative EEG findings (no evidence of epileptic abnormalities in postoperative EEG) 1.84 (1.15 to 2.96), 0.01 No EEG performed postoperatively (no evidence of epileptic abnormalities in postoperative EEG) 0.80 (0.37 to 1.73), 0.58 Resection of the anatomical lesion (reference category unclear) 1.22 (0.96 to 1.56), 0.11 Proven incomplete resection of the anatomical lesion (proven complete resection of anatomical lesion) 2.61 (1.58 to 4.33), <0.0001 Multivariable Cox regression model (TTD): seizure recurrences during/after ASM withdrawal, aHR (95%CI), p-value Shorter time interval from surgery to complete ASM discontinuation, per 3 months (longer time to complete ASM discontinuation): 0.90 (0.83 to 0.98), 0.02	

Study details	Participants	Methods	Results	Comments
			Epilepsy etiology(reference category unclear) 0.70 (0.48 to 1.03), 0.07 Number of ASMs used at time of surgery(reference category unclear) 0.71 (0.42 to 1.20), 0.20 Type of surgery(reference category unclear) 0.80 (0.41 to 1.57), 0.51 Hemispherectomy (lobar resection) 1.84 (0.45 to 7.57), 0.40 Multilobar resection (lobar resection) 0.82 (0.18 to 3.77), 0.80 Immediate postoperative seizure freedom (delayed seizure freedom) 2.47 (0.31 to 19.7), 0.39 Previous surgery (no previous surgery) 2.65 (0.61 to 11.6), 0.19 Postoperative EEG findings (reference category unclear) 0.71 (0.41 to 1.25), 0.24 Epileptic abnormalities on postoperative EEG findings (no evidence of epileptic abnormalities in postoperative EEG) 0.95 (0.36 to 2.51), 0.92	

Study details	Participants	Methods	Results	Comments
			No EEG performed (no evidence of epileptic abnormalities in postoperative EEG) 0.41 (0.09 to 1.81), 0.24 Resection of the anatomical lesion(reference category unclear) 1.30 (0.88 to 1.94), 0.19 Proven incomplete resection of the anatomical lesion (proven complete resection of anatomical lesion) 4.9 (2.08 to 11.52), <0.0001	
Full citation Braathen, G., Melander, H., Early discontinuation of treatment in children with uncomplicated epilepsy: a prospective study with a model for prediction of outcome, Epilepsia Epilepsia, 38, 561-9, 1997 **Ref Id** 1304230 **Country/ies where the study was carried out** Sweden **Study type** Retrospective cohort **Study dates** Not reported, but last follow-up check was in November 1995	**Number** N=161 children with epilepsy who became seizure free after treatment with ASM and in whom treatment was subsequently discontinued **Characteristics** Sex, age, presence/absence of LDs were not reported. All included patients were described as "children", and only those between 2 and 17 y/o were included (see inclusion criteria). All patients included were treated medically. **Inclusion criteria** • Those aged 2 to 17 years old **Exclusion criteria**	**Follow-up duration** Mean 5.8 years **Statistical analysis** Cox proportional-hazards regression model for survival data was used to identify predictor variables with potential influences on the recurrence rate after ASM discontinuation. Significant variables in univariate analyses were included in the multivariate regression analyses, along with the identified EEG variables. **No details on adjustment for confounders are reported.**	**Results** Multivariate analyses of predictor variables for relapse rate after discontinuation of treatment (reference category), aHR (95% CI), p-value Duration of treatment <1 year (duration of treatment > 1 year) 0.35 (0.19 to 0.62), p=0.0003 Favourable age at seizure onset* (non-favourable age at seizure onset) 0.44 (0.24 to 0.79), p=0.006 History of febrile convulsions in children with complex partial seizures (no history of febrile seizures) 0.28 (0.02 to 1.42), =0.14	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: High risk (authors did not describe the source of population in adequate detail) **Study Attrition**: Low risk (reasons to loss to follow-up are provided) **Prognostic Factor Measurement**: High risk (parents were asked to provide information about the prognostic variables under study, which may lead to substantial risk of bias) **Outcome Measurement**: Moderate risk (unclear how the outcome was measured)

Study details	Participants	Methods	Results	Comments
Funding Not reported	• Those with a major neurological disability (such as severe LDs or cerebral palsy). Note that those with LDs who had a normal CT scan were not excluded • Epileptic syndromes with known poor outcomes, such as infantile spasms or Lennox-Gastaut syndrome • Those who had been previously treated with ASMs		Diagnostic class 1* (diagnostic classes 2 and 3) 2.75 (1.47 to 6.27), p=0.003 Irregular spike-wave after 1 year of treatment (regular spike wave 3.09 (1.47 to 6.27), p=0.003 3-Hz spike wave activity on EEG after 6 months of treatment (no 3 Hz spike wave activity on EEG) 7.15 (2.01 to 20.00), p=0.005 *Favourable age at seizure onset was defined as: >10 years for children with rolandic epilepsies and <10 years for children with other seizure types; in order to enter *'diagnostic class' in the multivariate analysis, diagnostic class 1 (benign partial epilepsy with centrotemporal [rolandic] spikes [BECT] and simple partial seizures [SPS]) and diagnostic class 2 (primarily generalised tonic-clonic seizures [GTCS], GTCS during the night, autoimmune epilepsy, and GTCS as the only ictal manifestation in children with rolandic spikes) were compared with diagnostic class 3 (complex partial seizures [CPS])	**Study Confounding**: Low risk (multivariate logistic regression analyses were performed) **Statistical Analysis and Reporting**: Low risk (the selected statistical model is adequate for the design of the study) **Overall Quality: Low**
Full citation Caviedes, B. E., Herranz, J. L., Seizure recurrence	**Number** Total N = 226	**Follow-up duration** Mean (SD), years 5.85 (3.87)	**Results** Potential risk factors for relapse after ASM withdrawal in	**Limitations**

Study details	Participants	Methods	Results	Comments
and risk factors after withdrawal of chronic antiepileptic therapy in children, Seizure, 7, 107-114, 1998 **Ref Id** 1245492 **Country/ies where the study was carried out** Spain **Study type** Retrospective cohort study **Study dates** 1977 to 1994 **Funding** No information	**Characteristics** Gender, n Male = 116 Age of onset, mean (SD), months 53.25 (35.35) **Inclusion criteria** • Children diagnosed as epileptic (with two or more epileptic seizures, and with ictal and/or interictal paroxysmal EEG abnormalities) and • evaluated as outpatients between 1977 and 1994 at the University Hospital 'Marqués de Valendecilla' Neuropediatry Department. **Exclusion criteria** • Children with a single epileptic seizure and/or febrile seizures	**Statistical analysis** Chi-square test analysis of variance of continuous variables was used to carry out univariate analysis. Multivariate analysis was performed using the Cox proportional hazards model. **No details on adjustment for confounders are reported.**	226 patients (reference category), aRR (95% CI) Focal epilepsy (generalised) = 3.09 (1.72 to 5.54) Abnormal neurological examination (normal neurological examination) = 2.59 (1.22 to 5.51) Location of paroxystic activity Frontal (reference category unclear) 3.89 (1.23 to 12.29) Parietal (reference category unclear) 2.86 (1.23 to 6.69) Seizure type Simple partial (reference category unclear) 1.89 (0.96 to 3.71) Absences/spasm (reference category unclear) 0.37 (0.14 to 0.92) Valproate administered (carbamazepine, phenobarbitone or primidone, phenytoin) = 3.48 (1.87 to 6.46) Poor school progress (good school progress) = 1.28 (1.06 to 1.53) Age >5 years at onset of withdrawal (age < 5 years at onset of withdrawal) = 1.25 (1.12 to 1.39)	Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (method used to identify population were not clearly defined, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unsure if measurement is valid and reliable for all participants and unclear if method and setting of measurement is the same for all participants; may likely introduce substantial bias). **Outcome Measurement**: Low risk (unsure if the method and setting of outcome measurement is the same for all participants, but unlikely to introduce substantial bias) **Study Confounding**: High risk (no definition or method of measurement for confounders, and unsure if confounders were measured in the same setting for all participants)

Study details	Participants	Methods	Results	Comments
			Potential risk factors of seizure relapse after ASM withdrawal in 136 children with focal epilepsies only (reference category) RR (95% CI) Abnormal neurological exploration (normal neurological examination) 3.67 (1.61 to 8.36) Interval between seizures < 1 month at disease onset (interval > 1 month at disease onset) 3.33 (1.25 to 8.82) Carbamazepine administered (phenobarbitone or primidone, phenytoin, valproate) 0.46 (0.17 to 1.22) Valproate administered (carbamazepine, phenobarbitone or primidone, phenytoin) 3.31 (1.41 to 7.72) Age at onset of withdrawal > 6 years (age at onset of withdrawal < 6 years) 1.22 (1.07 to 1.39) Frontal paroxystic activity (reference category unclear) 6.50 (1.89 to 22.29) Abnormal EEG prior to withdrawal (normal EEG prior to withdrawal) 2.21 (0.96 to 5.06)	**Statistical Analysis and Reporting**: Low risk (no areas for concern in this domain) **Overall Quality: Moderate** **Other information** Risk factors of seizure relapse after ASM withdrawal in 136 children with focal epilepsies, RR (95% CI) were also presented, but this is not a population or subgroup of interest.

Study details	Participants	Methods	Results	Comments
			Risk factors of seizure relapse after ASM withdrawal in 90 children with generalised epilepsies only (reference category) RR (95% CI) Pathological neonatal period (normal neonatal period) 1.34 (1.09 to 1.65) Age > 10 years at first seizure (age < 10 years at first seizure) 1.03 (1.01 to 1.06) Mean duration of seizures < 1 minute (mean duration of seizures > 1 minute) 0.19 (0.03 to 0.96) Poor school progress (good school progress) 2.01 (1.22-3.31) Generalised groups of irregular spike-wave in EEG (unclear 19.42 (3.63 to 103.67)	
Full citation Dooley, J., Gordon, K., Camfield, P., Camfield, C., Smith, E., Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: A prospective study, Neurology, 46, 969-974, 1996 **Ref Id** 1245423	**Number** Total N = 97 **Characteristics** Gender, n Boys = 50 Girls = 47 Age at seizure onset, mean (SD), months 65.9 (45.89)	**Follow-up duration** Follow-up from start of medication taper, mean (SD); range, months 32.4 (13.1); 12 to 57 **Statistical analysis** Kaplan-Meier survival analysis was used to analyse the probability of remaining seizure free as a function of time.	**Results** Risk factor for seizure recurrence (reference category), aRR (95% CI) Female (male) 3.82 (1.73 to 8.44) Age at seizure onset > 120 months (age at seizure onset < 120 months) 5.64 (2.38 to 13.34)	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: High risk (population source, sampling frame and method to identify sufficient sample were not adequately described) **Study Attrition**: Low risk (No attrition reported)

Study details	Participants	Methods	Results	Comments
Country/ies where the study was carried out Canada **Study type** Prospective cohort study **Study dates** March 1, 1989 to February 28, 1993 **Funding** Not reported	Age at attaining seizure control, mean (SD), months 86.95 (49.2) **Inclusion criteria** • Children with a history of two or more afebrile seizures who were 12 to 13 months seizure free when seen in follow-up and were on ASM monotherapy. **Exclusion criteria** • Patients with juvenile myoclonic epilepsy	Log rank test was used to evaluate prognostic factors affecting seizure relapse. Cox's proportional hazard regression model was used to perform a multivariate analysis to determine in a stepwise fashion the factors that were most strongly related to the outcome. No details on adjustment for confounders are reported.	Seizure type Generalised (rolandic) 2.99 (1.38 to 6.48) Partial (rolandic) 8.92 (4.11 to 19.34) Neurological abnormalities (no neurological abnormalities) 2.98 (1.34 to 6.65)	**Prognostic Factor Measurement**: Low risk (the method and setting of measurement of the prognostic variables is the same for all study participants) **Outcome Measurement**: Low risk (the method and setting of outcome measurement is the same for all study participants) **Study Confounding**: Low risk (no concerns in this domain) **Statistical Analysis and Reporting**: Low risk (the selected statistical model is adequate for the design of the study) **Overall Quality: Moderate**
Full citation Karalok, Z. S., Guven, A., Ozturk, Z., Gurkas, E., Risk factors for recurrence after drug withdrawal in childhood epilepsy, Brain and Development, 42, 35-40, 2020 **Ref Id** 1247427 **Country/ies where the study was carried out** Turkey **Study type** Retrospective observational study	**Number** N = 284 **Characteristics** Gender, n (%) Girls = 137 (48.2) Boys = 147 (51.8) Age at onset, n(%) <6years = 114 (40.1) ≥6 years = 170 (59.9) History of febrile seizures, n(%) Positive = 52 (18.3) Negative = 232 (81.7) Family history of epilepsy, n(%)	**Follow-up duration** Mean (range) years: 8.3 (3-17) **Statistical analysis** Multivariate Cox regression was performed for factors that had statistically significant values up to 0.25 in the univariate analysis. No details on adjustment for confounders are reported.	**Results** Risk factors of seizure recurrence after ASM withdrawal (reference category), aHR (95% CI), p-value Electroclinical-classification - genetic/structural-metabolic & unknown (reference category unclear) 2.15 (1.21 to 3.82), 0.009 Seizure-free period <3 years before withdrawal (seizure-free period > 3 years before withdrawal) = 2.62 (1.17 to 5.88), 0.019	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (exclusion criteria not provided, but unlikely introduce substantial bias) **Study Attrition**: Low risk (no concerns in this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unclear validity and reliability of measurement, may likely introduce substantial bias)

Study details	Participants	Methods	Results	Comments
Study dates January 1997 to December 2014 **Funding** Not reported	Positive = 29 (10.2) Negative = 255 (89.8) First EEG, n(%) Normal = 46 (16.2) Abnormal = 237 (83.8) Etiological epilepsy classification, n(%) Genetic/structural-metabolic = 214 (75.4) Unknown = 70 (24.6) Treatment response time, n(%) <1 year = 206 (72.5) >1 year = 78 (27.5) Number of ASMs, n(%) Monotherapy = 258 (90.8) Polytherapy = 26 (9.2) Pre-withdrawal EEG, n(%) Normal = 262 (92.6) Abnormal = 21 (7.4) Cognitive impairment, n(%) Positive = 83 (30) Negative = 201 (70) Seizure free time, n(%) 2-3 years = 212 (74.6) >3years = 72 (25.4) **Inclusion criteria** • onset of epilepsy at between 1 month and 16 years of age;			**Outcome Measurement**: Moderate risk (no definition of outcome, method of measurement not reported, may likely introduce substantial bias) **Study Confounding**: Low risk (no areas of concern in this domain) **Statistical Analysis and Reporting**: Low risk (no areas of concern in this domain) **Overall Quality: Moderate** **Other information** Idiopathic epileptic syndromes named as genetic; symptomatic epilepsy named as structural/metabolic and cryptogenic group named as unknown epilepsy. The duration of withdrawal period changed from 6 months to 1 year. When patients were taking more than one ASMs, withdrawal began with one of the ASMs first. When the previous drug had been stopped, then we started to reduce the second one. In case of seizure recurrence during withdrawal period, stopping of ASM was terminated.

Study details	Participants	Methods	Results	Comments
	• seizure-free for 2 years or more before withdrawal; • having dates about seizure onset, medication, blood levels of ASMs, and electroencephalography (EEG) findings; • at least 3 years follow-up time after withdrawal **Exclusion criteria** Not reported			
Full citation Lachhwani, D. K., Loddenkemper, T., Holland, K. D., Kotagal, P., Mascha, E., Bingaman, W., Wyllie, E., Discontinuation of Medications After Successful Epilepsy Surgery in Children, Pediatric Neurology, 38, 340-344, 2008 **Ref Id** 1246137 **Country/ies where the study was carried out** US **Study type** Retrospective cohort **Study dates** Not reported, but patients underwent epilepsy surgery between 1978 and 2001	**Number** N=97 **Characteristics** Female sex, n (%): 50 (51.5) Median age (range): 11 years (3 months to 18 years) Epilepsy onset: between birth and 13 years Median time from seizure onset to epilepsy surgery (range): 5.5 years (2 months to 18 years) Presence/absence of learning difficulties was not reported. All patients were treated surgically **Inclusion criteria** • those who were under 18 years old and had surgery	**Follow-up duration** 24 months after surgery **Statistical analysis** Cox proportional hazard multivariable survival analysis were used to assess the recurrent probability after ASM discontinuation following epilepsy surgery. Adjustment was made for baseline characteristics with p-value <0.20 multivariably (age at epilepsy onset, age at surgery, delay between onset of epilepsy and surgery, preoperative seizure frequency, preoperative presence of bilateral sharp waves/contralateral seizures on EEG, resection type, histopathology, and presence of sharp waves on postoperative EEG)	**Results** Multivariable predictors of seizure recurrence by cut-off point for post-operative ASM use (reference category), aHR (95% CI), p-value ≤6 months (> 6 months): 5.8 (1.8 to 17.5), p=0.03. Adjusted for malformation of cortical development. ≤12 months (> 12 months): 1.4 (0.85 to 6.7), p=0.58 Adjusting for malformation of cortical development, age at surgery, and age at onset. ≤24 months (> 24 months): 1.3 (0.4 to 3.8), p=0.64. Adjusted for malformation of cortical development, age at surgery, and age at onset.	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (adequate participation in the study by eligible persons) **Study Attrition**: Low risk (reasons for loss to follow-up are provided) **Prognostic Factor Measurement**: Moderate risk (the method and setting of measurement of prognostic factors in the same for all study participants, although no formal definition for prognostic factors was provided, but most of them are objective measures, so unlikely to have introduced substantial bias) **Outcome Measurement**: Low risk (the method and setting of

Study details	Participants	Methods	Results	Comments
Funding Not reported	for medically refractory epilepsy • those who were seizure-free or had only limited non-disabling auras • had ≥12 months follow-up after ASM discontinuation **Exclusion criteria** Not reported			outcome measurement is the same for all study participants) **Study Confounding**: Low risk (important potential confounders are accounted for in the study design; multivariate logistic regression analyses were performed) **Statistical Analysis and Reporting**: Low risk (the selected statistical model is adequate for the design of the study) **Overall Quality: High**
Full citation Lamberink, H. J., Otte, W. M., Geerts, A. T., Pavlovic, M., Ramos-Lizana, J., Marson, A. G., Overweg, J., Sauma, L., Specchio, L. M., Tennison, M., Cardoso, T. M. O., Shinnar, S., Schmidt, D., Geleijns, K., Braun, K. P. J., Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis, The Lancet Neurology, 16, 523-531, 2017 **Ref Id** 916547	**Number** Out of 33 authors contacted, 10 agreed to participate and provide data for the IPD meta-analysis N=1771 patients, of which n=2 had to be removed because of too much missing information, N=1769 patients included in final analysis. **Characteristics** Female sex, n (%): 842 (48) Age at onset (childhood, 0 to 10 y/o), n (%): 1087 (61) Age at onset (adolescent, 11 to 17 y/o), n (%): 387 (22) Age at onset (adult, ≥18 y/o), n (%): 295 (17)	**Follow-up duration** Maximum follow-up after start of antiepileptic drug withdrawal was 23 years (median 5.3, IQR 3.0 to 10.0) For those with seizure recurrence, the follow-up after the recurrence was a median of 3.7 years (range 0 to 20.0, IQR 1.0 to 7.0) Median time to ASM withdrawal after the last seizure was a median of 33 months (range 3 to 385, IQR 24 to 48). **Statistical analysis** Random effects proportional hazards regression was conducted, using prognostic	**Results** Multivariate predictors of seizure recurrence, final prediction model (reference category) aHR (95% CI, p-value) Epilepsy duration before remission in years: non linearly related outcome, no estimate available Seizure free interval before ASM withdrawal in years: non linearly related outcome, no estimate available Age at onset of epilepsy*: non linearly related outcome, no estimate available History of febrile seizures (no history of febrile seizures): 1.40 (1.13 to 1.73), p=0.0020	**Limitations** Systematic review limitations assessed with the ROBIS checklist **Identifying concerns in the review process** Domain 1: concerns regarding specification of study eligibility criteria: low Domain 2: concerns regarding methods used to identify and/or select studies: low Domain 3: concerns regarding methods used to collect data and appraise studies: low Domain 4: concerns regarding the synthesis and findings: low **Risk of bias in the review** A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?: yes

Study details	Participants	Methods	Results	Comments
Country/ies where the study was carried out The IPD meta-analysis was conducted in The Netherlands. Individual studies were conducted in Brazil, The Netherlands, UK, Servia, Spain, Italy, US **Study type** Individual participant data (IPD) meta-analysis of prognostic studies **Study dates** Last search was carried out on Nov 6, 2014 **Funding** Epilepsiefonds	Age at withdrawal of ASMs, years (range): 15 (0 to 84) History of neonatal seizures, n (%): 53 (3) Developmental delay, n (%): 262 (15) History of epileptic encephalopathy, n (%): 24 (2) All patients were medically treated, none received surgery. **Inclusion criteria** • Prospective, retrospective, RCTs • Original full-text articles reporting on a cohort of patients who started ASM withdrawal • Reporting on seizure recurrence during and after ASM withdrawal **Exclusion criteria** • Surgical cohorts • Studies including <30 participants • Studies including acute symptomatic seizures	factors. Based on the strongest contributing predictors, a backward selection of variables was done until the most optimum model was selected. Missing data were dealt with by multiple imputations. 2 cases had to be removed because of too much missing information. Calibration plots were created and, for validation, a c statistic was computed and adjusted for optimism by using 200 bootstrap samples. Internal-external cross-validation was done to assess the validity of the model across different samples.	≥10 seizures before remission (< 10 seizures before remission) 1.38 (1.17 to 1.63), p=0.0002 Self-limiting epilepsy syndrome, formerly called "benign course", for example: absence epilepsy, benign epilepsy with centrotemporal spikes (Rolandic epilepsy), Panayiotopoulos syndrome (absence of a self-limiting epilepsy syndrome): 0.57 (0.44 to 0.72), p<0.0001 Developmental delay (no evidence of developmental delay): 1.23 (1.01 to 1.50), p=0.0420 Epileptiform abnormality on EEG before withdrawal (no epileptiform abnormality on EEG): 1.50 (1.25 to 1.80), p<0.0001 *The study described a U-shaped relationship, with an elevated risk at birth, that falls to no-risk by age 3 to 4 years, when it begins to raise again, until age 10, and plateaus until age 25	B. Was the relevance of identified studies to the review's research questions appropriately considered?: yes C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?: yes Risk of bias in the review: LOW **Other information** The studies included in this IPD were individually checked to assess whether they reported any other relevant outcome for the review protocol apart from risk factors for seizure recurrence, but no additional outcomes had been reported. For some of the predictors, estimates were not available due to collinearity (correlation between the predictor variable and the outcome). Indirectness: 3% of the included population presented with neonatal seizures. Lossius 2008 was not captured by this IPD meta-analysis because the data did not arrive on time for the authors to analyse it. The study authors were contacted to confirm this.
Full citation	**Number** Total N = 150	**Follow-up duration**	**Results**	**Limitations**

Study details	Participants	Methods	Results	Comments
Lossius, M. I., Hessen, E., Mowinckel, P., Stavem, K., Erikssen, J., Gulbrandsen, P., Gjerstad, L., Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus Study), Epilepsia, 49, 455-463, 2008 **Ref Id** 1217518 **Country/ies where the study was carried out** Norway **Study type** Prospective, randomised-controlled double-blind study **Study dates** Recruitment: October 1999 to March 2004. Follow-up for 12 months. Additional follow-up data on medication and seizures were collected for all but 3 patients in November 2006. **Funding** Study received financial support from: • The Norwegian Foundation for	Withdrawal group n = 72 Non-withdrawal group n = 78 **Characteristics** **Withdrawal group** Age, Mean (range), years = 40 (19-65) Female patients n(%) = 41 (57) Epilepsy onset, n(%) 0–11 years = 4 (6) 11–18 years = 22 (31) 18–60 years = 46(64) Seizure-free, n(%) 2–3 years = 6 (8) 3–5 years = 21 (29) >5 years = 45 (63) Epilepsy type, n(%) Localization related = 55 (76) Generalized = 17 (24) Unclassified = 0 Seizure type, n(%) Partial epilepsy • Secondarily generalized tonic–clonic seizures = 44 (61) • Complex partial seizures = 26 (36)	Median follow-up = 47 months (41 months for patients off medication) **Statistical analysis** Student's t-test and chi-square test were used to test group differences for continuous and categorical variables, respectively. Kaplan Meier curve with log- rank test was used for occurrence of seizures. Odds ratios (95% CI) for seizure relapse were estimated with logistic regression analyses. Variables of importance were tested in logistic bivariate models to assess possible predictors for seizure relapse in the withdrawal group No details on adjustment for confounders are reported with regards to multivariate analysis of predictors.	Bivariate logistic analysis of predictors of seizure freedom from seizures (reference category), aOR (95% CI), p value Odds of remaining seizure free for 1 year with prior use of CBZ (prior use of any other ASM) 6.33 (1.23 to 32.25), p-value not reported Odds of remaining seizure-free at 41 months after withdrawal with prior use of CBZ (prior use of any other ASM) 2.86 (1.31 to 6.26), 0.01 Odds of remaining seizure free at 1 year for those with normal neurological examination (abnormal neurological evaluation) 2.77 (1.18 to 142.86), 0.036	Methodological limitations assessed using the Cochrane risk of bias tool for randomised trials (Version 2.0) **Domain 1: Randomisation: Some concerns** 1.1: No, no pre-determined randomisation code was used. Patients were randomised in blocks of 10. 1.2: No information, there is no information on concealment of allocation 1.3: No, no significant differences between groups at baseline **Domain 2: Deviations from intended interventions: Low risk** 2.1: No, double blind study 2.2: No, double blind study **Domain 3: Missing outcome data: Low risk** 3.1: Yes, nearly all patients had data available. 10 patients were withdrawn between randomisation and intervention and 1 other patient during analysis. **Domain 4: Measurement of the outcome: Low risk** 4.1: No, Cognitive function, EEG and HRQOL were assessed using validated tools/equipment. Seizure recurrence was assessed in interview with patient

Study details	Participants	Methods	Results	Comments
Health and Rehabilitation (EXTRA FUND) • The Norwegian Epilepsy Association • The Norwegian Chapter of the International League Against Epilepsy	• Simple partial seizures = 17 (24) • Unclassified seizures = 1 (1) Generalized epilepsy • Primarily generalized tonic–clonic seizures = 16 (22) • Absences = 1 (1) • Other = 1 (1) <u>Normal neurological status, n (%)</u> 68 (94) <u>MRI pathology, n (%)</u> 16 (23) <u>Known etiology, n (%)</u> 20 (28) <u>Epileptic activity on the EEG, n (%)</u> 25 (34) <u>Serum concentration in therapeutic range, n (%)</u> 55 (76) <u>Medication, n (%)</u> Carbamazepine = 41 (57) Valproate = 15 (21) Phenytoin = 8 (11) Phenobarbital = 3 (4) Lamotrigine = 5 (7) **Non-withdrawal group**			4.2: No, Outcomes were unlikely to differ between intervention groups as standard methods of assessing outcomes were used 4.3: Probably no, double blind study **Domain 5: Selection of the reported result: Some concerns** 5.1: Probably no, there is no information to show that there was a pre-specified analysis plan 5.2: No information, there is no information to show that there was a pre-specified analysis plan 5.3: No information, there is no information to show that there was a pre-specified analysis plan **Domain 6: Overall judgment 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** Within 12 months, five of the 77 non-withdrawers (7%) and 11 of the 72 withdrawers (15%) had experienced seizure relapse (RR 2.46; 95% CI: 0.85–7.08; p = 0.095)

Study details	Participants	Methods	Results	Comments
	Age, Mean (range), years = 37(18-66) Female patients n(%) = 39 (50) Epilepsy onset, n (%) 0–11 years = 10 (13) 11–18 years = 22 (28) 18–60 years = 46(59) Seizure-free, n (%) 2–3 years = 3 (4) 3–5 years = 20 (26) >5 years = 55 (71) Epilepsy type, n (%) Localization related = 59 (76) Generalized = 17 (22) Unclassified = 2 (3) Seizure type, n (%) Partial epilepsy • Secondarily generalized tonic–clonic seizures = 52 (68) • Complex partial seizures = 19 (25) • Simple partial seizures = 19 (25) • Unclassified seizures = 0 Generalized epilepsy • Primarily generalized tonic–clonic seizures = 14 (18) • Absences = 1 (1) • Other = 1 (1)			

Study details	Participants	Methods	Results	Comments
	Normal neurological status, n(%) 72 (92) MRI pathology, n (%) 21 (28) Known etiology, n (%) 23 (30) Epileptic activity on the EEG, n (%) 35 (45) Serum concentration in therapeutic range, n (%) 63 (81) Medication, n (%) Carbamazepine = 52 (67) Valproate = 18 (23) Phenytoin = 5 (6) Phenobarbital = 2 (3) Lamotrigine = 1 (1) **Inclusion criteria** • Epilepsy (at least two unprovoked seizures) • Two years seizure freedom or longer • Monotherapy • Age: 18–67 years • If prior withdrawal attempted and unsuccessful, five years seizure freedom or longer is needed			

Study details	Participants	Methods	Results	Comments
	Exclusion criteria • Juvenile myoclonic epilepsy (JME) • Polytherapy • Paroxysmal epileptiform activity in patients with primarily generalized epilepsy • Two prior withdrawal attempts • Pregnant or seeking pregnancy • Mental retardation • Progressive neurological disease • Other serious disease which may influence the health status of the patient in the study period • Comedication (except postmenopausal hormone substitution, hormonal contraceptives, acetylic acid, antihypertensiva and thyroxin)			
Full citation Menon, R., Rathore, C., Sarma, S. P., Radhakrishnan, K., Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery, Neurology, 79, 770-776, 2012 **Ref Id** 1246542	**Number** N=94 **Characteristics** Age at onset, mean years (SD): No recurrence: 7.4 (5) Recurrence: 7.2 (6.4) Age at surgery, mean years (SD): No recurrence: 17.6 (7.7)	**Follow-up duration** All patients were followed-up at 3 months, at 1 year and then at yearly intervals after surgery **Statistical analysis** Time-to-event curves from Kaplan Meier estimates were used to assess the probability of ASM freedom	**Results** Predictors of seizure recurrence (reference category) on attempted ASM withdrawal by logistic regression analysis, aOR (95% CI), p-value Longer preoperative duration of epilepsy (shorter preoperative duration of epilepsy) 1.07 (1.01 to 1.14), p=0.020. NB no	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (adequate participation in the study by eligible persons) **Study Attrition**: Low risk reasons for loss to follow-up are provided)

Study details	Participants	Methods	Results	Comments
Country/ies where the study was carried out India **Study type** Retrospective cohort **Study dates** Not reported, but patients who underwent surgery between November 1997 to May 2008 were included **Funding** Not reported	Recurrence: 22.1 (10) All patients underwent surgery. Presence/absence of LDs was not reported **Inclusion criteria** • Those who underwent extratemporal resections with temporal lobe resections either for dual pathology or as part of a multilobar resection between November 1997 and May 2008 **Exclusion criteria** • Those who underwent hemispherectomy/hemispherotomy	following surgery. Multivariate logistic regression analyses were performed for variables fixed as 0.05 and for removal 0.10. Analyses performed with SPSS. There is a clear statement that the estimates presented have been adjusted, however no further details on this are included.	details on how 'longer' was defined are provided. Interictal epileptiform discharges on 1-year postoperative EEG (no interictal epileptiform discharges on 1 year post-operative EEG) 3.12 (1.20 to 8.08), p=0.019	**Prognostic Factor Measurement**: Moderate risk (the method and setting of measurement of prognostic factors in the same for all study participants, although no formal definition for prognostic factors was provided, but most of them are objective measures, so unlikely to have introduced substantial bias) **Outcome Measurement**: Low risk (the method and setting of outcome measurement is the same for all study participants) **Study Confounding**: Low risk (important potential confounders are accounted for in the study design; multivariate logistic regression analyses were performed) **Statistical Analysis and Reporting**: Low risk (the selected statistical model is adequate for the design of the study) **Overall Quality: High**
Full citation Ohta, H., Ohtsuka, Y., Tsuda, T., Oka, E., Prognosis after withdrawal of antiepileptic drugs in childhood-onset cryptogenic localization-related epilepsies, Brain and Development, 26, 19-25, 2004	**Number** Total N= 82 **Characteristics** Gender Male = 47 Female = 35 Average age at onset (range)	**Follow-up duration** Average follow-up period from start of ASM discontinuation to last visit 4 years 7 months Average follow-up period from complete discontinuation of ASM to last visit	**Results** Multivariate analysis for predictive factors for relapse (reference category), aHR (95% CI) Age at onset of epilepsy ≥ 6 years (age at onset of epilepsy	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Moderate risk (source and method used to identify population were not clearly defined and key characteristics were not adequately

Study details	Participants	Methods	Results	Comments
Ref Id 1245846 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Study dates** January 1, 1980, to December 31, 1981 **Funding** Not reported	3 years 10 months (7 months to 14 years 2 months) Average age at start of ASM withdrawal (range) 12 years and 4 months (6 years 2 months to 31 years 7 months) Average age at complete discontinuation of ASM (range) 13 years 6 months (6 years 2 months to 26 years 9 months) Average tapering period 1 year 6 months **Inclusion criteria** • age at first visit of less than 15 years, • follow-up period of more than 5 years, • suffering from cryptogenic localization-related epilepsies, and • the patient underwent ASM withdrawal during the follow-up period. **Exclusion criteria** • Patients with neonatal seizures, febrile seizures, or other acute symptomatic seizures who did not have a clear history of epilepsy	2 years 9 months (in patients without any relapse of seizures). **Statistical analysis** Incidence rate of relapse calculated as number of events/person-months. Incidence rate of relapse in patients with potential predictive factor of relapse divided by incidence rate of relapse in patients without predictive factor of relapse equals the relapse rate ratio. To detect potential predictive factors for relapse, hazard ratio using Cox proportional hazards model was estimated. Chi-square or Fisher's exact tests were used to test differences of count data (relapse rate for each potential predictive factor for relapse). No details on adjustment for confounders are reported.	< 6 years) = 19.24 (1.83 to 202.44) Time from start of ASM treatment to seizure control ≥ 5 years (time from start of ASM treatment to seizure control < 5 years) = 9.85 (1.33 to 73.05) Number of seizures before seizure control ≥ 5 (number of seizures before seizure control < 5) = 7.32 (0.65 to 82.44) Number of ASMs before seizure control ≥ 2 (number of ASMs before seizure control < 2) = 0.30 (0.03 to 2.69) Complex partial seizure (simple partial seizure, secondarily generalised seizure) = 3.50 (0.60 to 20.35)	described, likely to introduce substantial bias) **Study Attrition**: Low risk (no attrition reported) **Prognostic Factor Measurement**: Low risk (no definition of prognostic factors, unlikely to introduce substantial bias) **Outcome Measurement**: Low risk (no definition of outcome measure, but unlikely to introduce substantial bias) **Study Confounding**: Low risk (no definition of confounders, but unlikely to introduce substantial bias) **Statistical Analysis and Reporting**: Low risk (only statistically significant results were reported, but unlikely to introduce substantial bias) **Overall Quality: High**
Full citation	**Number** Total, N = 161	**Follow-up duration** Follow up duration	**Results**	**Limitations**

Study details	Participants	Methods	Results	Comments
Ou, S., Li, R., Wang, L., Xia, L., Zhou, Q., Pan, S., Long-term outcome of seizure-free patients and risk factors of relapse following antiepileptic drug withdrawal, Epilepsy and Behavior, 88, 295-300, 2018 **Ref Id** 1247170 **Country/ies where the study was carried out** China **Study type** Retrospective observational study **Study dates** November 1, 2008 to December 20, 2017 **Funding** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors	Seizure free group, n(%) = 89 (55.3) Relapse group, n(%) = 72 (44.7) **Characteristics** Gender, n Male = 96 Female = 65 Age at onset, n Total patients 0-18 years = 111 >18 years = 50 Seizure free group 0-18 years = 64 >18 years = 25 Relapse group 0-18 years = 47 >18 years = 25 **Inclusion criteria** • patients were diagnosed as having epilepsy (defined as two or more unprovoked seizures occurring at least 24 h apart); • patients had obtained complete seizure control for at least 2 years through regular treatment and attempted ASM withdrawal;	All participants; Mean (SD; range), months 41.97 (31.19; 0.5-156) Seizure free group; Mean (SD), months 60.21 (20.32) Relapse group; Mean (SD), months 19.12 (27.17) **Statistical analysis** To evaluate the risk factors of relapse for continuous variables and categorical variables, student t-test and chi-square test were used, respectively. Multivariate analyses was carried out using the Cox proportional hazards model to obtain a hazard ratio (HR) and 95% confidence interval (95% CI) for each independent variable. To calculate the cumulative probability of seizure recurrence following ASM withdrawal, the Kaplan- Meier method was used. No details on adjustment for confounders are reported.	Risk factors for seizure recurrence (reference category), aHR (95% CI); p-value Multiple seizure types (single seizure type) 2.554 (0.443 to 14.728); 0.294 Perinatal injury (no perinatal injury) 3.731 (1.346 to 10.417); 0.011 Seizures that were not controlled in the first 6 months (seizures that were controlled in first 6 months) 2.381 (1.114 to 5.102); 0.025 Combination of ASMs (monotherapy) 1.908 (0.570 to 6.410); 0.295	Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (method used to identify population were not clearly defined, but unlikely to introduce substantial bias) **Study Attrition**: Low risk (no area of concern for this domain) **Prognostic Factor Measurement**: Moderate risk (partial definition of prognostic factors, unsure if measurement is valid and reliable for all participants and unclear if method and setting of measurement is the same for all participants; may likely introduce substantial bias) **Outcome Measurement**: Low risk (unsure if the method and setting of outcome measurement is the same for all participants, but unlikely to introduce substantial bias) **Study Confounding**: Moderate risk (no definition or method of measurement for confounders, and unsure if confounders were measured in the same setting for all participants)

Study details	Participants	Methods	Results	Comments
	• the duration of the follow-up time since the start of withdrawal was at least 3 years or until epilepsy relapse; • detailed patient information was recorded **Exclusion criteria** • patients who presented with an acute symptomatic seizure • patients with juvenile myoclonic epilepsy • patients with progressive encephalopathy, such as brain tumours • patients with a history of epilepsy surgery • poor compliance during the period of drug withdrawal			**Statistical Analysis and Reporting**: Low risk (no areas for concern in this domain) **Overall Quality: Moderate**
Full citation Park, K. I., Lee, S. K., Chu, K., Jung, K. H., Bae, E. K., Kim, J. S., Lee, J. J., Lee, S. Y., Chung, C. K., Withdrawal of antiepileptic drugs after neocortical epilepsy surgery, Annals of Neurology, 67, 230-238, 2010 **Ref Id** 1246343 **Country/ies where the study was carried out** Korea	**Number** N=223 **Characteristics** Age, sex, presence/absence of LDs were not reported. All patients underwent surgery. **Inclusion criteria** • Those who underwent resectional surgery between November 1994 and January 2005 **Exclusion criteria**	**Follow-up duration** Mean (range): 72.6 months (12 to 138 months) **Statistical analysis** Predictors of seizure recurrence were calculated by performing a stepwise Cox proportional hazard analysis of independent variables with p-values ≤0.10 in the univariate analysis. No details on adjustment for confounders are reported.	**Results** Multivariate analysis of potential variables influencing seizure recurrence after ASM reduction following epilepsy surgery (reference category), aHR (95% CI), p-value Time to ASM reduction <9 months (≥ 9 months): 2.83 (1.62 to 4.94), p< 0.001 Normal MRI results (abnormal MRI) 1.96 (1.15 to 3.34), p=0.01	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: High risk (authors did not describe the source of population in adequate detail) **Study Attrition**: Low risk (reasons to loss to follow-up are provided) **Prognostic Factor Measurement**: Low risk (the method and setting of measurement of

Study details	Participants	Methods	Results	Comments
Study type Retrospective cohort **Study dates** Not reported, but patients underwent surgery between November 1994 and January 2005 **Funding** Ministry of Health and Welfare, Republic of Korea	• Those undergoing reoperation of neocortical epileptogenic regions		Seizure recurrence before ASM reduction (no seizure recurrence before ASM reduction) 2.43 (1.37 to 4.31), p=0.002 Epilepsy duration >11 years (≤11 years): 1.75 (1.09 to 2.81), p=0.02 Cortical dysplasia (no evidence of cortical dysplasia): 1.07 (0.61 to 1.87), p=0.81 Preoperative number of ASMs (reference category unclear) 1.21 (0.93 to 1.57), p=0.16 Incomplete resection (complete resection) 1.62 (0.91 to 2.89), p=0.10.	the prognostic variables is the same for all study participants) **Outcome Measurement**: Low risk (the method and setting of outcome measurement is the same for all study participants) **Study Confounding**: Low risk (multivariate logistic regression analyses were performed) **Statistical Analysis and Reporting**: Low risk (the selected statistical model is adequate for the design of the study) **Overall Quality: Moderate**
Full citation Rathore, C., Panda, S., Sarma, P. S., Radhakrishnan, K., How safe is it to withdraw antiepileptic drugs following successful surgery for mesial temporal lobe epilepsy?, Epilepsia, 52, 627-635, 2011 **Ref Id** 1246450 **Country/ies where the study was carried out** India **Study type**	**Number** N=258 (n= 64 with seizure recurrence and n=194 seizure-free) **Characteristics** <u>Age at epilepsy onset:</u> Seizure recurrence group, mean years (SD): 9.13 (7.85) Seizure free group, mean years (SD): 9.39 (6.69) <u>Time to complete ASM discontinuation:</u> Seizure recurrence group, mean months (SD): 45.41 (16.77)	**Follow-up duration** Mean (SD): 8 years (2 years) **Statistical analysis** The risk factors for seizure recurrence following attempted ASM withdrawal were studied. Those who had a seizure recurrence on ASM tapering were compared to those without seizure recurrence. Factors found to be significant on univariate analysis were entered into multivariate logistic regression analysis	**Results** <u>Multivariable analysis for predictors of seizure recurrence on attempted ASM withdrawal (reference category), aOR (95% CI), p-value</u> Absence of definitive hippocampal sclerosis (HS) on pathology (presence of definitive hippocampal sclerosis on pathology) 2.34 (1.02 to 5.38), p=0.04 Interictal epileptiform discharges (IEDs) on 1 year anterior temporal lobectomy (ATL)	**Limitations** <u>Methodological limitations assessed using the QUIPS Checklist</u> **Study Participation**: Low risk (adequate participation in the study by eligible persons) **Study Attrition**: Low risk reasons for loss to follow-up are provided) **Prognostic Factor Measurement**: Moderate risk (the method and setting of measurement of prognostic factors in the same for all study partici-

Study details	Participants	Methods	Results	Comments
Prospective cohort **Study dates** Not reported, but patients who underwent surgery between January 1996 to December 2002 were included **Funding** Not reported	Seizure free group, mean months (SD): 44.19 (20.64) No information of sex or presence/absence of LDs were reported. All patients underwent epilepsy surgery **Inclusion criteria** • Those who underwent surgery between January 1996 to December 2002 for hippocampal sclerosis • Those who had completed a minimum of 5 years of postoperative follow-up. **Exclusion criteria** • Those who underwent surgery for extratemporal lobe epilepsy or predominantly for temporal neocortical epilepsy	with forward stepwise (likelihood ratio) method. All analyses were performed with SPSS. There is a clear statement that the estimates presented have been adjusted, however no further details on this included are included.	EEG (absence of interictal epileptiform discharges on 1 year anterior temporal lobectomy EEG 2.23 (1.01 to 5), p=0.05 Seizure recurrence before attempted ASM withdrawal (no seizure recurrence before attempted ASM withdrawal) 1.70 (0.89 to 2.36), p=0.112 Age at anterior temporal lobectomy ≥30 years (age at anterior temporal lobectomy < 30 years) 1.38 (0.65 to 2.92), p=0.398 Epilepsy duration ≥20 years (epilepsy duration < 20 years) 1.65 (0.79 to 3.45), p=0.181	pants, although no formal definition for prognostic factors was provided, but most of them are objective measures, so unlikely to have introduced substantial bias). **Outcome Measurement**: Low risk (the method and setting of outcome measurement is the same for all study participants) **Study Confounding**: Low risk (important potential confounders are accounted for in the study design; multivariate logistic regression analyses were performed) **Statistical Analysis and Reporting**: Low risk (the selected statistical model is adequate for the design of the study) **Overall Quality: High**
Full citation Su, L., Di, Q., Yu, N., Zhang, Y., Predictors for relapse after antiepileptic drug withdrawal in seizure-free patients with epilepsy, Journal of Clinical Neuroscience, 20, 790-794, 2013 **Ref Id** 1155867	**Number** Total enrolled N = 99 Total included in analysis, N = 86 (13 excluded from analysis because there was loss to follow-up or incomplete record of analysis). Early ASM withdrawal group n(%) 44 (51.2) Delayed ASM withdrawal group n(%)	**Follow-up duration** Mean, years (SD) 2.1 (1.5) **Statistical analysis** Cox proportional hazards model was used to investigate significant variables from the univariate analyses in multivariate analyses to obtain a hazard ratio (HR) for each independent variable.	**Results** Risk factor for seizure recurrence (reference category), multivariate aHR (95% CI) Epileptiform EEG abnormalities after withdrawal (normal epileptiform EEG after withdrawal) = 4.810 (2.220-10.420) Early withdrawal of ASMs after 2-3 years seizure free (de-	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: High risk (source, method used to identify population, recruitment period and participation were not clearly defined) **Study Attrition**: Moderate risk (no information on those lost to follow up, may likely introduce substantial bias)

Study details	Participants	Methods	Results	Comments
Country/ies where the study was carried out China **Study type** Prospective observational study **Study dates** 2001 - 2009 **Funding** Supported by: • grants from the Nanjing Medical Major Scientific and Technological Development Foundation • the Health Department Preventive Medicine Scientific Research Foundation of Jiangsu province, China.	42 (48.8) **Characteristics** <u>Age at time of ASM withdrawal, median, years (Range)</u> 18 (6-67) <u>Age at seizure onset, median, years (Range)</u> 13 (1-65) <u>Gender, n (%)</u> Male = 44 (51.2) Female = 42 (48.8) <u>Etiology, n(%)</u> Symptomatic or cryptogenic = 33 (38.4) Idiopatic = 53 (61.6) <u>Seizure type, n(%)</u> Partial seizure = 49 (57) General seizure = 37(43) <u>Number of seizure types, n(%)</u> 1 = 69(80.2) 2 = 15 (17.4) 3 = 2 (2.3) <u>Timing of withdrawal, n(%)</u> Early = 44 (51.2) Delayed 42 (48.8) <u>Brain CT scan/abnormalities, n(%)</u> Yes = 14 (16.3) No = 72 (83.7)	No details on adjustment for confounders are reported.	layed withdrawal of ASMs after 3 years seizure free) = 0.999 (0.969 - 1.029)	**Prognostic Factor Measurement**: Low risk (no areas of concern in this domain) **Outcome Measurement**: Low risk (no areas of concern in this domain) **Study Confounding**: Low risk (confounders adequately measured) **Statistical Analysis and Reporting**: Low risk (no areas of concern in this domain) **Overall Quality: Moderate** **Other information** Maximum interval between the start of ASM withdrawal and seizure relapse was 74 months.

Study details	Participants	Methods	Results	Comments
	Seizure frequency before epilepsy control, n (%) >1 seizure monthly = 20 (23.3) ≤ 1 seizure monthly = 66 (76.7) EEG at diagnosis, n (%) Epileptiform = 34 (39.5) Not epileptiform = 52 (60.5) EEG at withdrawal, n (%) Epileptiform = 5 (5.8) Not epileptiform = 81 (94.2) EEG during withdrawal, n (%) Epileptiform = 10 (11.6) Not epileptiform = 60 (69.8) Not Applicable = 16 (18.6) EEG after withdrawal, n (%) Epileptiform = 18 (20.9) Not epileptiform = 45 (52.3) Not Applicable = 23 (26.7) ASM at time of withdrawal, n(%) Monotherapy = 82 (95.3) Polytherapy (ASMs withdrawn sequentially) = 4 (4.7) **Inclusion criteria** • Patients with a seizure-free period of more than 2 years and without a history of withdrawal attempts **Exclusion criteria**			

Study details	Participants	Methods	Results	Comments
	• Patients with acute symptomatic seizures or seizures provoked by external factors such as alcohol withdrawal or sleep deprivation; • patients with types of seizures that could not be counted accurately, including typical absence, myoclonic and atonic seizures; • patients with types of seizures that have definitely high- or low recurrence risk, such as Lennox–Gastaut syndrome, West syndrome, juvenile myoclonic epilepsy and benign childhood epilepsy with centrotemporal spikes; • patients with an underlying malignancy, progressive or degenerative disease, or serious systemic illness; • pregnant and lactating women; • patients with incomplete documentation of seizure history • patients with either seizure clusters (at least three seizures occurring within 24 hours), or status epilepticus as these types of seizures are difficult to count and may have a different prognosis from the rest of the study population.			

Study details	Participants	Methods	Results	Comments
Full citation Tang, X., Yu, P., Ding, D., Ge, Y., Shi, Y., Wang, P., Zhu, G., Hong, Z., Risk factors for seizure reoccurrence after withdrawal from antiepileptic drugs in individuals who have been seizure-free for over 2 years, PLoS ONE, 12 (8) (no pagination), 2017 **Ref Id** 1247086 **Country/ies where the study was carried out** China **Study type** Retrospective observational study **Study dates** January 1, 2007 to March 2012 **Funding** Not reported	**Number** Total patients withdrawn from ASM N = 195 **Characteristics** Gender, n Male = 90 Female = 105 Age mean, year (SD) 29.66 (13.19) Age at onset, mean, year (SD) 18.23 (13.63) Age at drug withdrawal, Mean, year (SD) 25.89 (13.42) Cluster seizure within first 24 hours, n 10 Severity of epilepsy before onset of ASM treatment Seizure frequency, mean (SD) = 6.08 (4.02) Course of disease >6 months, % = 68 Epilepsy classification, n (%) Cryptogenic epilepsy = 50 (28.9) Idiopathic epilepsy = 73 (42.2) Symptomatic epilepsy = 50 (28.9) Abnormal EEG findings, n	**Follow-up duration** Follow-up period after ASM withdrawal, median (P25-P75), months Non-relapsed group = 24 (19.8) Period of time from ASM withdrawal to relapse Mean (SD), months 15.91 (2.71) **Statistical analysis** Cox regression model was used to perform multivariate analysis statistically significant variables associated with relapsed group or variables with clinical significance. No details on adjustment for confounders are reported.	**Results** Risk of seizure recurrence after drug withdrawal (reference category), aHR (95% CI) Received more than one ASM type (received only 1 ASM type) 2.53 (1.24 -5.16) Course of epilepsy longer than 6 months prior to initiation of ASM treatment (course of epilepsy shorter than 6 months prior to initiation of ASM treatment) 1.47 (1.004 - 2.15)	**Limitations** Methodological limitations assessed using the QUIPS Checklist **Study Participation**: Low risk (no areas of concern in this domain) **Study Attrition**: Low risk (no attrition, no area of concern in this domain) **Prognostic Factor Measurement**: Low risk (no definition of prognostic factors but unlikely to introduce substantial bias) **Outcome Measurement**: Moderate risk (unclear if method of measurement for all participants were the same, may likely introduce substantial bias) **Study Confounding**: Moderate risk (partial definition of confounders and unclear if method of measurement for all participants were the same, may likely introduce substantial bias) **Statistical Analysis and Reporting**: Low risk (only statistically significant results were reported, but unlikely to introduce substantial bias) **Overall Quality: Moderate**

Study details	Participants	Methods	Results	Comments
	114 Received more than one ASM, n 12 Completely seizure free after initiating ASMs, n 106 Change in ASM therapy, n 41 Seizure free period before drug withdrawal, mean, months (SD) 43.59 (25.26) **Inclusion criteria** • Between 14 and 80 years of age • History of seizures according to the 1981 classification system of the International League Against Epilepsy (ILAE1981) • Had received continuous treatment with a stable dose of one or two different ASMs • Reporting being seizure free for at least 2 years prior to drug withdrawal **Exclusion criteria** • Younger than 14 or older than 80 years			

Study details	Participants	Methods	Results	Comments
	• History of irregular ASM treatment.			

aHR: adjusted hazard ratio; aOR: adjusted odd ration; aRR: adjusted risk ratio; ASM: antiseizure medication; ATL: anterior temporal lobectomy; BECT: benign partial epilepsy with centrotemporal spikes; CI: confidence interval; CPS: complex partial seizures; CT: computerised tomography; EEG: electroencephalogram; GTCS: generalised tonic-clonic seizures; IED: interictal epileptiform discharges; ILAE: International League Against Epilepsy; IPD: individual population data; IQR: interquartile range; JME: juvenile myoclonic epilepsy; LD: learning disability; MRI: magnetic resonance imaging; MTS: mesial temporal sclerosis; QUIPS: Quality in Prognostic Studies; RCT: randomised controlled trial; SD: standard deviation; SPS: simple partial seizures; SPSS: statistical package for the social sciences; TTD: time to discontinuation; TTR: time to reduction

1 Appendix E – Forest plots

2 Forest plots for review question: What are the criteria for stopping antiseizure 3 medications in people with epilepsy?

4 No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F – Adapted GRADE tables

Clinical evidence profile tables for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

Medically treated population: age at epilepsy onset was mixed

Table 5: Clinical evidence profile for independent association between epilepsy signs and symptoms and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
≥10 seizures before remission (< 10 seizures before remission)	Seizure recurrence	1 (Lamberink 2017), 1769 participants	Systematic review and individual participant data (IPD) meta-analysis	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	aHR (95% CI) 1.38 (1.17 to 1.63)	⊕⊕OO LOW
History of febrile seizures (no history of febrile seizures)	Seizure recurrence	1 (Lamberink 2017), 1769 participants	Systematic review and IPD meta-analysis	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	aHR (95% CI) 1.40 (1.13 to 1.73)	⊕⊕OO LOW
Self-limiting epilepsy syndrome (absence of a self-limiting epilepsy syndrome)[b]	Seizure recurrence	1 (Lamberink 2017), 1769 participants	Systematic review and IPD meta-analysis	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	aHR 0.57 (0.44 to 0.72)	⊕⊕⊕O MODERATE
Multiple co-occurring seizure types (single seizure type)	Seizure recurrence	1 (Ou 2018), 161 participants	Retrospective cohort study	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[3]	None	aHR (95% CI) 2.55 (0.44 to 14.72)	⊕OOO VERY LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Seizures that were not controlled in the first 6 months of treatment (seizures that were controlled in first 6 onths)	Seizure recurrence	1 (Ou 2018), 161 participants	Retrospective cohort study	Serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 2.38 (1.11 to 5.10)	⊕⊕OO LOW

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[b] Formerly called "benign course", for example: absence epilepsy, benign epilepsy with centrotemporal spikes (rolandic epilepsy), Panayiotopoulos syndrome
[1] Population is indirect (3% of the included population presented with neonatal seizures)
[2] 95% CI crosses 1 MID (1.25)
[3]Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[4] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 6: Clinical evidence profile for independent association between epilepsy aetiology and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Perinatal injury (no perinatal injury)	Seizure recurrence	1 (Ou 2018), 161 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 3.73 (1.34 to 10.41)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1]Serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 7: Clinical evidence profile for independent association between epilepsy duration and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Course of epilepsy (onger than 6 months prior to initiating of antiseizure medication (ASM) treatment (course of epilepsy shorter than 6 months prior to initiating treatment)	Seizure recurrence	1 (Tang 2017), 195 participants	Retrospective observational study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 1.47 (1.00 to 2.15)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Table 8: Clinical evidence profile for independent association between time-related factors and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Early withdrawal of ASMs after 2-3 years seizure free (delayed withdrawal after 3 years seizure free)	Seizure recurrence	1 (Su 2013), 86 participants	Prospective observational cohort study	Serious[1]	No inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 0.99 (0.96 to 1.02)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 9: Clinical evidence profile for independent association between MRI and EEG investigations and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	**Outcome**	**Number of studies & participants**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[a] (95% CI)**	
Epileptiform EEG abnormalities before withdrawal (no epileptiform EEG abnormalities before withdrawal)	Seizure recurrence	1 (Lamberink 2017), 1769 participants	Systematic review and IPD meta-analysis	No serious risk of bias	No serious inconsistency	Serious[1]	No serious imprecision	None	aHR (95% CI) 1.50 (1.25 to 1.80)	⊕⊕⊕O MODERATE
Epileptiform EEG abnormalities after withdrawal (no epileptiform EEG abnormalities after withdrawal)	Seizure recurrence	1 (Su 2013), 86 participants	Prospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 4.810 (2.22 to 10.42)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] Population is indirect (3% of the included population presented with neonatal seizures)
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS

Table 10: Clinical evidence profile for independent association between anti-seizure medications and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Prior use of carbamazepine (CBZ) compared(prior use of any other ASM)	Remaining seizure free for 1 year	1 (Lossius 2008), 150 participants	RCT	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aOR (95% CI) 6.33 (1.23 to 32.25)	⊕⊕OO LOW
Prior use of CBZ (prior use of any other ASM)	Remaining seizure free for 41 months	1 (Lossius 2008), 150 participants	RCT	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aOR (95% CI) 2.86 (1.31 to 6.26)	⊕⊕⊕O MODERATE
Combination of ASMs (monotherapy)	Seizure recurrence	1 (Ou 2018), 161 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	aHR (95% CI) 1.90 (0.57 to 6.41)	⊕OOO VERY LOW
Received more than 1 ASM type (received only 1 ASM type)	Seizure recurrence	1 (Tang 2017), 195 participants	Retrospective observational study	Serious[2]	No inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 2.53 (1.24 to 5.16)	⊕⊕OO LOW

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] 95% CI crosses 1 MID (1.25)
Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[3] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 11: Clinical evidence profile for independent association between neurological and IQ-related factors and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Developmental delay (no evidence of developmental delay)	Seizure recurrence	1 (Lamberink 2017), 1769 participants	Systematic review and IPD meta-analysis	No serious risk of bias	No serious inconsistency	Serious[1]	Serious[2]	None	aHR (95% CI) 1.23 (1.01 to 1.50)	⊕⊕OO LOW
Normal neurological examination (abnormal neurological examination)	Remaining seizure free for 1 year	1 (Lossius 2008), 150 participants	RCT	Serious[3]	No serious inconsistency	No serious indirectness	Serious[2]	None	aOR (95% CI) 2.77 (1.18 to 142.86)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Population is indirect (3% of the included population presented with neonatal seizures)*
[2] *95% CI crosses 1 MID (1.25)*
[3] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2*

Medically treated population: those who were children at epilepsy onset

Table 12: Clinical evidence profile for independent association between epilepsy signs and symptoms and seizure recurrence

Quality assessment									Effect	
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	Quality
History of febrile convulsions in children with complex partial seizures (no history of febrile convulsions)	Seizure recurrence	1 (Braathen 1997), 161 participants	Retrospective cohort study	Very serious1	No serious inconsistency	No serious indirectness	Very serious2	None	aHR (95% CI) 0.28 (0.02 to 1.42)	⊕OOO VERY LOW
Seizure type: simple partial (unclear)	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious3	No serious inconsistency	No serious indirectness	Serious2	None	aRR (95% CI) 1.89 (0.96 to 3.71)	⊕⊕OO LOW
Seizure type: absences/spasms (unclear)	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious3	No serious inconsistency	No serious indirectness	Serious4	None	aRR (95% CI) 0.37 (0.14 to 0.92)	⊕⊕OO LOW
Interval between seizures < 1 month at disease onset (interval > 1 month at disease on-set) – patients with focal epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious3	No serious inconsistency	No serious indirectness	Serious5	None	aRR (95% CI) 3.33 (1.25 to 8.82)	⊕⊕OO LOW
Mean duration of seizures < 1 minute (mean duration of seizures > 1 minute) – patients with generalised epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious3	No serious inconsistency	No serious indirectness	Serious4	None	aRR (95% CI) 0.19 (0.03 to 0.96)	⊕⊕OO LOW
Seizure type: Generalisedb (rolandic)	Seizure recurrence	1 (Dooley 1996), 97 participants	Prospective cohort study	Serious3	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 2.99 (1.38 to 6.48)	⊕⊕⊕O MODERATE

Quality assessment									Effect	
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	Quality
Seizure type: partialb,c (rolandic)	Seizure recurrence	1 (Dooley 1996), 97 participants	Prospective cohort study	Serious3	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 8.92 (4.11 to 19.34)	⊕⊕⊕O MODERATE
Number of seizures before seizure control ≥ 5 (number of seizures before seizure control < 5)	Seizure recurrence	1 (Ohta 2004), 82 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious2	None	aHR (95% CI) 7.32 (0.65 to 82.44)	⊕⊕OO LOW
Complex partial seizure (simple partial seizure, secondarily generalised seizure)	Seizure recurrence	1 (Ohta 2004), 82 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious2	None	aHR (95% CI) 3.50 (0.60 to 20.35)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[b] *Benign rolandic seizures is the reference category*
[c] *Partial seizures which combined both simple and partial seizures*
[1] *Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[3] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[4] *95% CI crosses 1 MID (0.8)*
[5] *95% CI crosses 1 MID (1.25)*

Table 13: Clinical evidence profile for independent association between epilepsy aetiology and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Pathological neonatal period (normal neonatal period) – patients with generalised epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR (95% CI) 1.34 (1.09 to 1.65)	⊕⊕OO LOW
Electroclinical classification (genetic/structural-metabolic and unknown)	Seizure recurrence	1 (Karalok 2020), 284 participants	Retrospective cohort study	Serios[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 2.15 (1.21 to 3.82)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Table 14: Clinical evidence profile for independent association between time-related factors and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Duration of ASM withdrawal < 6 months (duration of ASM withdrawal > 6 months)	Recurrence rate	1 (Altunbasak 1999), 97 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR (95% CI) 0.21 (0.04 to 0.95)	⊕⊕OO LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	**Outcome**	**Number of studies & participants**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[a] (95% CI)**	
Duration of ASM withdrawal < 6 months (duration of ASM withdrawal > 6 months)	Recurrence time	1 (Altunbasak 1999), 97 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR (95% CI) 0.27 (0.07 to 0.92)	⊕⊕OO LOW
Duration of treatment < 1 year (duration of treatment > 1 year)	Recurrence rate	1 (Braathen 1997), 161 participants	Retrospective cohort study	Very serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 0.35 (0.19 to 0.62)	⊕⊕OO LOW
Seizure-free time <3 years (seizure-free time > 3 years)	Seizure recurrence	1 (Karalok 2020), 284 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	aHR (95% CI) 2.62 (1.17 to 5.88)	⊕⊕OO LOW
Time from start of ASM treatment to seizure control ≥ 5 years (time from start of ASM treatment to seizure control < 5 years)	Seizure recurrence	1 (Ohta 2004), 82 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 9.85 (1.33 to 73.05)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] Serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] 95% CI crosses 1 MID (0.8)
[3] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[4] 95% CI crosses 1 MID (1.25)

Table 15: Clinical evidence profile for independent association between MRI and EEG investigations and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Irregular spike-wave after 1 year of treatment (regular spike wave)	Recurrence rate	1 (Braathen 1997), 161 participants	Retrospective cohort study	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 3.09 (1.47 to 6.27)	⊕⊕OO LOW
3-Hz spike wave activity on EEG after 6 months of treatment (no 3-Hz spike wave activity)	Recurrence rate	1 (Braathen 1997), 161 participants	Retrospective cohort study	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 7.15 (2.01 to 20.00)	⊕⊕OO LOW
Abnormal EEG prior to withdrawal (normal EEG prior to withdrawal) – patients with focal epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	aRR (95% CI) 2.21 (0.96 to 5.06)	⊕⊕OO LOW
Location of paroxystic activity: frontal (unclear) - all patients	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	aRR (95% CI) 3.89 (1.23 to 12.29)	⊕⊕OO LOW
Location of paroxystic activity: frontal (unclear) – patients with focal epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 6.50 (1.89 to 22.29)	⊕⊕OO LOW
Location of paroxystic activity: parietal (unclear) – all patients	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	aRR (95% CI) 2.86 (1.23 to 6.69)	⊕⊕OO LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Generalised groups of irregular spike-wave in EEG (unclear) – patients with generalised epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 19.42 (3.63 to 103.67)	⊕⊕OO LOW

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] Serious risk of bias in the evidence contributing to the outcomes as per QUIP
[3] 95% CI crosses 1 MID (1.25)

Table 16: Clinical evidence profile for independent association between diagnostics and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Diagnostics class 1[b] (diagnostic classes 2 and 3	Recurrence rate	1 (Braathen 1997), 161 participants	Retrospective cohort study	Very serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 2.75 (1.47 to 6.27)	⊕⊕OO LOW
Focal epilepsy (generalised)	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 3.09 (1.72 to 5.54)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk

[b] *'diagnostic class' in the multivariate analysis, diagnostic class 1 (benign partial epilepsy with centrotemporal [rolandic] spikes [BECT] and simple partial seizures [SPS]) and diagnostic class 2 (primarily generalised tonic-clonic seizures [GTCS], GTCS during the night, autoimmune epilepsy, and GTCS as the only ictal manifestation in children with rolandic spikes) were compared with diagnostic class 3 (complex partial seizures [CPS])*
[1] *Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*

Table 17: Clinical evidence profile for independent association between anti-seizure medications and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	**Outcome**	**Number of studies & participants**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[a] (95% CI)**	
Valproate administered (carbamazepine, phenobarbitone or primidone, phenytoin) – all patients	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 3.48 (1.87 to 6.46)	⊕⊕⊕O MODERATE
Carbamazepine administered (phenobarbitone or primidone, phenytoin, valproate) – patients with focal epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[1]	None	aRR (95% CI) 0.46 (0.17 to 1.22)	⊕⊕⊕O MODERATE
Valproate administered (car-bamazepine, phenobarbitone or primidone, phenytoin) – patients with focal epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 3.31 (1.41 to 7.72)	⊕⊕⊕O MODERATE

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (0.8)*

Table 18: Clinical evidence profile for independent association between demographic factors and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Age at seizure onset > 2 years (age of seizure onset < 2 years)	Recurrence rate	1 (Altunbasak 1999), 97 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 7.42 (1.30 to 42.2)	⊕⊕OO LOW
Age at seizure onset > 2 years (age of seizure onset < 2 years)	Recurrence time	1 (Altunbasak 1999), 97 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 6.82 (1.41 to 33)	⊕⊕OO LOW
Favourable age at seizure onset[b]	Recurrence rate	1 (Braathen 1997), 161 participants	Retrospective cohort study	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	aHR (95% CI) 0.28 (0.02 to 1.42)	⊕OOO VERY LOW
Age > 10 years at first seizure (age < 10 years at first seizure) – patients with generalised epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 1.03 (1.01 to 1.06)	⊕⊕OO LOW
Age >5 years at onset of withdrawal (age < 5 years at onset of withdrawal) – all patients	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	aRR (95% CI) 1.25 (1.12 to 1.39)	⊕⊕OO LOW
Female (male)	Seizure recurrence	1 (Dooley 1996), 97 participants	Prospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 3.82 (1.73 to 8.44)	⊕⊕⊕O MODERATE
Age at seizure onset > 120 months	Seizure recurrence	1 (Dooley 1996), 97 participants	Prospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 5.64 (2.38 to 13.34)	⊕⊕⊕O MODERATE

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Age at onset of epilepsy ≥ 6 years (age at onset < 6 years)	Seizure recurrence	1 (Ohta 2004), 82 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 19.24 (1.83 to 202.44)	⊕⊕⊕O MODERATE

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[b] *Favourable age at seizure onset was defined as: >10 years for children with rolandic epilepsies and <10 years for children with other seizure types*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[3] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[4] *95% CI crosses 1 MID (1.25)*

Table 19: Clinical evidence profile for independent association between neurological/IQ factors and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Abnormal neurological examination (normal neurological examination) – all patients	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR (95% CI) 2.59 (1.22 to 5.51)	⊕⊕OO LOW
Abnormal neurological examination (normal neurological examination) – patients with focal epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 3.67 (1.61 to 8.36)	⊕⊕OO LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	**Outcome**	**Number of studies & participants**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[a] (95% CI)**	
Poor school progress (good school progress) – all patients	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR (95% CI) 1.28 (1.06 to 1.53)	⊕⊕OO LOW
Poor school progress (good school progress) – patients with generalised epilepsy only	Seizure recurrence	1 (Caviedes 1998), 226 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR (95% CI) 2.01 (1.22 to 3.31)	⊕⊕OO LOW
Neurological abnormalities (no neurological abnormalities)	Seizure recurrence	1 (Dooley 1996), 97 participants	Prospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aRR (95% CI) 2.98 (1.34 to 6.65)	⊕⊕⊕O MODERATE

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Surgically treated population; age at epilepsy onset was not reported/ mixed

Table 20: Clinical evidence profile for independent association between epilepsy signs and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Delayed remission after hospital discharge (immediate remission)	Seizure recurrence	1 (Berg 2006), 291 participants	Prospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR[b] (95% CI) 2.26 (1.15 to 4.48)	⊕⊕OO LOW
Continued auras, after adjustment for delayed remission following hospital discharge (no persistent auras)	Seizure recurrence	1 (Berg 2006), 291 participants	Prospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aRR[b] (95% CI) 2.06 (0.95 to 4.49)	⊕⊕OO LOW
Seizure recurrence before ASM reduction (no seizure recurrence before ASM reduction)	Seizure recurrence	1 (Park 2010), 223 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 2.43 (1.37 to 4.31)	⊕⊕⊕O MODERATE

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[b] *Rate ratio*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Table 21: Clinical evidence profile for independent association between epilepsy duration and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Epilepsy duration >11 years (≤11 years)	Seizure recurrence	1 (Park 2010), 223 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 1.75 (1.09 to 2.81)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Table 22: Clinical evidence profile for independent association between MRI and EEG investigations and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Normal MRI results (abnormal MRI)	Seizure recurrence	1 (Park 2010), 223 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 1.96 (1.15 to 3.34)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Table 23: Clinical evidence profile for independent association between ASMs and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Time to ASM reduction <9 months (≥ 9 months)	Seizure recurrence	1 (Park 2010), 223 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 2.83 (1.62 to 4.94)	⊕⊕⊕O MODERATE
Preoperative number of ASMs (unclear)[b]	Seizure recurrence	1 (Park 2010), 223 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 1.21 (0.93 to 1.57)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[b] *In the group of people who relapsed, n=10 took 1 ASM preoperatively; n=30 took 2 ASMs preoperatively; n=38 took ≥3 ASMs preoperatively. In the group of people who did not relapse, n=19 took 1 ASM; n=24 took 2 ASMs; n=26 took ≥3 ASMs*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Table 24: Clinical evidence profile for independent association between type of surgery and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Incomplete resection (complete resection)	Seizure recurrence	1 (Park 2010), 223 participants	Retrospective cohort study	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 1.62 (0.91 to 2.89)	⊕⊕OO LOW

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *Serious risk of bias in the evidence contributing to the outcomes as per QUIPS*
[2] *95% CI crosses 1 MID (1.25)*

Surgically treated population; those who were children at epilepsy onset

Table 25: Clinical evidence profile for independent association between epilepsy signs and symptoms and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Immediate postoperative seizure freedom (delayed seizure freedom)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 0.58 (0.29 to 1.14)	⊕⊕⊕O MODERATE
Epileptic abnormalities on postoperative EEG findings (no evidence of epileptic ab-normalities in postoperative EEG)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	aHR (95% CI) 1.84 (1.15 to 2.96)	⊕⊕⊕O MODERATE
Proven incomplete resection of the anatomical lesion (Proven complete resection of anatomical lesion)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 2.61 (1.58 to 4.33)	⊕⊕⊕⊕ HIGH
Immediate postoperative seizure freedom (delayed seizure freedom)	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 444 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	none	aHR (95% CI) 2.47 (0.31 to 19.7)	⊕⊕OO LOW
Epileptic abnormalities on postoperative EEG findings (no evidence of epileptic ab-normalities in	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 444 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	none	aHR (95% CI) 0.95 (0.36 to 2.51)	⊕⊕OO LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
postoperative EEG)										
Seizure recurrence before attempted ASM withdrawal (no seizure recurrence before attempted ASM withdrawal)	Seizure recurrence	1 (Rathore 2011), 258 participants	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	none	aOR (95% CI) 1.70 (0.89 to 2.36)	⊕⊕⊕O MODERATE

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *95% CI crosses 1 MID (0.8)*
[2] *95% CI crosses 1 MID (1.25)*
[3] *95% CI crosses 2 MIDs (0.8 and 1.25)*

Table 26: Clinical evidence profile for independent association between epilepsy aetiology and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Epilepsy aetiology (malformations of cortical development)[b]	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 0.97 (0.81 to 1.15)	⊕⊕⊕⊕ HIGH
Epilepsy aetiology[b]	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 444 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 0.70 (0.48 to 1.03)	⊕⊕⊕O MODERATE

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Absence of definitive hippocampal sclerosis (HS) on pathology (presence of definitive hippocampal sclerosis on pathology)	Seizure recurrence	1 (Rathore 2011), 258 participants	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	aOR (95% CI) 2.34 (1.02 to 5.38)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[b] Focal cortical dysplasia was used as the reference category to compare it with tumour, vascular pathology, hippocampal sclerosis, Rasmussen's encephalitis, other
[1] 95% CI crosses 1 MID (0.8)
[3] 95% CI crosses 1 MID (1.25)

Table 27: Clinical evidence profile for independent association between epilepsy duration and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Longer preoperative duration of epilepsy (shorter preoperative duration of epilepsy)	Seizure recurrence	1 (Menon 2012), 94 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aOR (95% CI) 1.07 (1.01 to 1.14)	⊕⊕⊕⊕ HIGH
Epilepsy duration ≥ 20 years (epilepsy duration < 20 years)	Seizure recurrence	1 (Rathore 2011), 258 participants	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aOR (95% CI) 1.65 (0.79 to 3.45)	⊕⊕⊕O MODERATE

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk

[1] *95% CI crosses 1 MID (1.25)*

Table 28: Clinical evidence profile for independent association between time-related factors and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Shorter time interval from surgery to start of ASM reduction, per 3 months (longer time from surgery to start of ASM discontinuation)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 0.94 (0.89 to 1)	⊕⊕⊕⊕ HIGH
Shorter time interval from surgery to complete ASM discontinuation, per 3 months (longer time from surgery to complete ASM discontinuation)	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 0.90 (0.83 to 0.98)	⊕⊕⊕⊕ HIGH

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*

Table 29: Clinical evidence profile for independent association between EEG and MRI investigations and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other considerations	Relative[a] (95% CI)	
Multifocal MRI lesions (no evidence of multifo-cal MRI lesions)	Seizure recur-rence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 2.27 (1.23 to 4.20)	⊕⊕⊕O MODERATE
Postoperative electroen-cephalogram (EEG) findings (unclear)	Seizure recur-rence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Very serious[2]	None	aHR (95% CI) 1.04 (0.78 to 1.39)	⊕⊕OO LOW
No EEG performed post-operatively (no evidence of epileptic abnormalities in postoperative EEG)	Seizure recur-rence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Very serious[2]	None	aHR (95% CI) 0.80 (0.37 to 1.73)	⊕⊕OO LOW
Postoperative EEG find-ings (unclear)	Seizure recur-rence in those with ASM discontin-uation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Serious[3]	None	aHR (95% CI) 0.71 (0.41 to 1.25)	⊕⊕⊕O MODERATE
No EEG performed post-operatively (no evidence of epileptic ab-normali-ties in postoperative EEG)	Seizure recur-rence in those with ASM discontin-uation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Very serious[2]	None	aHR (95% CI) 0.41 (0.09 to 1.81)	⊕⊕OO LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirect-ness	Imprecision	Other considerations	Relative[a] (95% CI)	
Interictal epileptiform discharges (IEDs) on 1-year postoperative EEG (no interictal epileptiform discharges on 1-year postoperative EEG)	Seizure recur-rence	1 (Menon 2012), 94 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Serious[1]	None	aOR (95% CI) 3.12 (1.20 to 8.08)	⊕⊕⊕O MODERATE
IEDs on 1-year anterior temporal lobectomy (ATL) EEG (absence of IEDs on 1-year ATL EEG)	Seizure recur-rence	1 (Rathore 2011) 258 participants	Prospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Serious[1]	None	aOR (95% CI) 2.23 (1.01 to 5)	⊕⊕⊕O MODERATE

[a] *Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk*
[1] *95% CI crosses 1 MID (1.25)*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25)*
[3] *95% CI crosses 1 MID (0.8)*

Table 30: Clinical evidence profile for independent association between ASMs and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors exam-ined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Number of ASMs used at time of surgery (unclear)	Seizure recur-rence in those with ASM reduc-tion	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Very serious[1]	None	aOR (95% CI) 0.98 (0.75 to 1.27)	⊕⊕OO LOW
Number of ASMs used at time of surgery (unclear)	Seizure recur-rence in those	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious in-consistency	No serious indirectness	Serious[2]	None	aOR (95% CI) 0.71 (0.42 to 1.20)	⊕⊕⊕O MODERATE

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	**Outcome**	**Number of studies & participants**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[a] (95% CI)**	
	with ASM discontinuation									
ASMs discontinued ≤ 6 months after surgery (ASMs discontinued > 6 months after surgery)	Seizure recurrence	1 (Lachhwani 2008), 97 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 5.8 (1.8 to 17.5)	⊕⊕⊕⊕ HIGH
ASMs discontinued ≤ 12 months after surgery (ASMs discontinued > 12 months after surgery)	Seizure recurrence	1 (Lachhwani 2008), 97 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[3]	None	aHR (95% CI) 1.4 (0.85 to 6.7)	⊕⊕⊕O MODERATE
ASMs discontinued ≤ 24 months after surgery (ASMs discontinued > 24 months after surgery)	Seizure recurrence	1 (Lachhwani 2008), 97 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	aHR (95% CI) 1.3 (0.4 to 3.8)	⊕⊕OO LOW

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] 95% CI crosses 2 MIDs (0.8 and 1.25)
[2] 95% CI crosses 1 MID (0.8)
[3] 95% CI crosses 1 MID (1.25)

Table 31: Clinical evidence profile for independent association between type of surgery and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Type of surgery (unclear)[b]	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 1.16 (0.85 to 1.60)	⊕⊕⊕O MODERATE
Type of surgery: hemispherectomy (lobar resection)[c]	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 2.28 (1.03 to 5.04)	⊕⊕⊕O MODERATE
Type of surgery: multilobar resection (lobar resection)[c]	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 1.70 (0.85 to 3.43)	⊕⊕⊕O MODERATE
Resection of the anatomical lesion (unclear)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 1.22 (0.96 to 1.56)	⊕⊕⊕O MODERATE
Proven incomplete resection of the anatomical lesion (proven complete resection of anatomical lesion)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 2.61 (1.58 to 4.33)	⊕⊕⊕⊕ HIGH
Type of surgery (unclear)[b]	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	aHR (95% CI) 0.80 (0.41 to 1.57)	⊕⊕OO LOW
Type of surgery: hemispherectomy (lobar resection)[c]	Seizure recurrence in those	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	aHR (95% CI) 1.84 (0.45 to 7.57)	⊕⊕OO LOW

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	**Outcome**	**Number of studies & participants**	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Relative[a] (95% CI)**	
	with ASM discontinuation									
Type of surgery: multilobar resection (lobar resection)[c]	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	aHR (95% CI) 0.82 (0.18 to 3.77)	⊕⊕OO LOW
Resection of the anatomical lesion (unclear)	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 1.30 (0.88 to 1.94)	⊕⊕⊕O MODERATE
Proven incomplete resection of the anatomical lesion (proven complete resection of the anatomical lesion)	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	aHR (95% CI) 4.9 (2.08 to 11.52)	⊕⊕⊕⊕ HIGH
Age at anterior temporal lobectomy ≥ 30 years (age at anterior temporal lobectomy < 30 years)	Seizure recurrence	1 (Rathore 2011) 258 participants	Prospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	None	aOR (95% CI) 1.38 (0.65 to 2.92)	⊕⊕OO LOW

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[b] Type of surgery was classified as lobar (including tailored) resection, multilobar resection, or hemispherectomy
[c] Reference group is lobar resection subclassified as frontal, temporal, parietal and occipital
[1] 95% CI crosses 1 MID (1.25)
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Table 32: Clinical evidence profile for independent association between previous interventions and seizure recurrence

Quality assessment									Effect	Quality
Potential risk factors examined (reference category)	Outcome	Number of studies & participants	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative[a] (95% CI)	
Previous surgery (no previous surgery)	Seizure recurrence in those with ASM reduction	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	aHR (95% CI) 2.28 (1.02 to 5.10)	⊕⊕⊕O MODERATE
Previous surgery (no previous surgery)	Seizure recurrence in those with ASM discontinuation	1 (Boshuisen 2012), 766 participants	Retrospective cohort study	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[2]	none	aHR (95% CI) 2.65 (0.61 to 11.6)	⊕⊕OO LOW

[a] Adjusted relative estimates and 95% CIs >1 represent an increased risk; relative estimates and 95% CIs <1 represent a decreased risk
[1] 95% CI crosses 1 MID (1.25)
[2] 95% CI crosses 2 MIDs (0.8 and 1.25)

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

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

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

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

Appendix J – Economic analysis

Economic evidence analysis for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

Clinical studies

Table 33: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Aidaros, M. A., Siam, A. G., Effect of the Duration of Withdrawal of Antiepileptic Drugs on the Risk of Seizure Recurrence in Childhood Epilepsy, Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 47, 593-598, 2010	Method of analysis does not meet inclusion criteria - no multivariate analysis
Aldenkamp, A. P., Alpherts, W. C. J., Blennow, G., Elmqvist, D., Heijbel, J., Nilsson, H. L., Sandstedt, P., Tonnby, B., Wahlander, L., Wosse, E., Withdrawal of antiepileptic medication in children - Effects on cognitive function: The multicenter Holmfrid study, Neurology, 43, 41-50, 1993	No outcome of interest
Anonymous,, Prognostic index for recurrence of seizures after remission of epilepsy. Medical Research Council Antiepileptic Drug Withdrawal Study Group, BMJ, 306, 1374-8, 1993	This study included the same population as MRC 1991, study included in Lamberink 2017
Anonymous,, Antiepileptic drug withdrawal in children, Prescrire International, 20, 245, 2011	Method of analysis does not meet inclusion criteria - no multivariate analysis
Arts, W. F. M., Visser, L. H., Loonen, M. C. B., Tjiam, A. T., Stroink, H., Stuurman, P. M., Poortvliet, D. C. J., Follow-up of 146 children with epilepsy after withdrawal of antiepileptic therapy, Epilepsia, 29, 244-250, 1988	No relevant summary statistics were reported
Ayuga Loro, F., Gisbert Tijeras, E., Brigo, F., Rapid versus slow withdrawal of antiepileptic drugs, The Cochrane database of systematic reviews, 1, CD005003, 2020	Systematic review - relevant studies (Serra 2005, Tennison 1994) are included in Lamberink 2017
Azar, N. J., Lagrange, A. H., Wang, L., Song, Y., Abou-Khalil, B. W., Transient improvement after brief antiepileptic drug withdrawal in the epilepsy monitoring unit - possible relationship to AED tolerance, Epilepsia, 51, 811-817, 2010	Very short follow-up; patients were assessed in an epilepsy monitoring unit
Berg, A. T., Shinnar, S., Relapse following discontinuation of antiepileptic drugs: A meta-analysis, Neurology, 44, 601-608, 1994	Systematic review which combined studies reporting risk factors from multivariate and univariate analysis. Studies were checked for inclusion
Bouma, P. A. D., Peters, A. C. B., Brouwer, O. F., Long term course of childhood epilepsy following relapse after antiepileptic drug withdrawal, Journal of Neurology Neurosurgery and Psychiatry, 72, 507-510, 2002	No relevant summary statistics were reported, only p-values were provided as part of the multivariate results
Callaghan, N., Garrett, A., Coggin, T., Withdrawal of anticonvulsant drugs in patients free of seizures for two years. A prospective study, New England Journal of Medicine, 318, 942-946, 1988	Unclear method of reporting results; relative risks were reported, but 95% CI were not provided
Chadwick, D., Does withdrawal of different antiepileptic drugs have different effects on seizure	This study included the same population as MRC 1991, study included in Lamberink 2017

Study	Reason for Exclusion
recurrence? Further results from the MRC Antiepileptic Drug Withdrawal Study, Brain, 122, 441-8, 1999	
Creed, J. A., Son, J., Farjat, A. E., Swisher, C. B., Early withdrawal of non-anesthetic antiepileptic drugs after successful termination of non-convulsive seizures and nonconvulsive status epilepticus, Seizure, 54, 45-50, 2018	Population does not meet inclusion criteria
Duncan, J. S., Shorvon, S. D., Trimble, M. R., Withdrawal symptoms from phenytoin, carbamazepine and sodium valproate, Journal of Neurology Neurosurgery and Psychiatry, 51, 924-928, 1988	No outcome of interest
Duncan, J. S., Shorvon, S. D., Trimble, M. R., Discontinuation of phenytoin, carbamazepine, and valproate in patients with active epilepsy, Epilepsia, 31, 324-333, 1990	Method of analysis does not meet inclusion criteria - no multivariate analysis
Emerson, R., D'Souza, B. J., Vinning, E. P., Stopping medication in children with epilepsy. Predictors of outcome, New England Journal of Medicine, 304, 1125-1129, 1981	No relevant summary statistics were reported, only p-values were provided as part of the multivariate results
Galimberti, C. A., Manni, R., Parietti, L., Marchioni, E., Tartara, A., Drug withdrawal in patients with epilepsy: prognostic value of the EEG, Seizure : the journal of the British Epilepsy Association, 2, 213-220, 1993	No relevant summary statistics were reported â□“ study reported regression coefficients and P-values
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	No results - methods of study described.
Hessen, E., Lossius, M. I., Reinvang, I., Gjerstad, L., Influence of major antiepileptic drugs on attention, reaction time, and speed of information processing: Results from a randomized, double-blind, placebo-controlled withdrawal study of seizure-free epilepsy patients receiving monotherapy, Epilepsia, 47, 2038-2045, 2006	No outcomes of interest
Hessen, E., Lossius, M. I., Reinvang, I., Gjerstad, L., Improvement in speeded cognitive processing after anti-epileptic drug withdrawal - A controlled study in mono-therapy patients, Progress in Neurotherapeutics and Neuropsychopharmacology, 3, 199-209, 2008	No outcome of interest
Incecik, F., Herguner, O. M., Altunbasak, S., Mert, G., Kiris, N., Risk of recurrence after discontinuation of antiepileptic drug therapy in children with epilepsy, Journal of Pediatric Neurosciences, 9, 100-104, 2014	No relevant summary statistics were reported
Kudo, T., Amano, K., Yagi, K., Seino, M., A retrospective study on discontinuation of antiepileptic drugs following seizure remission, Japanese Journal of Psychiatry & Neurology, 48, 249-53, 1994	Method of analysis does not meet inclusion criteria

Study	Reason for Exclusion
Kudo, T., Nishida, T., Yagi, K., Discontinuation and duration of antiepileptic drug therapy: a retrospective study of factors for specific epileptic syndromes, Epilepsia, 45 Suppl 8, 26-32, 2004	Method of analysis does not meet inclusion criteria
Lamberink, H. J., Otte, W. M., Geleijns, K., Braun, K. P., Antiepileptic drug withdrawal in medically and surgically treated patients: a meta-analysis of seizure recurrence and systematic review of its predictors, Epileptic disorders : international epilepsy journal with videotape, 17, 211-228, 2015	Systematic review - risk factors for relapse in people with epilepsy were reported, but only the number of studies showing significance were reported and no relevant summary statistics were provided. Studies were checked for inclusion
Matricardi, M., Brinciotti, M., Benedetti, P., Outcome after discontinuation of antiepileptic drug therapy in children with epilepsy, Epilepsia, 30, 582-589, 1989	No relevant summary statistics were reported â□“ study reported regression coefficients and P-values
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	No outcome of interest
Peters, A. C. B., Brouwer, O. F., Geerts, A. T., Arts, W. F. M., Stroink, H., Van Donselaar, C. A., Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy, Neurology, 50, 724-730, 1998	No relevant summary statistics were reported
Rana, R., Das, S., Ramesh, S., Chidambaramnathan, S., Swami, A., Singh, A., Seizure relapse based upon withdrawal period of antiepileptic drugs in pediatric epilepsy patients, Archives of Pharmacy Practice, 5, 118-124, 2014	Study design does not meet inclusion criteria - narrative review
Ranganathan, L. N., Ramaratnam, S., Rapid versus slow withdrawal of antiepileptic drugs, Cochrane Database of Systematic Reviews, 2006	Systematic review- the only relevant study (Tennison 1994) is included in Lamberink 2017
Sillanpaa, M., Schmidt, D., Prognosis of seizure recurrence after stopping antiepileptic drugs in seizure-free patients: A long-term population-based study of childhood-onset epilepsy, Epilepsy and Behavior, 8, 713-719, 2006	Method of analysis does not meet inclusion criteria
Sirven, J. I., Sperling, M., Wingerchuk, D. M., Early versus late antiepileptic drug withdrawal for people with epilepsy in remission, Cochrane database of systematic reviews (Online), CD001902, 2001	Systematic review â□“ The included studies do not assess risk factors in relation to the outcomes of interest. These evaluate whether an early AED withdraw is more beneficial than a late withdraw, therefore reported outcomes are not relevant for inclusion
Specchio, L. M., Beghi, E., Should antiepileptic drugs be withdrawn in seizure-free patients?, CNS Drugs, 18, 201-212, 2004	Study design does not meet inclusion criteria - narrative review
Strozzi, I., Nolan, S. J., Sperling, M. R., Wingerchuk, D. M., Sirven, J., Early versus late antiepileptic drug withdrawal for people with epilepsy in remission, The Cochrane database of systematic reviews, 2, CD001902, 2015	Systematic review â□“ The included studies do not assess risk factors in relation to the outcomes of interest. These evaluate whether an early AED withdraw is more beneficial than a late withdraw, therefore reported outcomes are not relevant for inclusion

Study	Reason for Exclusion
Thurston, J. H., Thurston, D. L., Hixon, B. B., Keller, A. J., Prognosis in childhood epilepsy. Additional follow-up of 148 children 15 to 23 years after withdrawal of anticonvulsant therapy, New England Journal of Medicine, 306, 831-836, 1982	No relevant summary statistics were reported, only p-values were provided as part of the multivariate results
Van Schooneveld, M. M. J., Van Erp, N., Boshuisen, K., Meekes, J., Braun, K. P. J., Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery, Epilepsy Research, 107, 200-203, 2013	No outcome of interest
Yardi, R., Irwin, A., Kayyali, H., Gupta, A., Nair, D., Gonzalez-Martinez, J., Bingaman, W., Najm, I. M., Jehi, L. E., Reducing versus stopping antiepileptic medications after temporal lobe surgery, Annals of Clinical and Translational Neurology, 1, 115-123, 2014	No relevant summary statistics were reported, only p-values were provided as part of the multivariate results
Zhang, L., Jiang, X. Y., Zhou, D., Zhang, H., Bao, S. M., Li, J. M., Postoperative seizure outcome and timing interval to start antiepileptic drug withdrawal: A retrospective observational study of non-neoplastic drug resistant epilepsy, Scientific reports, 8, 13782, 2018	Method of analysis does not meet inclusion criteria - no multivariate analysis for population of interest

Economic studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix L – Research recommendations

Research recommendations for review question: What are the criteria for stopping antiseizure medications in people with epilepsy?

No research recommendations were made for this review question.