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[Intervention Review]

Rapid versus slow withdrawal of antiepileptic drugs

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ABSTRACT

Background

The ideal objective of treating a person with epilepsy is to induce remission (free of seizures for some time) using antiepileptic drugs (AEDs) and withdraw the AEDs without causing seizure recurrence. Prolonged usage of AEDs may have long-term adverse effects. Hence, when a person with epilepsy is in remission, it is logical to attempt to discontinue the medication. The timing of withdrawal and the mode of withdrawal arise while contemplating withdrawal of AEDs. This review examines the evidence for the rate of withdrawal of AEDs (whether rapid or slow tapering) and its effect on seizure recurrence.

This is an updated version of the original Cochrane Review published in 2006, Issue 2.

Objectives

To quantify risk of seizure recurrence after rapid (tapering period of three months or less) or slow (tapering period of more than three months) discontinuation of antiepileptic drugs in adults and children with epilepsy who are in remission, and to assess which variables modify the risk of seizure recurrence.

Search methods

For the latest update, on 9 April 2019, we searched: Cochrane Register of Studies (CRS Web, which includes the Cochrane Epilepsy Group Specialized Register, CENTRAL, and ClinicalTrials.gov), MEDLINE (Ovid; 8 April 2019), the WHO International Clinical Trials Registry Platform, and SCOPUS. There were no language restrictions.

Selection criteria

Randomized controlled trials that evaluate withdrawal of AEDs in a rapid or slow tapering after varying periods of seizure control in people with epilepsy.

Data collection and analysis

Review authors independently assessed the trials for inclusion and extracted the data. The outcomes assessed included seizure freedom after one, two, or five years of AED withdrawal; time to recurrence of seizure following withdrawal; occurrence of status epilepticus; mortality; morbidity due to seizure, such as injuries, fractures, and aspiration pneumonia; and quality of life (assessed by validated scale).

Main results

In this review update, we have included one new study. The new study randomized 57 children with epilepsy with seizure freedom for at least two years to taper the AED during over one or six months. The study was not blinded and there were no details of randomization. Over the period of 54 months of follow-up, 20/30 participants in the one-month group remained seizure-free compared to 15/27 participants

in the six-month group (no evidence of a difference). There was no information on time of seizure recurrence for each group to allow a comparison.

One trial had already been included in the previous version of the review; it involved 149 children. There was a non-significant trend toward a lower risk of seizure recurrence after one year of AED withdrawal in participants allocated to slow tapering (risk ratio (RR) 0.76, 95% confidence interval (CI) 0.58 to 1.01; $P = 0.06$; very low-certainty evidence). At the end of two years, 30 participants were seizure free in the rapid-tapering group and 29 participants in the slow-tapering group (RR 0.87, 95% CI 0.58 to 1.29; $P = 0.48$; very low-certainty evidence). At the end of five years, 10 participants were seizure free in the rapid-tapering group and six participants in the slow-tapering group (RR 1.40, 95% CI 0.54 to 3.65; $P = 0.49$; very low-certainty evidence). There were no data for the other outcomes.

Due to the methodological heterogeneity and the difference in the duration of tapering we did not perform a quantitative synthesis of these studies.

Authors' conclusions

Since the last version of this review was published, we found one new pediatric study. In view of methodological deficiencies, and small sample size of the two included studies, we cannot draw any reliable conclusions regarding the optimal rate of tapering of AEDs. Using GRADE, we assessed the certainty of the evidence as very low for outcomes for which data were available. We judged both studies to be at high risk of bias.

Further studies are needed in adults and children to investigate the optimal rate of withdrawal of AEDs and to study the effects of variables such as seizure types, etiology, mental retardation, electroencephalography abnormalities, presence of neurologic deficits, and other comorbidities on the rate of tapering.

PLAIN LANGUAGE SUMMARY

Rapid versus slow withdrawal of antiepileptic medicines

Background

Epilepsy is a disorder where recurrent seizures (fits) are caused by abnormal electrical discharges of the brain. Antiepileptic medicines are used to prevent these seizures. Regular intake of antiepileptic medicines may have long-term side effects. When in remission (free of seizures for some time), it is logical to attempt to stop the medicines. Two important issues are how and when to stop them.

Aim of the review

This review analyzed the various studies for evidence regarding rapidity of withdrawal of antiepileptic medicines. We included randomized controlled trials evaluating the rapid or slow withdrawal (tapering down) of these medicines after varying periods of seizure control in people with epilepsy.

Results

We included only two small studies conducted in 206 children with epilepsy. The included studies found no difference in the proportion of participants remaining seizure-free between the rapid and the slow-tapering groups at different time points. There were no data for other measures such as status epilepticus (a long seizure), death, illness relating to seizures, and quality of life. We found no completed trials investigating antiepileptic medicine withdrawal in adults.

Currently, one Italian trial is ongoing that is investigating if a slow or a rapid withdrawal schedule of antiepileptic medicine influences return of seizures (relapse) in adults with focal or generalized epilepsy who have been seizure free for at least two years (no preliminary results available).

Reliability of the evidence

Evidence from the two included studies was of very low reliability. Both studies were conducted in a small number of participants and there were not enough data to detect a difference between the groups. Furthermore, they included only children, hence the results cannot be generalized to adults. Therefore, no reliable evidence is currently available on the optimal rate of tapering of antiepileptic medicines.

The evidence is current to April 2019.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Rapid versus slow withdrawal of antiepileptic drugs

Rapid versus slow withdrawal of antiepileptic drugs

Patient or population: epilepsy

Setting: outpatients

Intervention: rapid AED withdrawal

Comparison: slow AED withdrawal

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with slow AED withdrawal	Risk with rapid AED withdrawal				
Seizure freedom after 1 year of AED withdrawal	Study population		RR 0.76 (0.58 to 1.01)	149 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	Non-significant trend toward a lower risk of seizure recurrence after 1 year of AED withdrawal in participants allocated to slow tapering.
	647 per 1000	492 per 1000 (330 to 654)				
Seizure freedom after 2 years of AED withdrawal	Study population		RR 0.87 (0.58 to 1.29)	149 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	No evidence of a difference, but the CI was wide and equivalence could not be inferred.
	426 per 1000	371 per 1000 (235 to 533)				
Seizure freedom after 5 years of AED withdrawal	Study population		RR 1.40 (0.54 to 3.65)	149 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	No evidence of a difference, but the CI was wide and equivalence could not be inferred.
	88 per 1000	124 per 1000 (46 to 290)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AED: antiepileptic drug; **CI:** confidence interval; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- ^aDowngraded one level; information from one study with high risk of performance bias; plausible bias likely to seriously alter the results.
^bDowngraded one level; information from one study.
^cDowngraded one level; small number of participants included in this study; no statistical power was calculated.

BACKGROUND

This review is an update of a previously published review in the *Cochrane Database of Systematic Reviews* (2006, Issue 2; Ranganathan 2006).

Description of the condition

Epilepsy is a chronic disorder of the brain characterized by an enduring predisposition to epileptic seizures (Fisher 2014). It is estimated that approximately one third of people with epilepsy achieves seizure freedom with one or more antiepileptic drugs (AED) (Brodie 2012). Furthermore, epilepsy can be defined as 'resolved' for people who either had an age-dependent epilepsy syndrome (e.g. childhood absence epilepsy) but are now past the applicable age or for people who "have remained seizure-free for the last 10 years and off anti-seizure medicines for at least the last five years" (Fisher 2014).

Description of the intervention

The ideal objective of treating a person with epilepsy is to induce remission with AEDs and withdraw the AEDs without causing seizure recurrence. Some people with epilepsy may prefer to continue taking AEDs lifelong rather than risk a seizure recurrence. However, prolonged use of AEDs may have long-term adverse effects and may potentially affect prognosis or quality of life. The adverse effects of AEDs on cognition and behavior and the social stigma associated with epilepsy are increasingly recognized. When a person with epilepsy is in remission (free of seizures for some time), then it is logical to attempt to discontinue the medication.

How the intervention might work

The rate of recurrence of seizures after withdrawal of AEDs among people with epilepsy who are in remission is estimated to be between 29% and 40% at two years (Berg 1994; MRC 1991; MRC 1993). Thus, the decision to discontinue AEDs depends on the chance of remaining seizure free after drug withdrawal, the presence of factors predictive of higher risks of seizure recurrence, and the medical and social consequence of drug withdrawal compared with continuation of treatment. There are several factors that contribute to the risk of relapse. They are age at onset of seizure; age at treatment withdrawal; family history of epilepsy; recognized etiology of epilepsy; electroencephalogram (EEG) abnormalities; number of seizures preceding remission; duration of seizure-free period on treatment; and number of drugs needed to control the epilepsy.

Why it is important to do this review

The physician contemplating withdrawal of AEDs is faced with two important considerations: timing of withdrawal and mode of withdrawal. The timing of withdrawal (duration of seizure freedom before attempting to withdraw an AED) has not been clearly defined. The American Academy of Neurology drafted guidelines and recommended two to five seizure-free years before withdrawing the drugs (AAN 1996). One study from the UK required the seizure-free period to be at least two years (MRC 1991; MRC 1993). One systematic review found that the pooled risk ratio (RR) for seizure relapse in early (less than two years) versus late (more than two years) AED withdrawal was 1.34 (95% confidence interval (CI) 1.13 to 1.59; number needed to treat for an additional harmful effect 8), indicating that AED withdrawal in people who are

not seizure free for at least two years is associated with a higher recurrence rate (Strozzi 2015).

There is no consensus on the mode of withdrawal. Tapering of AEDs ranges from rapid withdrawal to slow withdrawal spread over a period of two years (Bouma 1987; Duncan 1987; Oller-Daurella 1975; Overweg 1981; Shinnar 1994). In other studies, the tapering period has come down to three to six months, reflecting a different clinical approach (Arts 1988; Callaghan 1988; Emerson 1981; Juul-Jensen 1964; MRC 1991; Tennison 1994), but as yet there is no consensus in this tapering regimen. Risk of seizure relapse due to rapidity of drug discontinuation is not well defined.

We arbitrarily defined rapid tapering as when the AED(s) was/were tapered and discontinued within three months and slow tapering as when the AED(s) was/were tapered and discontinued over more than three months.

In this systematic review, we examined whether the rapidity of withdrawal of AEDs among people with epilepsy who are in remission influences the recurrence of seizures and ultimate prognosis or quality of life. We also examined the effect of variables such as age of seizure onset, seizure types, presence of neurologic deficits, mental subnormality, etiology of epilepsy, EEG findings, or duration of seizure freedom on the risk of recurrence of seizures with the two tapering regimens.

OBJECTIVES

To quantify risk of seizure recurrence after rapid (tapering period of three months or less) or slow (tapering period of more than three months) discontinuation of antiepileptic drugs in adults and children with epilepsy who are in remission, and to assess which variables modify the risk of seizure recurrence.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials that evaluated rapid or slow AED withdrawal after varying periods of seizure control (remission) in people with epilepsy.

The studies could be double blind, single blind, or unblinded.

We excluded studies involving highly specific patient samples such as neonates.

Types of participants

Men, women, and children (excluding neonates) of any age, with a diagnosis of epilepsy and who had been seizure free for a described time.

Participants may have had onset of epilepsy at any age and the seizure types could have been either focal or generalized.

Types of interventions

Studies involving rapid or slow withdrawal of AEDs. The studies may have also compared rapid or slow withdrawal with continued treatment.

Types of outcome measures

Primary outcomes

1. Seizure freedom after one year of AED withdrawal.
2. Seizure freedom after two years of AED withdrawal.
3. Seizure freedom after five years of AED withdrawal.

Secondary outcomes

1. Time to recurrence of seizure following withdrawal.
2. Occurrence of status epilepticus.
3. Mortality.
4. Morbidity due to seizure such as injuries, fractures, aspiration pneumonia, etc.
5. Quality of life (assessed by validated scales).

Search methods for identification of studies

Electronic searches

We ran searches for the original review in 2005 and subsequent searches in April 2019. For the latest update, we searched the following databases on 9 April 2019.

1. Cochrane Register of Studies (CRS Web), which includes the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomized controlled trials from ClinicalTrials.gov, using the search strategy set out in [Appendix 1](#).
2. MEDLINE (Ovid, 1946 to 8 April 2019) using the strategy outlined in [Appendix 2](#).
3. WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) using the strategy outlined in [Appendix 3](#).
4. SCOPUS (from 1823) citation search using the strategy outlined in [Appendix 4](#).

Searching other resources

We checked cross-references from identified studies and from previous systematic reviews on the topic of AED withdrawal. We contacted colleagues and experts in the field regarding any studies that we had missed (by e-mail on 2 July 2019).

There were no language restrictions on our searching activities.

Data collection and analysis

We performed analyses using Review Manager 5 ([Review Manager 2014](#)).

Selection of studies

Two review authors (FAL and EGT) independently screened titles and abstracts of the electronic search results, and assessed the potentially relevant trials for inclusion, with disagreements resolved by discussion.

Data extraction and management

Two review authors (FAL and EGT) independently extracted the following data and resolved differences of opinion by discussion.

1. Study methods
 - a. Design (e.g. parallel or crossover design).
 - b. Randomization method (allocation concealment and list generation).
 - c. Blinding method.
2. Participants
 - a. Number (total/per group).
 - b. Age and sex distribution.
 - c. Seizure type and epilepsy syndrome.
 - d. Duration of epilepsy.
 - e. Etiology of epilepsy.
 - f. Neurologic deficits.
 - g. Mental subnormality;
 - h. Duration of seizure freedom.
 - i. EEG abnormality before tapering.
 - j. Loss to follow-up.
3. Rapidity of AED withdrawal.
4. Duration of follow-up.
5. Outcome data as described above including the certainty of seizure recurrence.

We contacted authors of identified studies to request any missing data. If studies were only in abstract form or published without any clear description of the methodology employed, we contacted the original trialists for clarification.

Assessment of risk of bias in included studies

Two review authors (FAL and FB) independently assessed the risk of bias associated with included studies using the Cochrane 'Risk of bias' tool, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The Cochrane 'Risk of bias' tool comprises seven specific parameters: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other bias. For each entry, review authors made the judgement ('low' risk of bias, 'high' risk of bias, or 'unclear' risk of bias) and provided support for the decision by an agreed review author comment or by a quote taken from the corresponding publication. We resolved any disagreements by discussion.

Measures of treatment effect

We reported dichotomous outcomes (proportion of participants who remained seizure free) as Mantel-Haenszel risk ratio (RR) with 95% confidence intervals (CIs).

We reported time to event outcomes (e.g. time to seizure recurrence) as hazard ratios with 95% CIs.

We planned to report time to seizure recurrence as risk difference with 95% CIs.

Unit of analysis issues

We planned to deal with any unit of analysis issues according to the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

Primary analysis was by intention to treat, in which all participants were included in the treatment groups to which they were allocated, irrespective of the treatment or policy they received. Due to the small number of included studies, we performed no best-case or worst-case analyses.

Assessment of heterogeneity

We assessed clinical heterogeneity by evaluating similarities and differences in the methodologies and outcomes measured in the included studies and by visually inspecting forest plots. We planned to assess statistical heterogeneity using the χ^2 test and I^2 statistic as follows (Higgins 2011): 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% may indicate considerable heterogeneity. Our intention was to use a fixed-effect model if we did not find statistically significant heterogeneity between the included studies. If statistical heterogeneity had been present, we would have used a random-effects model. However, despite our primary intention, due to insufficient information on outcomes and too high methodological heterogeneity, we were unable to perform any meta-analyses.

Assessment of reporting biases

We sought all study protocols to identify any discrepancies between protocol and trial methodology.

Data synthesis

Provided we thought it clinically appropriate, and there was no important heterogeneity, we planned to summarize results in a meta-analysis. However, because of the high methodological heterogeneity with different duration of tapering periods, we could not perform a meta-analysis. Further research could allow results to be pooled, leading to a quantitative rather than a qualitative summary of results.

Subgroup analysis and investigation of heterogeneity

We did not carry out any subgroup analysis or formal investigation of heterogeneity.

Summary of findings and assessment of the certainty of the evidence

For the 2019 update, we presented the results for the primary outcomes in a 'Summary of findings' table. We used [GRADEpro GDT](#) software ([GRADEpro GDT](#)) and GRADE quality assessment criteria to evaluate the certainty of evidence derived from the studies included in this review (Guyatt 2008). To assess the overall certainty of evidence for each outcome, we downgraded the evidence from 'high certainty' by one level for serious (or by two for very serious) risk of bias, indirectness of evidence, inconsistency, imprecision of effect estimates, or potential publication bias. See [Summary of findings for the main comparison](#).

RESULTS

Description of studies

Results of the search

[Figure 1](#) summarizes the results of the searches and the process of screening and selecting studies for inclusion in the review. The 2019 search strategy yielded 113 results (Cochrane Register of Studies 42, MEDLINE 33, ICTRP 2, and SCOPUS 36); after removing 46 duplicates and 22 irrelevant items, we assessed 45 full-text articles for eligibility. Four studies were initially considered for possible inclusion (Serra 2005; Aidaros 2010; He 2016; Gasparini 2016); however, two were eventually excluded (Aidaros 2010; He 2016), as neither of them adopted a randomized controlled design (see [Characteristics of excluded studies](#) table); one study was ongoing and had no results (Gasparini 2016). Hence, since the last version of this review was published, we included one new study (Serra 2005).

Figure 1. Study flow diagram.

Included studies

See [Characteristics of included studies](#) table.

Tennison 1994

Tennison 1994 was included in the previous version of this systematic review. The study recruited 149 children with a mean age of seizure onset of four years, mean age of 11 years at the time of starting the tapering. They were seizure free for at least 18 months. The eligible children were randomly assigned to two groups by tosses of a coin. The first toss determined the rate of tapering (six weeks or nine months), and the second toss determined whether the tapering period would begin after a seizure freedom of two or four years. EEG obtained just before the tapering was normal in 40% of participants. The six-week tapering group (rapid-tapering group) had 81 participants out of whom 11 were lost to follow-up before the tapering began. The nine-month tapering group (slow-tapering group) had 68 participants, five of whom were lost to follow-up before the tapering began. Thus, the rapid-tapering group had 70 participants (41 boys and 29 girls) and the slow-tapering group had 63 participants (38 boys and 25 girls). Sixty-one participants had more than 10 seizures and 84 had focal seizures. The tapering period was divided into three equal parts (two weeks each in the six-week tapering group and three months each in the nine-month tapering group). The dose was reduced by 25% during each interval. The drugs were tapered sequentially if the participant was receiving more than one drug. Barbiturate was tapered last. Follow-up began at the start of drug tapering. All participants were followed up for at least 11 months. Cerebral palsy was present in 43 participants out of the 133, 22 in the rapid-tapering group and 21 in the slow-tapering group. Medications used included barbiturate, phenytoin, carbamazepine, and valproic acid. Twenty-four participants in the rapid-tapering group and 25 participants in the slow-tapering group were receiving two or more drugs. The mean duration of follow-up was 39 months (range 11 to 105 months).

Serra 2005

Serra 2005 was a randomized controlled study conducted in 57 children (24 girls, 33 boys; ages two to 16 years; mean 9.45 years) with a diagnosis of epilepsy controlled by an AED for at least two years. People with infantile spasms and neonatal seizures were excluded. Groups were similar at baseline regarding age, sex, type of epileptic syndrome, EEG abnormality, and AED. Thirty participants had idiopathic, 13 cryptogenic, and 14 symptomatic epilepsy. The etiology of symptomatic seizures was hypoxic-ischemic injury in four participants (28.5%); neurocysticercosis in

3 participants (21.4%); meningoencephalitis in four participants (28.5%); and tuberous sclerosis complex, hydrocephalus, and congenital toxoplasmosis in one participant each. The EEG was normal in 41 participants and abnormal in 15 participants (there was no information for one participant). All participants were receiving monotherapy: 35 (61.4%) received carbamazepine, 12 (21%) phenytoin, six (10.5%) valproic acid, and four (7%) phenobarbital. Participants were randomized to taper the AED during a period of one or six months. In the one-month AED withdrawal group, the dosage was reduced by 25% every 10 days; and in the six-month group, the dose was reduced by 25% every two months. Authors of this study analyzed the frequency of seizure recurrence according to the time of AED withdrawal over 54 months of follow-up.

Excluded studies

See [Characteristics of excluded studies](#) table.

When updating the previous version of the systematic review, two studies were initially considered for possible inclusion ([Aidaros 2010](#); [He 2016](#)); however, both were eventually excluded, as neither of them adopted a randomized controlled design.

The previous version of this review excluded nine studies ([Aidaros 2010](#); [Braathen 1996](#); [Gebremariam 1999](#); [Gherpelli 1992](#); [He 2016](#); [MRC 1991](#); [Peters 1998](#); [Todt 1984](#); [Verrotti 2000](#)).

Ongoing studies

Gasparini 2016

See [Characteristics of ongoing studies](#) table.

Gasparini 2016 is an Italian multicenter, prospective, randomized controlled trial which is ongoing. It aims to investigate if a slow or a rapid withdrawal schedule of AED monotherapy influences relapse rate in adults with focal or generalized epilepsy who have been seizure free for at least two years. Participants will be randomized to a slow (160 days) or a rapid (60 days) schedule, with follow-up of one year after randomization (expected sample size: 350 participants). The primary outcome is the time to seizure relapse; secondary outcomes are compliance to the assigned schedule; and occurrence of status epilepticus, seizure-related injuries, and mortality. No preliminary results are published.

Risk of bias in included studies

See [Figure 2](#); [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Funding source	Conflicts of interest
Serra 2005	?	?	-	-	-	?	+	+	?
Tennison 1994	+	+	-	-	-	+	+	?	?

Allocation

[Tennison 1994](#) was a randomized study, with random sequence generation based on coin tossing (low risk of selection bias); in this study, the clinical characteristics of the participants were similar across study groups. [Serra 2005](#) provided no information on the methods used to generate random sequence and allocate participants (unclear risk of selection bias); however, the clinical characteristics of the participants were similar across study groups.

Blinding

Neither study was blinded (high risk of performance and detection bias) ([Serra 2005](#); [Tennison 1994](#)).

Incomplete outcome data

[Tennison 1994](#) had no participants lost to follow-up after the allocation of participants to the two groups (low risk of attrition bias due to no missing outcome data). [Serra 2005](#) provided no information on participants lost to follow-up after randomization (unclear risk of attrition bias).

Selective reporting

Although we didn't find published protocols for either study, all outcomes outlined in the methods section of each trial were analyzed and reported in the results section of both studies, so we classified them as being at a low risk of reporting bias.

Other potential sources of bias

[Tennison 1994](#) did not reported whether the epilepsy types (idiopathic, cryptogenic, or symptomatic) were distributed equally among groups at baseline; at baseline, there was no difference between the two groups for this variable in [Serra 2005](#).

When more than one drug was withdrawn sequentially in [Tennison 1994](#), the tapering exceeded the six-week interval; the dose of barbiturates was tapered last. Of the 81 participants in the six-week tapering group, 63 completed the protocol and of the 68 in the nine-month tapering group, 48 completed the protocol correctly. Three participants continued therapy in the rapid-tapering group and nine continued in the slow-tapering group without tapering. Eleven participants in the rapid-tapering group and five in the

slow-tapering group were lost to follow-up before start of tapering period.

[Tennison 1994](#) provided no information on funding. [Serra 2005](#) received public funding from Fundação de Amparo à Pesquisa do Estado de São Paulo (São Paulo Research Foundation), maintained by endowments by the Brazilian State Government.

Neither study provided details on conflicts of interest.

Effects of interventions

See: [Summary of findings for the main comparison Rapid versus slow withdrawal of antiepileptic drugs](#)

Because of the methodological heterogeneity and the difference in the duration of tapering, we did not perform a quantitative synthesis of the two included studies.

Primary outcomes

Seizure freedom after one year of antiepileptic drug withdrawal

One study provided information on seizure freedom after one year of AED withdrawal ([Tennison 1994](#)). At the end of one year, 40/81 participants in the rapid-tapering group were seizure free at the end of one-year follow-up, compared to 44/68 in the slow-tapering group. There was a non-significant trend toward a lower risk of seizure recurrence after one year of AED withdrawal in participants allocated to slow tapering (RR 0.76, 95% CI 0.58 to 1.01; $P = 0.06$; [Analysis 1.1](#)). We downgraded the certainty of evidence from high to very low for serious risk of performance bias and for imprecision of effect estimates.

Seizure freedom after two years of antiepileptic drug withdrawal

One study provided information on seizure freedom after two years of AED withdrawal ([Tennison 1994](#)). At the end of two years, 30/81 participants in the rapid-tapering group and 29/68 in the slow-tapering group were free of seizures (RR 0.87, 95% CI 0.58 to 1.29; $P = 0.48$; [Analysis 1.2](#)). We downgraded the certainty of evidence from high to very low for serious risk of performance bias and for imprecision of effect estimates.

Seizure freedom after five years of antiepileptic drug withdrawal

One study provided information on seizure freedom after five years of AED withdrawal ([Tennison 1994](#)). At the end of five years of AED withdrawal, 10/81 participants in the rapid-tapering group and 6/68 in the slow-tapering group remained seizure free (RR 1.40, 95% CI 0.54 to 3.65; $P = 0.49$; [Analysis 1.3](#)). We downgraded the certainty of evidence from high to very low for serious risk of performance bias and for imprecision of effect estimates.

Seizure freedom at other time points

In [Tennison 1994](#), after three years of follow-up, 24/81 participants in the rapid-tapering group and 14/68 in the slow-tapering group remained seizure free (RR 1.44, 95% CI 0.81 to 2.56; no significant difference). At the end of the fourth year of follow-up, 18/81 participants in the rapid-tapering group and 8/68 in the slow-tapering group remained seizure free (RR 1.89, 95% CI 0.88 to 4.07; no significant difference).

In [Serra 2005](#), over the period of 54 months of follow-up, 20/30 participants in the one-month group compared to 15/27 participants in the six-month group remained seizure-free (no significant difference).

Factors associated with seizure recurrence

In [Tennison 1994](#), two factors were associated with higher risk of seizure recurrence: presence of mental retardation (RR 3.1, 95% CI 1.5 to 6.2) and spikes in the EEG at the start of the tapering period (RR 1.9, 95% CI 1.0 to 3.4). The following factors were not associated with higher risk of seizure recurrence: abnormal EEG at start of the tapering period (RR 1.7, 95% CI 0.9 to 3.0); presence of cerebral palsy (RR 1.1, 95% CI 0.5 to 2.1); barbiturate tapered (RR 1.4, 95% CI 0.8 to 20.4); family history of seizures (RR 0.6, 95% CI 0.4 to 1.1); history of status epilepticus (RR 0.7, 95% CI 0.3 to 2.0); history of febrile seizures (RR 0.9, 95% CI 0.4 to 2.3); history of generalized seizures (RR 1.2, 95% CI 0.7 to 2.3); history of more than 10 seizures (RR 1.2, 95% CI 0.7 to 2.1); age at onset of seizure (RR 1.0, 95% CI 0.9 to 1.1); and age at start of tapering period (RR 1.1, 95% CI 1.0 to 1.1).

[Serra 2005](#) did not provide data on risk factors for seizure recurrence during and after tapering of AEDs.

Secondary outcomes

Time to recurrence of seizure following withdrawal

One study provided information on time to recurrence of seizure following withdrawal, which ranged from 10 days to 4 years and 5 months (mean 13.2 months) ([Serra 2005](#)). There was no information on this outcome for each group to allow a comparison.

Occurrence of status epilepticus

No study provided information on occurrence of status epilepticus.

Mortality

No study provided information on mortality.

Morbidity due to seizures

No study provided information on morbidity due to seizures.

Quality of life

No study provided information on quality of life.

DISCUSSION

Since the last version of this review, we included one additional pediatric study ([Serra 2005](#)).

Summary of main results

See [Summary of findings for the main comparison](#).

The included studies found no evidence of a difference in the proportion of participants remaining seizure-free between the rapid and the slow-tapering groups at different time points, although in [Tennison 1994](#), there was a non-significant trend toward a lower risk of seizure recurrence after one year of AED withdrawal in participants allocated to slow tapering. However, these studies were probably not powered to detect a significant difference between the rapid and slow-tapering groups because of the small sample size.

There is very limited information on factors influencing the risk of seizure recurrence during and after tapering of AEDs. In [Tennison 1994](#), the presence of mental retardation or spikes in the EEG obtained just before the start of the tapering period were identified as risk factors for seizure recurrence.

One study provided information on time to recurrence of seizure following withdrawal; however, there was no information on this outcome for each group to allow a comparison ([Serra 2005](#)).

No data were available for the other outcomes such as status epilepticus, mortality, morbidity and quality of life.

Overall completeness and applicability of evidence

Both included studies were conducted in children, hence their generalizability to adults is limited. We found no completed trials investigating AED withdrawal in adults.

Currently, one Italian multicenter, prospective, randomized controlled trial is ongoing with the aim of investigating if a slow or a rapid withdrawal schedule of AED monotherapy influences relapse rate in adults with focal or generalized epilepsy who have been seizure free for at least two years ([Gasparini 2016](#); [Characteristics of ongoing studies](#) table). Participants will be randomized to a slow (160 days) or a rapid (60 days) schedule, with follow-up of one year after randomization (expected sample size: 350 participants). The primary outcome is the time to seizure relapse; secondary outcomes are compliance to the assigned schedule; and occurrence of status epilepticus, seizure-related injuries, and mortality. The study is currently ongoing, and no preliminary results have been published so far. According to investigators, such a study "should contribute to better define the best withdrawal period for AED treatment in adult patients with epilepsy" ([Gasparini 2016](#)).

Certainty of the evidence

[Tennison 1994](#) was small and not blinded. Although the procedure of randomization was adequate, protocol violation and loss to follow-up further reduced the reliability of results. Furthermore, when participants were receiving more than one drug, the tapering period exceeded the six-week/nine-month tapering. [Serra 2005](#) provided no details on the procedure of randomization, and was unblinded. In both studies, clinical characteristics of the participants were similar across study groups, suggesting that the randomization was effective in minimizing the risk of covariate imbalance.

The lack of blinding of participants appears to be a methodological limitation that is difficult to overcome in controlled trials where AED withdrawal is performed in different durations of tapering. Similarly, the blinding of healthcare providers can be difficult to establish at the start of a trial and to maintain throughout it, particularly if the study adopts a pragmatic design. Although the lack of blinding is unlikely to influence 'hard' outcomes such as seizure recurrence, it may influence subjective outcomes (e.g. quality of life), and increase the risk of performance and detection bias.

Both included studies were conducted in a small number of participants, without calculation of statistical power. Hence, it is possible that these studies were underpowered to detect a statistically significant and clinically relevant difference between

the groups; in this case, the lack of a significant difference could represent a false-negative result due to statistical error type II.

Because of these limitations, we were unable to form any firm conclusions from these two studies. Using GRADE, we assessed the certainty of the evidence as very low for outcomes for which data were available; we downgraded the evidence by two levels since data on seizure freedom were obtained from only one study judged at unclear or high risk of bias ([Tennison 1994](#)). Hence, we judged the certainty of the evidence for this outcome as very low (data do not provide a reliable indication of the likely effect; and the true effect is likely to be substantially different from the estimate of effect).

Potential biases in the review process

There were no major potential biases in the review process.

Agreements and disagreements with other studies or reviews

We found no other systematic review evaluating the rate of withdrawal of AEDs (whether rapid or slow tapering) and its effect on recurrence of seizure.

AUTHORS' CONCLUSIONS

Implications for practice

The conclusions remain the same as the previous update. In view of methodological deficiencies and small sample size of the two included studies, we are unable to derive any firm conclusions regarding the optimal rate of tapering of antiepileptic drugs (AEDs). Further trials are needed to assess the optimal rate of tapering of AEDs in adults and children whose seizures are well controlled with medication.

Implications for research

Further randomized controlled trials are needed to determine the optimal rate of tapering of AEDs in people in remission. The following questions need to be investigated.

1. What is the effect of structural lesions (neuroimaging abnormalities) of the brain on the rate of tapering?
2. What is the effect of mental retardation on the rate of tapering?
3. What is the effect of electroencephalogram abnormalities on the rate of tapering?
4. Do different AEDs (such as benzodiazepines, barbiturates) need to be tapered at different rates?
5. What should be the sequence of tapering for people receiving more than one AED?
6. What is the optimal rate of withdrawal of AEDs in children and adults?
7. What is the effect of rapid and slow AED withdrawal on time to recurrence of seizures, occurrence of status epilepticus, mortality, morbidity, and quality of life?

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REFERENCES

References to studies included in this review

Serra 2005 {published data only}

Serra JG, Montenegro MA, Guerreiro MM. Antiepileptic drug withdrawal in childhood: does the duration of tapering off matter for seizure recurrence?. *Journal of Child Neurology* 2005;**20**(7):624-6. [DOI: [10.1177/08830738050200071901](https://doi.org/10.1177/08830738050200071901); PUBMED: 16159535]

Tennison 1994 {published data only}

Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy: a comparison of a six-week and a nine-month taper period. *New England Journal of Medicine* 1994;**330**(20):1407-10. [DOI: [10.1056/NEJM199405193302002](https://doi.org/10.1056/NEJM199405193302002); PUBMED: 8159193]

References to studies excluded from this review

Aidaros 2010 {published data only}

Aidaros MA, Siam AG. 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* 2010;**47**(4):593-8.

Braathén 1996 {published data only}

Braathén G, Andersson T, Gylje H, Melander H, Naglo AS, Noren L, et al. Comparison between one and three years of treatment in uncomplicated childhood epilepsy: a prospective study. I. Outcome in different seizure types. *Epilepsia* 1996;**37**(9):822-32.

Gebremariam 1999 {published data only}

Gebremariam A, Mengesha W, Enqusilassie F. Discontinuing anti-epileptic medication(s) in epileptic children: 18 versus 24 months. *Annals of Tropical Paediatrics* 1999;**19**(1):93-9.

Gherpelli 1992 {published data only}

Gherpelli JL, Kok F, dal Forno S, Elkis LC, Lefevre BH, Diamant AJ. Discontinuing medication in epileptic children: a study of risk factors related to recurrence. *Epilepsia* 1992;**33**(4):681-6.

He 2016 {published data only}

He RQ, Zeng QY, Zhu P, Bao YX, Zheng RY, Xu HQ. Risk of seizure relapse after antiepileptic drug withdrawal in adult patients with focal epilepsy. *Epilepsy & Behavior* 2016;**64**(Pt A):233-8.

MRC 1991 {published data only}

Medical Research Council Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepileptic drug withdrawal in patients in remission. *Lancet* 1991;**337**(8751):1175-80.

Peters 1998 {published data only}

Peters AC, Brouwer OF, Geerts AT, Arts WF, Stroink H, Van Donselaar CA. Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy. *Neurology* 1998;**50**(3):724-30.

Todt 1984 {published data only}

Todt H. The late prognosis of epilepsy in childhood: results of a prospective follow-up study. *Epilepsia* 1984;**25**(2):137-44.

Verrotti 2000 {published data only}

Verrotti A, Morresi S, Basciani F, Cutarella R, Morgese G, Chiarelli F. Discontinuation of anticonvulsant therapy in children with partial epilepsy. *Neurology* 2000;**55**(9):1393-5.

References to ongoing studies

Gasparini 2016 {published data only}

Gasparini S, Ferlazzo E, Giussani G, Italiano D, Cianci V, Sueri C, et al. 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* 2016;**37**(4):579-83. [DOI: [10.1007/s10072-016-2483-3](https://doi.org/10.1007/s10072-016-2483-3); PUBMED: 26809952]

Additional references

AAN 1996

American Academy of Neurology – Quality Standards Subcommittee. Practice parameter: a guideline for discontinuing antiepileptic drugs in seizure-free patients--summary statement.. *Neurology* 1996;**47**(2):600-2.

Arts 1988

Arts WF, Visser LH, Loonen MC, Tjiam AT, Stroink H, Stuurman PM, et al. Follow-up of 146 children with epilepsy after withdrawal of antiepileptic therapy. *Epilepsia* 1988;**29**(3):244-50.

Berg 1994

Berg AT, Shinnar S. Relapse following discontinuation of antiepileptic drugs: a meta-analysis. *Neurology* 1994;**44**(4):601-8.

Bouma 1987

Bouma PA, Peters AC, Arts RJ, Stijnen T, Van Rossum J. Discontinuation of antiepileptic therapy: a prospective study in children. *Journal of Neurology, Neurosurgery, and Psychiatry* 1987;**50**(12):1579-83.

Brodie 2012

Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;**78**(20):1548-54.

Callaghan 1988

Callaghan N, Garrett A, Goggin T. Withdrawal of anticonvulsant drugs in patients free of seizures for two years: a prospective study. *New England Journal of Medicine* 1988;**318**(15):942-6.

Duncan 1987

Duncan JS, Shorvon SD. Rates of antiepileptic drug reduction in active epilepsy – current practice. *Epilepsy Research* 1987;**1**(6):357-64.

Emerson 1981

Emerson R, D'Souza BJ, Vining EP, Holden KR, Mellits ED, Freeman JM. Stopping medication in children with epilepsy: predictors of outcome. *New England Journal of Medicine* 1981;**304**(19):1125-9.

Fisher 2014

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;**55**(4):475-82.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), Accessed 16 July 2019).

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [DOI: [10.1136/bmj.39489.470347.AD](https://doi.org/10.1136/bmj.39489.470347.AD); PUBMED: 18436948]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Juul-Jensen 1964

Juul-Jensen P. Frequency of recurrence after discontinuance of anti-convulsant therapy in patients with epileptic seizures. *Epilepsia* 1964;**5**:352-63.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

MRC 1993

Medical Research Council Antiepileptic Drug Withdrawal Study Group. Prognostic index for recurrence of seizures after remission of epilepsy. *BMJ* 1993;**306**(6889):1374-8.

Oller-Daurella 1975

Oller-Daurella L, Pamies R, Oller LF. Reduction or discontinuance of antiepileptic drugs in patients seizure-free for more than 5 years. In: Janz D editor(s). *Epileptology: Proceedings of the Seventh International Symposium on Epilepsy*. Berlin (Germany): Georg Thieme Verlag, 1975:218-27.

Overweg 1981

Overweg J, Rowan AJ, Binnie CD, Oosting J, Nagelkerke NJ. Prediction of seizure recurrence after withdrawal of antiepileptic drugs. In: Dam M, Gram L, Penry JK editor(s). *Advances in Epileptology: the XIIth Epilepsy International Symposium*. New York: Raven Press, 1981:503-8.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Shinnar 1994

Shinnar S, Berg AT, Moshe SL, Kang H, O'Dell C, Alemany M, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. *Annals of Neurology* 1994;**35**(5):534-45.

Strozzi 2015

Strozzi I, Nolan SJ, Sperling MR, Wingerchuk DM, Sirven J. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: [10.1002/14651858.CD001902.pub2](https://doi.org/10.1002/14651858.CD001902.pub2)]

References to other published versions of this review

Ranganathan 2004

Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: [10.1002/14651858.CD005003](https://doi.org/10.1002/14651858.CD005003)]

Ranganathan 2006

Ranganathan LN, Ramaratnam S. Rapid versus slow withdrawal of antiepileptic drugs. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: [10.1002/14651858.CD005003.pub2](https://doi.org/10.1002/14651858.CD005003.pub2)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Serra 2005

Methods	Randomized, unblinded, prospective study
	Inclusion criteria: diagnosis of epilepsy and seizure control by an AED for ≥ 2 years.
	2 study arms: 1-month AED withdrawal group (rapid tapering) or 6-month AED withdrawal group (slow tapering).
	Type of randomization not specified.

Rapid versus slow withdrawal of antiepileptic drugs (Review)

Serra 2005 (Continued)

Mean duration of follow-up: 54 months (range: 6 months to 4 years and 3 months).

Participants	<p>Number of participants: 57</p> <p>33 boys and 24 girls</p> <p>Rapid-tapering group: 30 participants (17 boys and 13 girls)</p> <p>Slow-tapering group: 27 participants (16 boys and 11 girls)</p> <p>EEG was normal in 41 participants and abnormal in 15 participants. In 1 participant, EEG information was not available.</p> <p>All participants received 1 AED: 35 (61.4%) received carbamazepine, 12 (21%) phenytoin, 6 (10.5%) valproic acid, and 4 (7%) phenobarbital.</p> <p>No difference between the 2 groups according to age, gender, family history of epilepsy, type of epileptic syndrome, EEG abnormality, and AED ($P > 0.05$).</p>
Interventions	<p>Drug tapering: rapid vs slow</p> <p>Rapid tapering in 1 month ($n = 30$); dosage reduced by 25% every 10 days.</p> <p>Slow tapering in 6 months ($n = 27$); dosage reduced by 25% every 2 months.</p> <p>EEG was routinely performed prior to randomization.</p>
Outcomes	<p>Proportion of participants remaining seizure free after AED withdrawal</p> <p>Seizure recurrence</p> <p>Time for seizure recurrence</p>
Notes	<p>Total enrolled: not specified</p> <p>Loss to follow-up: not specified</p> <p>No flowchart</p> <p>Clinical characteristics of participants were similar across study groups.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias)	High risk	No blinding.

Rapid versus slow withdrawal of antiepileptic drugs (Review)

Serra 2005 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgment.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Funding source	Low risk	Reported (sponsored by a public Foundation).
Conflicts of interest	Unclear risk	Not specified.

Tennison 1994

Methods	<p>Randomized, unblinded, prospective study.</p> <p>2 study arms: 6-week AED withdrawal group (rapid tapering) or 9-month AED withdrawal group (slow-tapering group).</p> <p>Randomization by 2 coin tosses. The 1st toss for rate of tapering. The 2nd toss for deciding when the withdrawal of AEDs would begin, after 2 or 4 years.</p> <p>Mean duration of follow-up: 39 months (range: 11–105 months).</p>
Participants	<p>Total number enrolled: 149</p> <p>Mean age: 11 years</p> <p>Loss to follow-up: 16</p> <p>Number actually participated: 133</p> <p>79 boys and 54 girls</p> <p>Rapid-tapering group: 70 participants (41 boys and 29 girls)</p> <p>Slow-tapering group: 63 participants (38 boys and 25 girls)</p> <p>Total number of seizures > 10 events in 51%. 54% were free of seizure for 2 years and 46% for 4 years.</p> <p>63% had focal seizures.</p> <p>Mean age of onset of seizure: 4 years in rapid-tapering group, 5 years in slow-tapering group.</p> <p>Approximately 40% had normal EEG at the start of tapering period.</p> <p>24 participants in rapid-tapering group and 25 participants in slow-tapering group received ≥ 2 AEDs.</p>
Interventions	<p>Drug tapering: rapid vs slow</p> <p>Rapid tapering in 6 weeks (n = 70); tapering divided into 3 equal periods of 2 weeks each; dose reduction 25% during each period</p> <p>Slow tapering in 9 months (n = 63); tapering divided into 3 equal periods of 3 months each; dose reduction 25% during each period</p> <p>When participant had > 1 AED, each drug was tapered sequentially, barbiturates were the last to be tapered.</p> <p>EEG was performed in all participants before tapering began.</p>

Tennison 1994 (Continued)

Outcomes	Proportion of participants remaining seizure free after AED withdrawal	
	Seizure recurrence	
Notes	16 lost to follow-up	
	11 in rapid-tapering group, 5 in slow-tapering group	
	63/81 in rapid-tapering group, 48/68 in slow-tapering group completed the protocol correctly	
	Clinical characteristics of participants were similar across study groups.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate. Quote: "The eligible children were randomly assigned by two coin tosses."
Allocation concealment (selection bias)	Low risk	Investigators and participants were unable to predict to which group each of the participants was allocated.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Funding source	Unclear risk	Funding not reported.
Conflicts of interest	Unclear risk	Not specified.

AED: antiepileptic drug; EEG: electroencephalography; n: number of participants.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aidaros 2010	Compared rapid vs slow withdrawal of AEDs but was a non-randomized trial. Included 106 children with epilepsy in remission: 61 children underwent AEDs withdrawal over 6 months and 45 children underwent AED withdrawal over 3 months.

Study	Reason for exclusion
Braathen 1996	RCT in children, in whom AEDs were withdrawn after 1–3 years of seizure freedom. The drugs were tapered over 3-month period. Study did not compare rapid vs slow withdrawal.
Gebremariam 1999	RCT on the withdrawal of AEDs in children after 18 or 24 months of seizure freedom. AEDs tapered sequentially if > 1 AED. Each drug tapered by 1/4 dose every 2 weeks until completely stopped. Hence, taper period was variable for each child. Study did not compare rapid vs slow withdrawal.
Gherpelli 1992	Cohort study not specifically assessing drug titration. Predictive model related to other variables.
He 2016	Cohort study addressing rapid vs slow withdrawal of AEDs.
MRC 1991	Large RCT investigating the effects of gradual AED withdrawal compared to continuation of AED in people who had been seizure free for 2 years. Study did not compare rapid vs slow withdrawal.
Peters 1998	RCT investigated withdrawal of AEDs in children who were seizure free for 6 or 12 months. Withdrawal was over 4 weeks. Study did not address the rapid vs slow withdrawal.
Todt 1984	RCT of AED withdrawal after 1, 2, 3, and 4 years. Study did not compare rapid vs slow withdrawal.
Verrotti 2000	RCT of AED withdrawal in children after 1 or 2 years of seizure freedom. Study did not compare rapid vs slow withdrawal.

AED: antiepileptic drug; RCT: randomized controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

Gasparini 2016

Trial name or title	Rapid versus slow withdrawal of antiepileptic monotherapy in 2-year seizure-free adult patients with epilepsy (RASLOW) study.
Methods	Multicenter, prospective, randomized controlled study
Participants	Adults with focal or generalized epilepsy, who are seizure free on monotherapy for ≥ 2 years
Interventions	Slow (160 days) vs rapid (60 days) withdrawal schedule
Outcomes	Primary outcome: time to seizure relapse Secondary outcomes: compliance to the assigned schedule; and occurrence of status epilepticus, seizure-related injuries, and mortality
Starting date	Not reported
Contact information	Professor Umberto Aguglia, u.aguglia@tin.it
Notes	

DATA AND ANALYSES

Comparison 1. Rapid versus slow antiepileptic drug (AED) withdrawal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure freedom after 1 year of AED withdrawal	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 1.01]
2 Seizure freedom after 2 years of AED withdrawal	1	149	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.29]
3 Seizure freedom after 5 years of AED withdrawal	1	149	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.54, 3.65]

Analysis 1.1. Comparison 1 Rapid versus slow antiepileptic drug (AED) withdrawal, Outcome 1 Seizure freedom after 1 year of AED withdrawal.

Analysis 1.2. Comparison 1 Rapid versus slow antiepileptic drug (AED) withdrawal, Outcome 2 Seizure freedom after 2 years of AED withdrawal.

Analysis 1.3. Comparison 1 Rapid versus slow antiepileptic drug (AED) withdrawal, Outcome 3 Seizure freedom after 5 years of AED withdrawal.

APPENDICES

Appendix 1. CRS Web search strategy

1. MeSH DESCRIPTOR Epilepsy Explode All WITH QUALIFIER DT AND CENTRAL:TARGET
2. MESH DESCRIPTOR Seizures EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET
3. MeSH DESCRIPTOR Anticonvulsants Explode All AND CENTRAL:TARGET
4. MeSH DESCRIPTOR Midazolam Explode All AND CENTRAL:TARGET
5. MeSH DESCRIPTOR Methazolamide Explode All AND CENTRAL:TARGET
6. MeSH DESCRIPTOR Propofol Explode All AND CENTRAL:TARGET
7. MeSH DESCRIPTOR Temazepam Explode All AND CENTRAL:TARGET
8. MeSH DESCRIPTOR Thiopental Explode All AND CENTRAL:TARGET
9. (antiepilep* or anti-epilep* or anticonvulsant* or anti-convulsant* or AED or AEDs):AB,KW,MC,MH,TI AND CENTRAL:TARGET
10. (Acetazolamid* or Aedon or Aethosuximide or Alodorm or Amizepin* or Anteplepsin or Anxiloc or Arem or Ativan or Atretol or Avugane):AB,KW,MC,MH,TI AND CENTRAL:TARGET
11. (Baceca or Barbexaclon* or Beclamid* or Biston or Bomathal or Brivaracetam or Bromid*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
12. (Calepsin or Carbagen or Carbamazepin* or Carbamazepin* or Carbamezepin* or Carbatrol or Carbazepin* or Carbelan or Carbox or Carisbamat* or Castilium or CBZ or Celontin or Cerebyx or Chlonazepam or Chloracon or Chlorepin or Clorepin or Chlormethiazole or Clormethiazole or Clarmyl or Cloazepam or Clobam* or Clobator or Clobazam or Clofritis or Clonazepam* or Clonex or Clonopin or Clopax or Clorazepate or Comfyde or Convulex):AB,KW,MC,MH,TI AND CENTRAL:TARGET
13. (Dapaz or Dasuen or Delepsine or Depacon or Depak* or Depamide or Deproic or Desitin or Diacomit or Diamox or Diastat or Diazepam or Difenilhidantoin* or Dihydantoin or Dilantin or Dimethadione or Dimethyloxazolidinedione or Diphenin* or Diphenylan or Diphenylhydantoin* or Diphenylhydantoin* or Distraneurin or Divalpr* or Dormicum or DPA or Dwufenylohydantoin*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
14. (E2007 or Ecovia or Emeside or Epanutin or Epiject or Epilepax or Epilex or Epilim or Episenta or Epitol or Epival or Eptoin or Equanil or Equetro or Ergenyl or Erimin or Erlosamide or Eslicarbazepine or Estazolam or Ethadione or Ethosucci* or Ethosuxi* or Ethotoin or Ethylphenacemide or Etosuxi* or Euhypnos or Exalief or Excegran or Ezogabine):AB,KW,MC,MH,TI AND CENTRAL:TARGET
15. (Fanatrex or Felbam* or Felbatol or Fenitoin* or Fenytoin* or Fenobarbit* or Finlepsin or Fosphenytoin or Frisium or Fycompa):AB,KW,MC,MH,TI AND CENTRAL:TARGET
16. (Gabapentin* or Gabapetin* or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Grifoclobam):AB,KW,MC,MH,TI AND CENTRAL:TARGET

17. (Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel):AB,KW,MC,MH,TI AND CENTRAL:TARGET
18. (Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex):AB,KW,MC,MH,TI AND CENTRAL:TARGET
19. (Lacosamid* or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigin* or Lamotriline or Landsen or Levanxol or Levetiracetam* or Lexin or Liskantin or Loraz or Lorazepam* or Losigamon* or Lucium or Luminal or Lyrica):AB,KW,MC,MH,TI AND CENTRAL:TARGET
20. (Magnesium sulfat* or Magnesium sulphat* or Mebaral or Medazepam or Mephenytoin or Mephobarbit* or Mephytaletten or Meprobamate or Meprospan or Mesantoin or Mesuximide or Methazolamid* or Methsuximide or Methylacetazolamide or Methyloxazepam or Methylphenobarbit* or Midazolam or Miltown or Mogadon or Mylepsinum or Mylproin or Mysoline or Mystan):AB,KW,MC,MH,TI AND CENTRAL:TARGET
21. (Neogab or Neptazane or Nesdonal or Neurontin or Neurotop or Nimetazepam or Nitrados or Nitrazadon or Nitrazepam or Nobrium or Nocturne or Noiafren or Norkotral or Normison or Normitab or Nortem or Novo-Clopate or Nuctalon or Nupentin or Nydrane):AB,KW,MC,MH,TI AND CENTRAL:TARGET
22. (OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or Oxcarbamazepin* or Oxcarbazepin* or Oxydiazepam):AB,KW,MC,MH,TI AND CENTRAL:TARGET
23. (Pacisyn or Paraldehyde or Paramethadione or Paxadorm or Paxam or Peganone or Penthiobarbital or Pentothal or Perampanel or Petinutin or Petril or Phemiton or Phenacemide or Pheneturide or Phenobarbit* or Phensuximide or Phenylethylbarbit* or Phenylethylmalonylurea or Phenytek or Phenytoin* or Planum or Posedrine or Potiga or Pregabalin or Primidone or Prodilantin or Progabide or Prominal or Pronervon or Propofol or Prosom or Prysoline):AB,KW,MC,MH,TI AND CENTRAL:TARGET
24. (Ravotril or Remacemide or Remestan or Remnos or Resimatil or Restoril or Retigabine or Riluzole or Rilutek or Rivotril or Rudotel or Rufinamide or Rusedal or "RWJ-333369"):AB,KW,MC,MH,TI AND CENTRAL:TARGET
25. (Sabril or Seclar or Sederlona or Selenica or Seletacetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or SPD417 or Stavzor or Stazepin* or Stedesa or Stiripentol or Sulthiam* or Sultiam*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
26. (Talampanel or Taloxa or Tasedan or Tegretal or Tegretol or Telesmin or Temaze or Temazep* or Temesta or Temtabs or Tenox or Teril or Thiomibumal or Thionembutal or Thiopent* or Tiagabin* or Tiletamine or Timonil or Tiobarbit* or Tipiram* or Topamax or Topiram* or Tranmep or Tranxene or Trapanal or Tridione or Trileptal or Trimethadione or Trobalt):AB,KW,MC,MH,TI AND CENTRAL:TARGET
27. (Urbadan or Urbanil or Urbanyl):AB,KW,MC,MH,TI AND CENTRAL:TARGET
28. (Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro* or Versed or Vigabatrin* or Vimpat or Visano or VPA):AB,KW,MC,MH,TI AND CENTRAL:TARGET
29. (Xilep or "YKP 509" or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
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 AND CENTRAL:TARGET
31. ((duration or month or months or period or periods or rapid or slow) ADJ5 (discontinu* or withdraw* or taper*)):AB,KW,MC,MH,TI AND CENTRAL:TARGET
32. ((discontinu* or withdraw* or taper*) ADJ5 (duration or month or months or period or periods or rapid or slow)):AB,KW,MC,MH,TI AND CENTRAL:TARGET
33. #31 OR #32
34. #30 AND #33
35. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET
36. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET
37. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET
38. #35 OR #36 OR #37
39. eclampsia:TI AND CENTRAL:TARGET
40. #38 NOT #39

41. (relaps* or recur* or reoccur* or remission or prognos*):AB, TI AND CENTRAL:TARGET

42. MESH DESCRIPTOR Remission Induction EXPLODE ALL AND CENTRAL:TARGET

43. MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET

44. MESH DESCRIPTOR Prognosis AND CENTRAL:TARGET

45. MESH DESCRIPTOR Secondary Prevention EXPLODE ALL AND CENTRAL:TARGET

46. #41 OR #42 OR #43 OR #44 OR #45

47. #40 AND #46

48. #34 AND #47

49. MESH DESCRIPTOR Diet Therapy EXPLODE ALL AND CENTRAL:TARGET

50. (diet therapy):EH, EMT, MH AND CENTRAL:TARGET

51. ketogenic:TI AND CENTRAL:TARGET

52. #49 OR #50 OR #51

53. #48 NOT #52

Appendix 2. MEDLINE search strategy

This strategy was based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in [Lefebvre 2011](#).

1. exp *Epilepsy/dt [Drug Therapy]

2. exp Seizures/dt [Drug Therapy]

3. exp Anticonvulsants/

4. exp Midazolam/

5. exp Methazolamide/

6. exp Propofol/

7. exp Temazepam/

8. exp Thiopental/

9. (antiepilep\$ or anti-epilep\$ or anticonvulsant\$ or anti-convulsant\$ or AED or AEDs).tw.

10. (Acetazolamid\$ or Aedon or Aethosuximide or Alodorm or Amizepin\$ or Ant?lepin or Anxirloc or Arem or Ativan or Atretol or Avugane).tw.

11. (Baceca or Barbexaclon\$ or Beclamid\$ or Biston or Bomathal or Brivaracetam or Bromid\$).tw.

12. (Calepsin or Carbagen or Carbamazepen\$ or Carbamazepin\$ or Carbamezepin\$ or Carbatrol or Carbazepin\$ or Carbelan or Carisbamat\$ or Castilium or CBZ or Celontin or Cerebyx or Chlonazepam or Chloracon or C?lorepin or C?lormethiazole or Clarmyl or Cloazepam or Clobam\$ or Clobator or Clobazam or Clofritis or Clonazepam\$ or Clonex or Clonopin or Clopax or Clorazepate or Comfyde or Convulex).tw.

13. (Dapaz or Dasuen or Delepsine or Depacon or Depak\$ or Depamide or Deproic or Desitin or Diacomit or Diamox or Diastat or Diazepam or Difenilhidantoin\$ or Dihydantoin or Dilantin or Dimethadione or Dimethyloxazolidinedione or Diphenin\$ or Diphenylan or Diphenylhydantoin\$ or Diphenylhydantoin\$ or Distraneurin or Divalpr\$ or Dormicum or DPA or Dwufenylohydantoin\$).tw.

14. (E2007 or Ecovia or Emeside or Epanutin or Epject or Epilepax or Epilex or Epilim or Episenta or Epitol or Epival or Eptoin or Equanil or Equetro or Ergenyl or Erimin or Erlosamide or Eslicarbazepine or Estazolam or Ethadione or Ethosucci\$ or Ethosuxi\$ or Ethotoin or Ethylphenacemide or Etosuxi\$ or Euhypnos or Exalief or Excegran or Ezogabine).tw.

15. (Fanatrex or Felbam\$ or Felbatol or Fenitoin\$ or Fenobarbit\$ or Fenytoin\$ or Finlepsin or Fosphenytoin or Frisium or Fycompa).tw.

16. (Gabapentin\$ or Gabapetin\$ or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Grifoclobam).tw.

Rapid versus slow withdrawal of antiepileptic drugs (Review)

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17. (Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel).tw.
18. (Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex).tw.
19. (Lacosamid\$ or Lamict\$ or Lamitor or Lamitrin or Lamogine or Lamotrigin\$ or Lamotriline or Landсен or Levaxol or Levetiracetam\$ or Lexin or Liskantin or Loraz or Lorazepam\$ or Losigamon\$ or Lucium or Luminal or Lyrica).tw.
20. (Magnesium sulfat\$ or Magnesium sulphat\$ or Mebaral or Medazepam or Mephenytoin or Mephobarbit\$ or Mephytaletten or Meprobamate or Meprospan or Mesantoin or Mesuximide or Methazolamid\$ or Methsuximide or Methylacetazolamide or Methyloxazepam or Methylphenobarbit\$ or Midazolam or Miltown or Mogadon or Mylepsinum or Mylproin or Mysoline or Mystan).tw.
21. (Neogab or Neptazane or Nesdonal or Neurontin or Neurotop or Nimetazepam or Nitrados or Nitrazadon or Nitrazepam or Nobrium or Nocturne or Noiafren or Norkotral or Normison or Normitab or Nortem or Novo-Clopatе or Nuctalon or Nupentin or Nydrane).tw.
22. (OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or Oxcarbamazepin\$ or Oxcarbazepin\$ or Oxydiazepam).tw.
23. (Pacisyn or Paraldehyde or Paramethadione or Paxadorm or Paxam or Peganone or Penthobarbital or Pentothal or Perampanel \$ or Petinutin or Petril or Phemiton or Phenacemide or Pheneturide or Phenobarbit\$ or Phensuximide or Phenylethylbarbit\$ or Phenylethylmalonylurea or Phenytek or Phenytoin\$ or Planum or Posedrine or Potiga or Pregabalin or Primidone or Prodilantin or Progabide or Prominal or Pronervon or Propofol or Prosom or Prysoline).tw.
24. (Ravotril or Remacemide or Remestan or Remnos or Resimatil or Restoril or Retigabine or Riluzole or Rilutek or Riv?tril or Rudotel or Rufinamide or Rusedal or "RWJ-333369").tw.
25. (Sabril or Seclar or Sederlona or Selenica or Seletacetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or SPD417 or Stavzor or Stazepin\$ or Stedesa or Stiripentol or Sulthiam\$ or Sultiam\$).tw.
26. (Talampanel or Taloxa or Tasedan or Tegret?l or Telesmin or Temaze or Temazep\$ or Temesta or Temtabs or Tenox or Teril or Thiomеbunal or Thionembutal or Thiopent\$ or Tiagabin\$ or Tiletamine or Timonil or Tiobarbit\$ or Tipiram\$ or Topamax or Topiram\$ or Tranmep or Tranxene or Trapanal or Tridione or Trileptal or Trimethadione or Trobalt).tw.
27. (Urbadan or Urban?l).tw.
28. (Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro\$ or Versed or Vigabatrin\$ or Vimpat or Visano or VPA).tw.
29. (Xilep or "YKP 509" or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid\$).tw.
30. or/1-29
31. ((duration or month? or period? or rapid or slow) adj5 (discontin\$ or withdraw\$ or taper\$)).tw.
32. 30 and 31
33. exp Epilepsy/
34. exp Seizures/
35. (epilep\$ or seizure\$ or convuls\$).tw.
36. 33 or 34 or 35
37. exp *Pre-Eclampsia/ or exp *Eclampsia/
38. 36 not 37
39. (relaps\$ or recur\$ or reoccur\$ or remission or prognos\$).ti,ab.
40. exp REMISSION INDUCTION/ or exp RECURRENCE/ or PROGNOSIS/ or exp Secondary Prevention/ [PROGNOSIS deliberately not expanded]
41. 39 or 40
42. 38 and 41
43. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
44. clinical trials as topic.sh.

45. trial.ti.
46. 43 or 44 or 45
47. exp animals/ not humans.sh.
48. 46 not 47
49. 32 and 42 and 48
50. exp *Diet Therapy/ or diet therapy.fs. or ketogenic.ti.
51. 49 not 50
52. remove duplicates from 51

Appendix 3. ICTRP search strategy

withdrawal AND antiepileptic AND Epilepsy AND randomized

Appendix 4. SCOPUS search strategy

Searched for randomized controlled trials that cited Tennison M, Greenwood R, Lewis D, Thorn M. Discontinuing antiepileptic drugs in children with epilepsy. A comparison of a six-week and a nine-month taper period. *New England Journal of Medicine* 1994;330(20):1407-10.

List of citations

Refinement to [() AND (TITLE-ABS-KEY ((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") W/4 (analy* OR design OR evaluat* OR investigat* OR method OR procedure OR study OR studies OR trial)))]

WHAT'S NEW

Date	Event	Description
9 April 2019	New search has been performed	Searches updated 9 April 2019; one new study has been included (Serra 2005).
9 April 2019	New citation required but conclusions have not changed	Conclusions are unchanged.

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 2, 2006

Date	Event	Description
19 January 2013	New search has been performed	Searches updated December 2012. Two additional references added to Classification pending references, January 2013.
11 August 2009	Amended	Contact details updated.
3 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

All review authors participated in study selection, data extraction, and analysis.

All review authors contributed to the overall writing up of the review.

DECLARATIONS OF INTEREST

FAL: none known.

EGT: none known.

FB: has acted as a consultant and received travel support from Eisai; he has received payment for lectures from UCB Pharma.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

When updating the review, we distinguished between primary and secondary outcomes. Among primary outcomes, we added 'Seizure freedom after AED withdrawal assessed at one, two, and five years'.

We performed a more comprehensive assessment of bias, focusing on the following methodological issues and risk of bias: random sequence generation (selection bias); allocation concealment (selection bias); blinding (performance bias and detection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); and selective reporting (reporting bias).

We edited the review according to current Cochrane requirements ([Higgins 2011](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*administration & dosage] [adverse effects]; Epilepsy [*drug therapy]; Recurrence; Remission Induction; Risk Factors; Time Factors

MeSH check words

Child; Humans