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Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure (Review)

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[Intervention Review]

Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure

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ABSTRACT

Background

This is an updated version of the Cochrane review previously published in 2016.

There is considerable disagreement about the risk of recurrence following a first unprovoked epileptic seizure. A decision about whether to start antiepileptic drug treatment following a first seizure should be informed by information on the size of any reduction in risk of future seizures, the impact on long-term seizure remission, and the risk of adverse effects.

Objectives

To review the probability of seizure recurrence, seizure remission, mortality, and adverse effects of antiepileptic drug (AED) treatment given immediately after the first seizure compared to controls (placebo, deferred treatment, or no treatment) in children and adults.

Search methods

For the latest update, we searched the Cochrane Register of Studies (CRS Web) and MEDLINE (Ovid, 1946 to May 24, 2019) on 28 May 2019. There were no language restrictions. The Cochrane Register of Studies includes the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised or quasi-randomised, controlled trials from Embase, ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry Platform (ICTRP).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs that could be blinded or unblinded. People of any age with a first unprovoked seizure of any type. Included studies compared participants receiving immediate antiepileptic treatment versus those receiving deferred treatment, those assigned to placebo, and those untreated.

Data collection and analysis

Two review authors independently assessed the studies identified by the search strategy for inclusion in the review and extracted data. The certainty of the evidence for the outcomes was classified in four categories according to the GRADE approach. Dichotomous outcomes were expressed as Risk Ratios (RR) with 95% confidence intervals (CI). Time-to-event outcomes were expressed as Hazard Ratios (HR) with 95% CI. Only one trial used a double-blind design, and the two largest studies were unblinded. Most of the recurrences were generalised tonic-clonic seizures, a major type of seizures that is easily recognised, which should reduce the risk of outcome reporting bias.

Main results

After exclusion of irrelevant papers, six studies (eleven reports) were selected for inclusion. Individual participant data were available from the two largest studies for meta-analysis.

Selection bias and attrition bias could not be excluded within the four smaller studies, but the two largest studies reported attrition rates and adequate methods of randomisation and allocation concealment. Only one small trial used a double-blind design and the other trials were unblinded; however, most of the recurrences were generalised tonic-clonic seizures, a type of seizure that is easily recognisable.

Compared to controls, participants randomised to immediate treatment had a lower probability of relapse at one year (RR 0.49, 95% CI 0.42 to 0.58; 6 studies, 1634 participants; high-certainty evidence), at five years (RR 0.78; 95% CI 0.68 to 0.89; 2 studies, 1212 participants; high-certainty evidence) and a higher probability of an immediate five-year remission (RR 1.25; 95% CI 1.02 to 1.54; 2 studies, 1212 participants; high-certainty evidence). However, there was no difference between immediate treatment and control in terms of five-year remission at any time (RR 1.02, 95% CI 0.87 to 1.21; 2 studies, 1212 participants; high-certainty evidence). Antiepileptic drugs did not affect overall mortality after a first seizure (RR 1.16; 95% CI 0.69 to 1.95; 2 studies, 1212 participants; high-certainty evidence). Compared to deferred treatment, treatment of the first seizure was associated with a significantly higher risk of adverse events (RR 1.49, 95% CI 1.23 to 1.79; 2 studies, 1212 participants; moderate-certainty evidence). We assessed the certainty of the evidence as moderate to low for the association of higher risk of adverse events when treatment of the first seizure was compared to no treatment or placebo, (RR 14.50, 95% CI 1.93 to 108.76; 1 study; 118 participants) and (RR 4.91, 95% CI 1.10 to 21.93; 1 study, 228 participants) respectively.

Authors' conclusions

Treatment of the first unprovoked seizure reduces the risk of a subsequent seizure but does not affect the proportion of patients in remission in the long term. Antiepileptic drugs are associated with adverse events, and there is no evidence that they reduce mortality. In light of this review, the decision to start antiepileptic drug treatment following a first unprovoked seizure should be individualised and based on patient preference, clinical, legal, and sociocultural factors.

PLAIN LANGUAGE SUMMARY

Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure

Background

Antiepileptic drug treatment following a first seizure still remains a controversial issue. In this review, we summarised evidence about the effects of immediate treatment with antiepileptic drugs compared to control (placebo [an inactive dummy treatment], deferred or no treatment) on seizure recurrence, seizure remission, side effects and mortality (death).

The evidence is current to May 2019.

Methods

Our literature search found six studies (eleven reports) that included children, adults, or both, with a first unprovoked seizure of any type (focal, generalised or unclassified). They compared antiepileptic treatment given immediately after the first seizure versus deferred (delayed) treatment, placebo or no treatment. Some of the studies did not clearly describe their methods, or how many people dropped out of the study. In five out of the six studies, the participants, clinicians and researchers involved in the studies knew which groups participants were in (immediate or delayed treatment). However, as most seizure recurrences were generalised tonic-clonic seizures, a convulsive type of seizures that is easily recognisable, we do not think that knowing which group the participants were in influenced the results.

Results

Compared to controls, participants randomised to immediate treatment had a lower probability of seizure recurrence at one year and at five years (high-certainty evidence), although there was no difference between immediate treatment and control in terms of five-year remission at any time.

Immediate treatment did not contribute to the overall mortality of epilepsy after the first seizure (high-certainty evidence), but treatment of the first seizure was associated with a significantly higher risk of adverse events. The certainty of the evidence for side effects was moderate to low with variable reporting of the outcome in the included studies; there was moderate-certainty evidence that immediate treatment may result in more side effects than delayed treatment, but it was unclear if immediate treatment results in more side effects than placebo or no treatment.

Conclusions

In conclusion, treatment of the first unprovoked seizure seems to reduce the risk of relapse but does not affect the long-term prognosis of epilepsy. However, treatment seems to carry a higher risk of side effects. The decision to treat a first unprovoked seizure should be individualised and based on clinical, legal, and sociocultural factors.

Summary of findings 1. Immediate treatment compared to controls for first unprovoked seizure: seizure recurrence

Seizure recurrence						
Patient or population: patients with first unprovoked seizure **Settings:** hospitalised patients and outpatients **Intervention:** immediate treatment compared to control (see comments)						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control (see comments)	**Immediate treatment**				
Seizure recurrence at 5 years after randomisation Follow-up: 1 to 60 months	**469 per 1000**	**366 per 1000** (319 to 417)	**RR 0.78** (0.68 to 0.89)	1212 (2 studies)	⊕⊕⊕⊕ **High** [1]	Control treatment was deferred treatment.
Five-year immediate remission after randomisation Follow-up: 1 to 60 months	**180 per 1000**	**225 per 1000** (184 to 277)	**RR 1.25** (1.02 to 1.54)	1212 (2 studies)	⊕⊕⊕⊕ **High** [1]	Control treatment was deferred treatment.
Five-year remission at any time after randomisation Follow-up: 1 to 192 months	**307 per 1000**	**313 per 1000** (267 to 371)	**RR 1.02** (0.87 to 1.21)	1212 (2 studies)	⊕⊕⊕⊕ **High** [1]	Control treatment was deferred treatment.
Seizure recurrence at 1 year after randomisation Follow-up: 1 to 12 months	**389 per 1000**	**191 per 1000** (163 to 226)	**RR 0.49** (0.42 to 0.58)	1634 (6 studies)	⊕⊕⊕⊕ **High** [1,2]	Control treatments were placebo, no treatment or deferred treatment.
Mortality at the end of the follow-up Follow-up: 1 to 192 months	**41 per 1000**	**48 per 1000** (29 to 80)	**RR 1.16** (0.69 to 1.95)	1212 (2 studies)	⊕⊕⊕⊕ **High** [3]	Control treatment was deferred treatment.
Adverse events (control - deferred treatment) Follow-up: 1 to 192 months	**205 per 1000**	**305 per 1000** (252 to 366)	**RR 1.49** (1.23 to 1.79)	1212 (2 studies)	⊕⊕⊕⊖ **Moderate** [4]	

Adverse events (control - no treatment) Follow-up: 1 to 192 months	There were no adverse events in the control (no treatment) group	There were 13 adverse events in the immediate treatment group	**RR 14.50** (1.93 to 108.76)	118 (1 study)	⊕⊕⊖⊖ **Low** [5]
Adverse events (control - placebo) Follow-up: 1 to 192 months	**18 per 1000**	**87 per 1000** (19 to 388)	**RR 4.91** (1.10 to 21.93)	228 (1 study)	⊕⊕⊕⊖ **Moderate** [6]

The basis for the assumed risk was the event rate in the control groups across studies. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[1] Although outcome assessment was not blinded in all studies, most of the seizure recurrences were generalised tonic-clonic seizures, a type of seizures that is easily recognizable (all in Gilad 1996 and FIRST 1993, 552/693 in Marson 2005, not specified in the other studies), no downgrade made due to risk of bias.
[2]Point estimates varied widely across studies; however, all studies favoured immediate treatment and confidence limits largely overlapped. For this reason, inconsistency may not be important.
[3]Although the total number of participants did not reach the threshold for the optimal information size, we did not downgrade because the event rate was extremely low and the absolute difference of events between control and experimental group was very low.
[4] Downgraded once due to inconsistency; no adverse events were reported in one trial (FIRST 1993) and for 124 out of 402 participants in the other trial (Marson 2005).
[5] Downgraded twice due to very wide confidence intervals and low number of events; we are uncertain about this estimate.
[6] Downgraded once due to wide confidence intervals and low number of events.

BACKGROUND

This is an updated version of the Cochrane review previously published in 2016 (Leone 2016).

Description of the condition

First unprovoked seizures and epilepsy (two or more clinically unprovoked seizures) are fairly common presentations (incidence of first unprovoked seizure 33 to 98 per 100,000 per year; incidence of epilepsy 23 to 190 per 100,000 per year; prevalence of epilepsy 3 to 41 per 1000; lifetime risk of epilepsy 1% to 3%; Beghi 2007; Hauser 1990a). There is considerable disagreement about the risk of recurrence following a first unprovoked seizure. Estimates of recurrence rates over two and three years after the first seizure have varied between 23% (Pearce 1979), and 71% (Elwes 1985); these differences are likely due to selection bias and other methodological problems. In a population-based study, the risk of recurrence has been estimated at 14% at one year, 29% at three years, and 34% at five years (Hauser 1990b). In a systematic review and meta-analysis that included both prospective and retrospective observational studies, the pooled estimate of the risk of recurrence at two years after the first unprovoked seizure was 42% (95% confidence interval (CI), 39% to 44%; Berg 1991).

The more seizures an individual has had, the higher the risk of subsequent seizures; the risk of a recurrence following two seizures is approximately 73%, and after three seizures is 76% (Hauser 1998). There is agreement that antiepileptic drug treatment should be offered after a second seizure (and hence a diagnosis of epilepsy) (CGEE 1986; Mattson 1985; Mattson 1992), and approximately 70% of participants starting antiepileptic drug treatment will enter a five-year period of terminal remission from seizures (Annegers 1979).

Description of the intervention

The interventions assessed in this review are antiepileptic drugs (AEDs), which are usually taken in tablet form.

The value of AEDs for the treatment of a first unprovoked seizure has long been a subject of debate. Evidence against treatment of the first seizure was provided by observational studies, which reported no difference in the risk of recurrence between treated and untreated participants (Annegers 1986; Camfield 1985; Hauser 1990b; Hopkins 1988; Shinnar 1996). Some randomised trials demonstrated that AEDs can reduce the relapse of a first seizure (Camfield 1989; FIRST 1993; Gilad 1996); however, treatment of the first seizure and treatment of the relapse do not seem to affect the long-term remission of epilepsy (FIRST 1993; Marson 2005), and antiepileptic drug treatment may be associated with adverse effects as well as increased stigma.

How the intervention might work

There are many licensed antiepileptic drugs that prevent seizures through a variety of mechanisms. The efficacy and effectiveness of these drugs when used as initial monotherapy treatment in people with epilepsy has been shown in a Cochrane review with individual participant data network meta-analysis (Nevitt 2017).

Why it is important to do this review

A decision to start antiepileptic drug treatment following a first seizure should be addressed by information about the size of any reduction in risk of future seizures, impact on longer term seizure outcomes (seizure remission), and the risk of adverse effects. In this review, we assessed the outcomes associated with policies of immediate antiepileptic drug treatment following a first unprovoked seizure compared to policies where treatment was deferred or where participants received no treatment or a placebo treatment.

The decision to start antiepileptic drug treatment following a first seizure still remains a controversial issue. In this review, we summarised evidence from randomised and quasi-randomised controlled trials, assessing the benefits and harms of antiepileptic drug treatment following a first seizure.

OBJECTIVES

To review the probability of seizure recurrence, seizure remission, mortality, and adverse effects of antiepileptic drug (AED) treatment given immediately after the first seizure compared to controls (placebo, deferred treatment, or no treatment) in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs that could be blinded or unblinded.

Types of participants

People of any age with a first unprovoked seizure of any type (focal, generalised, or unclassified).

Types of interventions

Intervention group:

We included trials in which participants received immediate antiepileptic treatment (after the first seizure). We included trials in which participants were allocated a specific drug, and trials in which participants were randomised to start treatment, but where the choice of drug was made by the treating clinician.

Control group:

We included trials in which participants received deferred treatment, were given placebo, or were left untreated. For this latter group, AED treatment could be started if thought to be clinically indicated, usually following further seizures.

Types of outcome measures

Primary outcomes

1. Seizure recurrence five years after randomisation (in other words, the occurrence of one or more seizures in the five years following randomisation)
2. Five-year immediate remission after randomisation (in other words, the immediate achievement of a seizure-free period of five years following randomisation)

Secondary outcomes

1. Seizure recurrence at one year, two years after randomisation, or at any time after randomisation

2. Time-to-recurrence after the first seizure
3. Two-year immediate remission and two-year remission at any time during follow-up (in other words, the achievement of a seizure-free period of two years immediately after randomisation or at any time during the follow-up)
4. Five-year remission at any time during follow-up
5. Time-to-two-year and five-year remission
6. Mortality during follow-up
7. Adverse events

Search methods for identification of studies

Electronic searches

Searches were run for the original review in 2015. Subsequent searches were run in August 2017, April 2018, and May 2019. For the latest update, we searched the following databases on 28 May 2019:

1. Cochrane Register of Studies (CRS Web), using the search strategy shown in Appendix 1. This includes the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised or quasi-randomised, controlled trials from Embase, ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry Platform (ICTRP).
2. MEDLINE (Ovid, 1946 to May 24, 2019), using the search strategy shown in Appendix 2.

We imposed no language restrictions.

Searching other resources

Journal handsearching

We limited handsearching to the reference lists of the articles traced through electronic database searches. We contacted experts in the field when necessary. We did not search for unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (MAL, GG) independently assessed the studies identified by the search strategy for inclusion in the review, extracted data, and specified reasons for excluding studies. They resolved disagreements by discussion with a third author (EB). When required, they requested unpublished data directly from the relevant author.

In the case where one of the review authors was an investigator on an identified study, this review author did not take part in decision-making about that study. Instead, two review authors not involved in the study decided on its eligibility. Review authors resolved any disagreements on study inclusion by consensus.

Data extraction and management

The review authors extracted the following information. The review authors (EB, MAL, AGM) who were investigators on the two included studies did not participate in the extraction of data for those studies.

Trial methods

1. Method of generation of random list
2. Method of concealment of randomisation
3. Methods of blinding
4. Completeness of the follow-up
5. Whether protocol was mentioned or published

Participant characteristics

1. Total number of participants allocated to each group (treatment or control)
2. Age and gender
3. Seizure type (focal or generalised seizure)
4. Number of seizures at baseline and after randomisation period
5. Adverse events
6. The reason for participants' exclusion

Intervention types

1. Types and doses of drugs tested
2. Duration of pre-randomisation baseline period
3. Duration of treatment period

Outcomes

1. Number of participants experiencing each outcome (see Types of outcome measures)
2. Time at which recurrence was reported
3. Duration of follow-up

Individual Participant Data (IPD) were available for two studies (FIRST 1993; Marson 2005), in which three of the review authors were involved (EB, MAL and AGM). For these studies, dates of randomisation, recurrence of seizure, start of a two- and five-year remission period, end of follow-up, and date of death were used in analyses. Individual Participant Data were not requested for other included studies; published data were extracted and included in meta-analyses.

Assessment of risk of bias in included studies

Two review authors (MAL and EB) independently assessed all included studies for risk of bias. They resolved disagreements by discussion. Both authors performed independent assessments of the following domains; sequence allocation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. For each study, each domain was judged to be at low, high, or unclear risk of bias.

In the case where a review author was an investigator on an included study, two review authors not involved in the trial undertook the 'Risk of bias' assessment.

Measures of treatment effect

Dichotomous outcomes (proportion of participants with seizure recurrence, seizure remission, adverse effects and mortality rate) were expressed as Risk Ratios (RR) with 95% confidence intervals (CI). Time-to-event outcomes (time-to-seizure recurrence, time-to-remission, time-to-death) were expressed as Hazard Ratios (HR) with 95% CIs, to take account of the censored nature of the data.

Unit of analysis issues

Participants were the unit of randomisation and the unit of analysis in all included studies.

Dealing with missing data

We intended to use only published data in the review and to attempt to contact original trial authors if substantial missing data were present. In Gilad 1996, four participants failed to complete the study after randomisation: one for lack of compliance and three were lost to follow-up. These participants were not included in the statistical analyses. We did not attempt to impute any missing data.

For two included trials (FIRST 1993, Marson 2005) for which IPD were available, results reported in published papers were cross-checked against the IPD and databases were double-checked if the review authors found missing data or inconsistencies.

Assessment of heterogeneity

We assessed clinical heterogeneity by reviewing the differences across trials in the characteristics of recruited participants.
We assessed statistical heterogeneity using the Chi^2 test (P value threshold for heterogeneity was 0.10). We also calculated the I^2 statistic and interpreted it as follows, according to Chapter 9.5.2 of the Cochrane Handbook (Higgins 2011) and taking into account the design and participant characteristics of included studies:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

When substantial or considerable heterogeneity was detected (I^2> 50%), a random-effects model was also used.

Assessment of reporting biases

Since the number of assessed studies was low (N = 6), we did not use funnel plots to assess reporting bias. We asked authors of the included studies about unpublished studies. Where available, we compared protocols and published papers to make an assessment of selective outcome reporting bias.

Data synthesis

Individual participant data were available for two studies and were used for the time-to-event analyses (FIRST 1993; Marson 2005). For all the other analyses, we used both IPD and aggregate published data. We calculated Mantel-Haenszel Risk Ratios (RR) and their 95% CIs using a fixed and/or random-effects model (see Assessment of heterogeneity). We calculated overall estimates of Hazard ratios (HR) with 95% CIs using the generic inverse-variance method.

Subgroup analysis and investigation of heterogeneity

As a post hoc change from our protocol, we conducted subgroup analyses according to the type of control group (deferred treatment, no treatment, or placebo), which was only possible for the outcomes 'Seizure recurrence at one year' and 'Adverse events'.

Sensitivity analysis

When substantial or considerable heterogeneity was detected (I^2> 50%), a random-effects model was also used to investigate the robustness of results.

Summary of findings and assessment of the certainty of the evidence

The GRADE approach (Schünemann 2013) was employed to interpret findings and the GRADEpro GDT software (GRADEpro GDT 2020) allowed us to import data from Review Manager to create a 'Summary of findings' table. The table provides outcome-specific information concerning the overall certainty of evidence from studies included in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes we considered. The following outcomes were included in the 'Summary of findings' table: the two primary outcomes: seizure recurrence at 5 years after randomisation and five-year immediate remission after randomisation, and secondary outcomes: five-year remission at any time after randomisation, seizure recurrence at one year after randomisation, mortality and adverse events (subgrouped by control treatment).

We classified the certainty of the evidence for each outcome as high, moderate, low, or very low according to the GRADE approach. We presented the GRADE assessment results in Summary of findings 1.

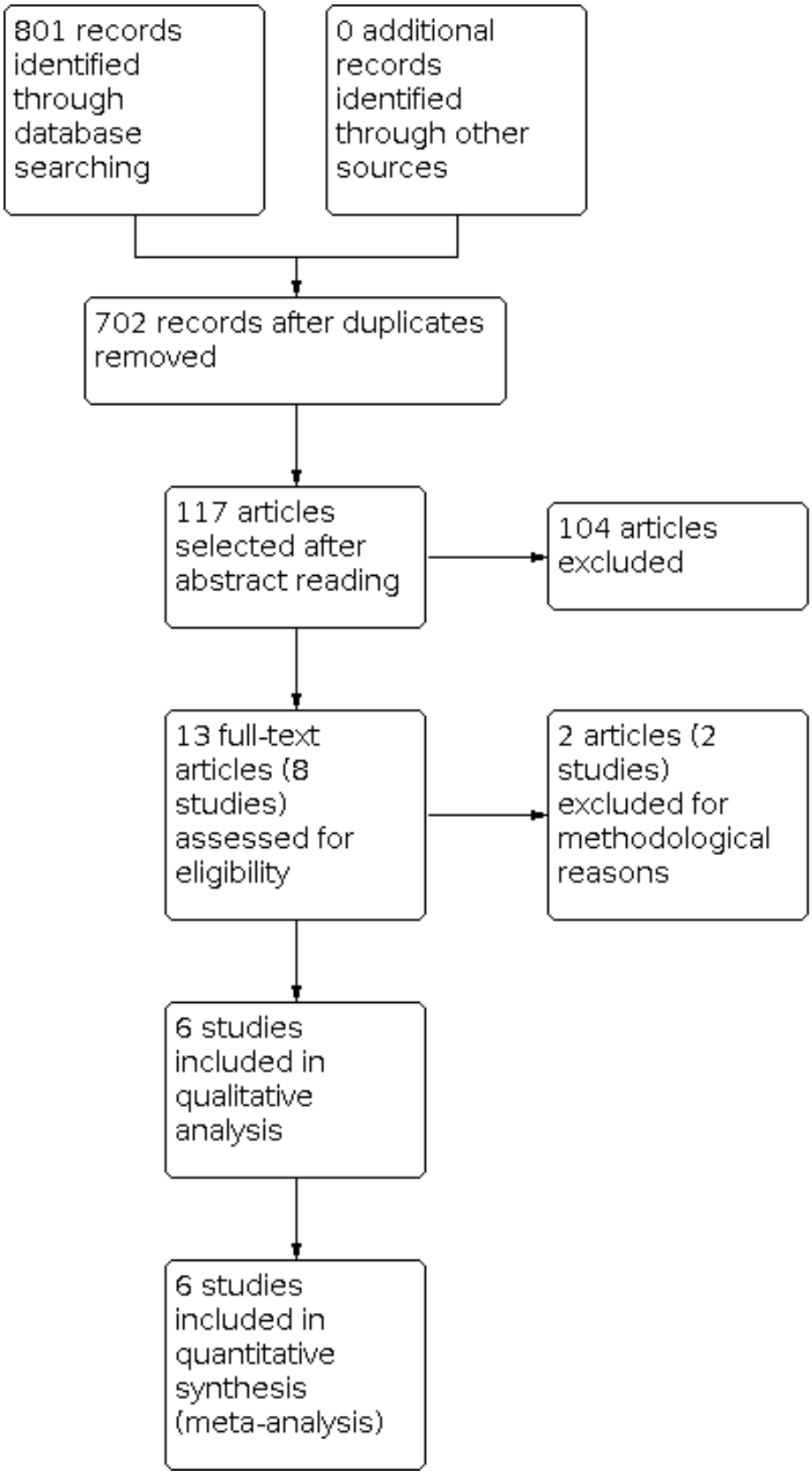
RESULTS

Description of studies

Results of the search

Our search strategy, including handsearching of the reference lists, identified a total of 801 articles. The abstracts of all reports were independently evaluated by two review authors (GG and ML): 788 (98.4%) of these were not relevant for this review and were excluded. Two reports were excluded with a specific reason after reading the full text (Characteristics of excluded studies). This left six studies (eleven reports) for inclusion (Characteristics of included studies and Figure 1).

Figure 1. Study flow diagram.



Included studies

The six studies recruited 1634 participants, 676 women and 958 men. Two of the studies recruited only adults (Chandra 1992; Gilad 1996), one only children (Camfield 1989), and the others recruited both adults and children. Two studies were multicentred (FIRST 1993, Marson 2005), one recruited participants in hospitals where the author was a consultant (Chandra 1992), and the others were single-centre studies. Reported exclusion criteria were: progressive neurological disease (Chandra 1992; Das 2000; FIRST 1993; Gilad 1996; Marson 2005), stroke and vascular malformation (Das 2000; Gilad 1996), neurocysticercosis and tuberculoma (Das 2000), meningitis (Chandra 1992), alcohol and drug abuse (FIRST 1993; Gilad 1996), history of febrile seizures (Das 2000), status epilepticus (Das 2000; Gilad 1996), prior AED use (FIRST 1993; Marson 2005), psychiatric diseases (FIRST 1993), refusal to enter the study (Camfield 1989), and absence of equipoise at randomisation (Marson 2005). Two studies did not apply exclusion criteria (Camfield 1989; Chandra 1992). In one study, all participants were randomised within 24 hours of their first seizure (Gilad 1996); in three studies, all participants were randomised within two weeks of their first seizure (Camfield 1989; Chandra 1992; FIRST 1993); and in one study, 70% of the participants were randomised within two months of their first seizure (Marson 2005). The time from first seizure to randomisation was not stated in the last study (Das 2000). Three studies included only generalised tonic-clonic seizures (Das 2000; FIRST 1993; Gilad 1996); the others included both generalised and focal seizures. Participants were allocated to the intervention group (N = 816) and to the control group (N = 818), which was divided between: deferred treatment (N = 606; FIRST 1993; Marson 2005), placebo (N = 113; Chandra 1992), or no treatment (N = 99; Camfield 1989; Das 2000; Gilad 1996). Individual participant data were available for two of the six studies, and accounted for 1212 participants, or 74% of the entire data set (FIRST 1993; Marson 2005).

Excluded studies

One controlled study was excluded because it was non-randomised (Gupta 1993). One study was excluded because of incomplete description of randomisation and unbalanced treatment groups, therefore it was unclear that the study was randomised (Najafi 2008).

Risk of bias in included studies

The results of our 'Risk of bias' evaluation are summarised in Figure 2 and Figure 3

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

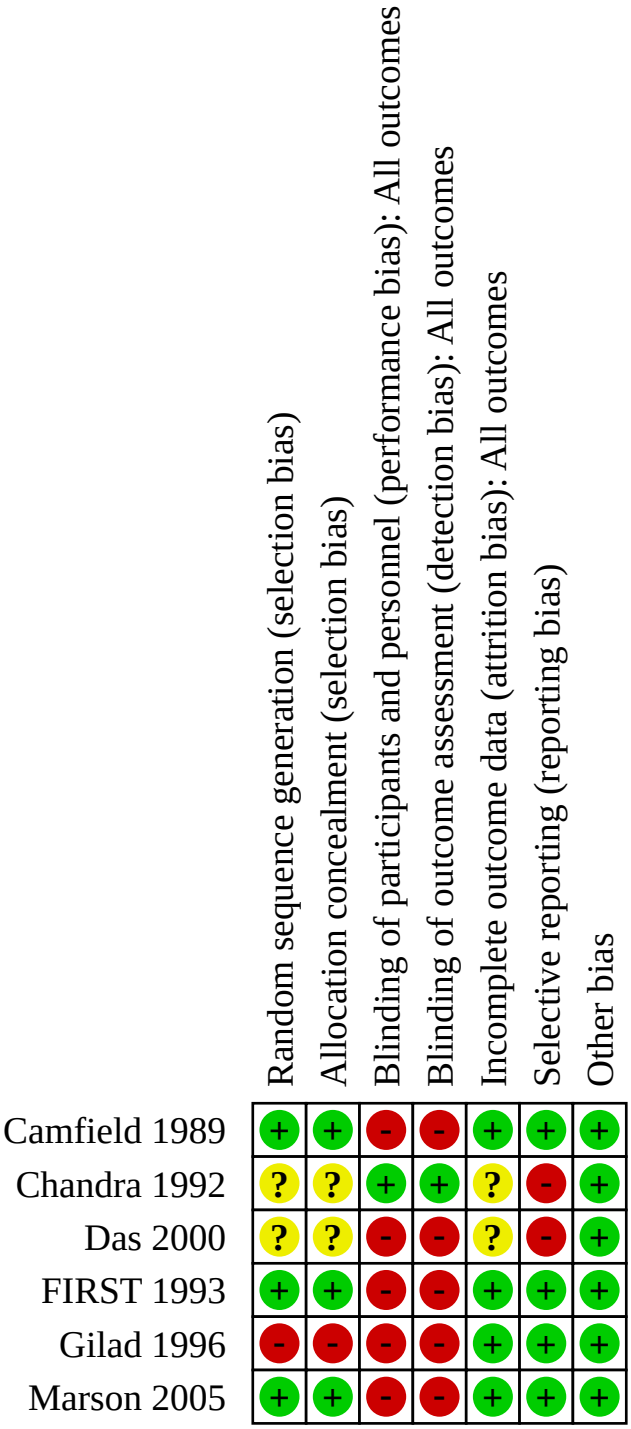
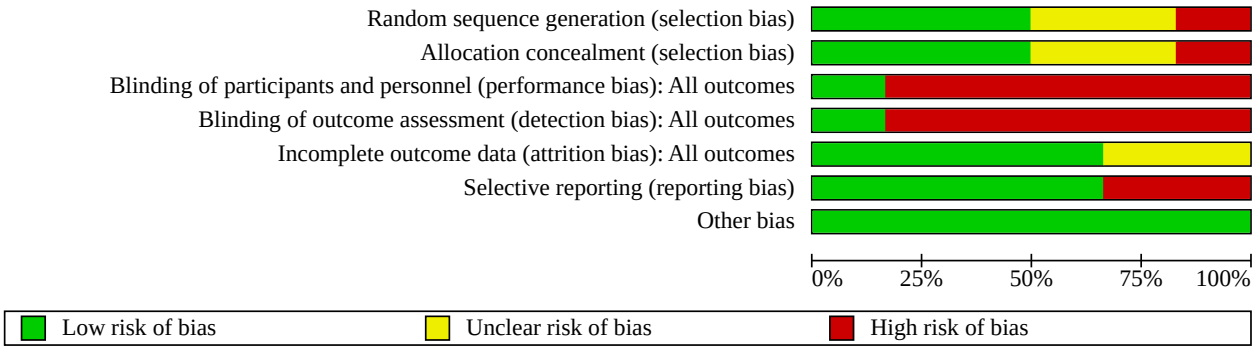


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Three studies were judged to be at low risk of bias, as they described block randomisation methods (Camfield 1989; FIRST 1993), or minimisation randomisation methods (Marson 2005). The same three studies were judged to be at low risk of bias regarding allocation concealment, as they described allocation via an independent centre (FIRST 1993; Marson 2005), or via sealed opaque envelopes (Camfield 1989). Two studies did not describe methods of randomisation and allocation concealment, so were judged to be of unclear risk of bias (Chandra 1992; Das 2000), and one study described an inadequate method of randomisation and allocation concealment (by admission number), so was judged to be at high risk of bias (Gilad 1996).

Blinding

Only one study (Chandra 1992) adopted adequate blinding procedures for participants, providers and outcome assessors. All the other studies were open-label randomised trials (high risk of bias).

Incomplete outcome data

Two studies reported complete follow-up and were considered to be at low risk of bias (Camfield 1989; Gilad 1996). Two studies were long-term studies (up to 16 years of follow-up) and incurred losses to follow-up over the study duration, however, the losses were balanced across the treatment groups and an intention-to-treat approach was used in the analyses of these studies in this review, so they were judged to be at low risk of bias (FIRST 1993; Marson 2005). Two studies (Chandra 1992; Das 2000) were rated as having unclear risk of bias because information regarding attrition rate was not available.

Selective reporting

Individual participant data were available for two studies (FIRST 1993, Marson 2005), with a low risk of bias. Only one study also published the protocol (FIRST 1993). Two studies did not mention the protocol but submitted the study to an Ethical Committee and reported all the clinical outcomes (Camfield 1989; Gilad 1996); they were considered at low risk of bias. Two studies did not mention protocol or Ethical Committee submission, and reported only seizure recurrence; they were considered to be at high risk of bias (Chandra 1992; Das 2000).

Other potential sources of bias

No other potential source of bias was found.

Three review authors (EB, MAL, AGM) are investigators of two of the included studies (FIRST 1993; Marson 2005). To minimise the risk of bias related to their involvement in these trials, we prespecified that data extraction and quality assessment would be performed by review authors not involved in the given trials.

Effects of interventions

See: **Summary of findings 1** Immediate treatment compared to controls for first unprovoked seizure: seizure recurrence

Please refer to Summary of main results and Summary of findings 1 for the primary and secondary outcomes.

Primary outcomes

Maximum follow-up in the included studies ranged from 9 months to 16 years.

Seizure recurrence at five years

Only two studies reported the primary outcome of seizure recurrence at five years (FIRST 1993, Marson 2005). The risk of recurrence at five years was significantly lower for those immediately treated (RR 0.78; 95% CI 0.68 to 0.89; P = 0.0003; Analysis 1.1).

Five-year immediate remission

Immediate antiepileptic drug treatment after the first seizure was associated with a higher probability of an immediate five-year remission period (in other words no further seizures for five years after the first seizure) (RR 1.25; 95% CI 1.02 to 1.54; P = 0.03; Analysis 2.1; FIRST 1993; Marson 2005).

Secondary outcomes

Seizure recurrence at one year, two years, or any time after randomisation

The risk of relapse was significantly lower for those randomised to immediate treatment after a first seizure (RR 0.49; 95% CI 0.42 to 0.58; P < 0.00001; Analysis 1.2) at one year, and at two years (RR 0.69; 95% CI 0.59 to 0.80; P < 0.00001; Analysis 1.4).

However, considerable heterogeneity was present between the trials (I^2 > 80%) for these two outcomes, therefore we also used a random-effects model to recalculate the risk ratio; the RR was 0.30; 95% CI 0.16 to 0.59; P = 0.0004 at one year and RR 0.58; 95% CI 0.37 to 0.89; P = 0.01 at two years after randomisation, indicating that when variation between trials was incorporated into analysis, early seizure recurrence was less probable when treatment was started immediately after the first seizure. For one-year seizure recurrence, point estimates varied widely across studies; however, all studies favoured immediate treatment and confidence limits largely overlapped, but for two-year seizure recurrence, one study (Gilad 1996) had very a different point estimate without any evident explanation.

We conducted a subgroup analysis for seizure recurrence at one year by type of control group (deferred treatment, no treatment, or placebo, see Analysis 1.3). The advantage for immediate treatment was largest compared to placebo control (RR 0.08; 95% CI 0.03 to 0.19; one study), followed by a no-treatment control (RR 0.24; 95% CI 0.14 to 0.43; three studies), and then the deferred treatment control (RR 0.68; 95% CI 0.57 to 0.82; two studies). However, the two studies with the deferred treatment control groups contributed the majority of the data (64.3%; FIRST 1993; Marson 2005). There was a statistically significant difference between subgroups (P < 0.00001) and 93.8% of the variability in the analysis was due to the difference in control groups.

We did not perform subgroup analyses for other outcomes, as the two studies with the deferred treatment control groups contributed 90% to 100% of the data (FIRST 1993, Marson 2005).

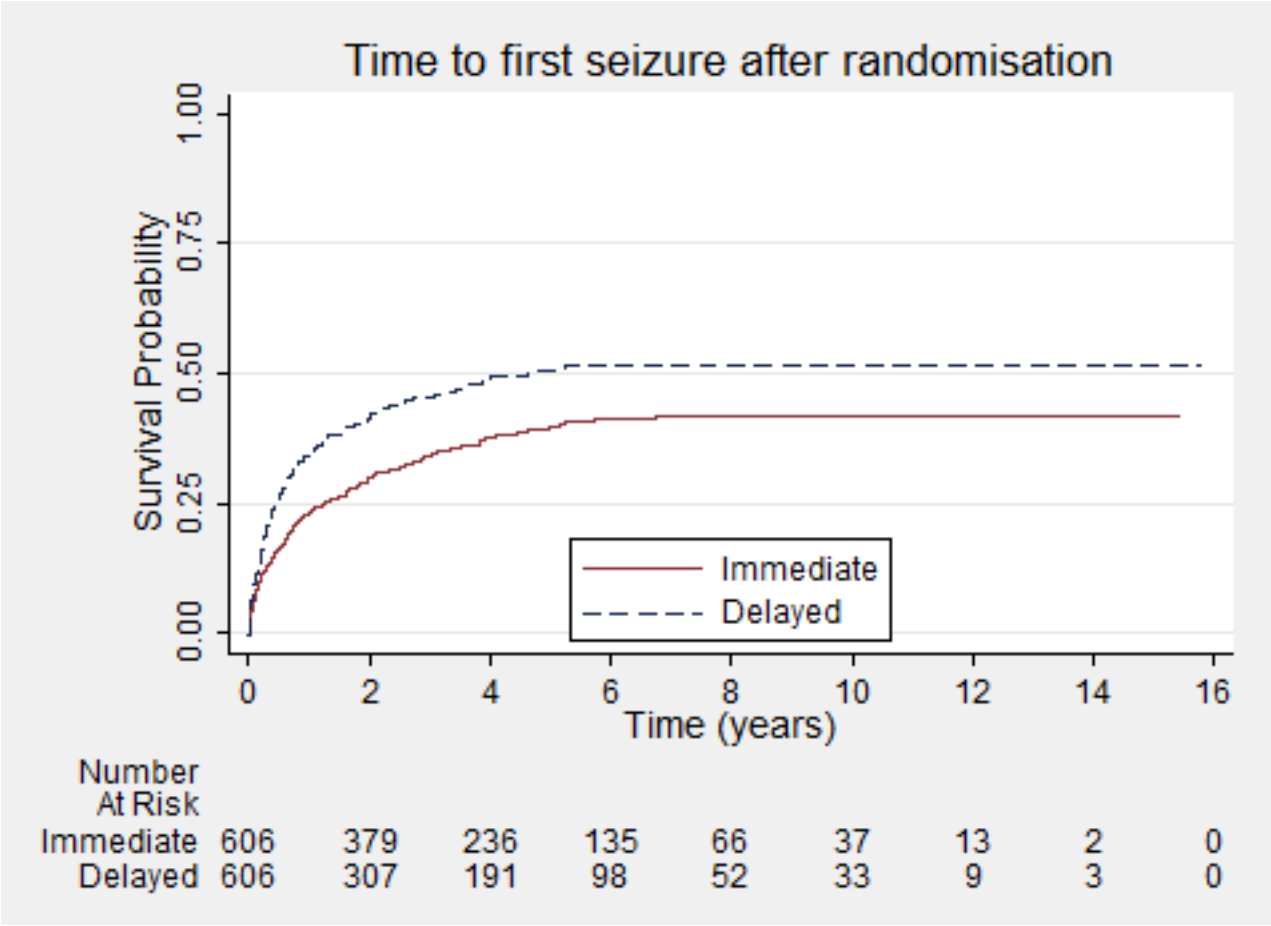
Individual participant data were available for the same two studies, allowing analysis of seizure recurrence at any time during the follow-up, which also showed an advantage for immediate treatment (RR 0.79; 95% CI 0.69 to 0.90; P = 0.0006; Analysis 1.5).

Time-to-recurrence after the first seizure

The time-to-event analysis with FIRST 1993 and Marson 2005 showed a hazard ratio (HR) of 0.70 (95% CI 0.59 to 0.83; P < 0.0001; Analysis 1.6), showing immediate treatment significantly delayed recurrence of seizures. The median time-to-seizure recurrence after randomisation was 736 days in the delayed (control) treatment group and 1165 days in the immediate treatment group.

The cumulative percentages of participants who experienced seizure recurrence from the immediate treatment group compared to the control group were 23.4% versus 34.3% at one year, 30.2% versus 41.4% at two years, and 39.6% versus 50.6% at five years (Figure 4). A log rank test showed a highly significant difference between the treatment groups (P < 0.001).

Figure 4. Cumulative incidence plot of time to first seizure after randomisation



Two-year immediate remission and two-year remission at any time during follow-up

In all studies, the start of a remission period was considered to be the date of onset of a remission period of two or five years.

Data were available from three studies to assess an immediate two-year remission period after randomisation (FIRST 1993; Gilad 1996; Marson 2005); the RR was 1.28; 95% CI 1.16 to 1.41; P < 0.00001; Analysis 2.2), calculated with a fixed-effect model, indicating that attaining immediate two-year remission was more frequent if treatment was started immediately after the first seizure. Considerable heterogeneity was present between the trials (I^2= 81%), therefore the risk ratio was recalculated with a random-effects model; the RR was 1.43; 95% CI 1.09 to 1.87; P = 0.01, indicating that when the variation between trials was incorporated into analysis, attaining two-year remission was still more frequent if treatment was started immediately after the first seizure.

However, in two of the studies where this outcome was available, the chance of attaining a two-year remission period at any time during the follow-up was not significantly different between immediate and deferred treatment (RR 1.03; 95% CI 0.98 to 1.09; P = 0.26; Analysis 2.3; FIRST 1993; Marson 2005).

Subgroup analyses were not performed for these outcomes as the two studies with the deferred treatment control contributed 90% to 100% of the data (FIRST 1993; Marson 2005).

Five-year remission at any time during follow-up

In all studies, the start of a remission period was considered to be the date of onset of a remission period of five years. Analysis 2.1 showed an advantage for immediate treatment for immediate five-year remission. However, the five-year remission period at any time was not significantly different between the immediate and deferred treatment groups (RR 1.02; 95% CI 0.87 to 1.21; P = 0.78; Analysis 2.4) in the two studies where this outcome was available (FIRST 1993; Marson 2005).

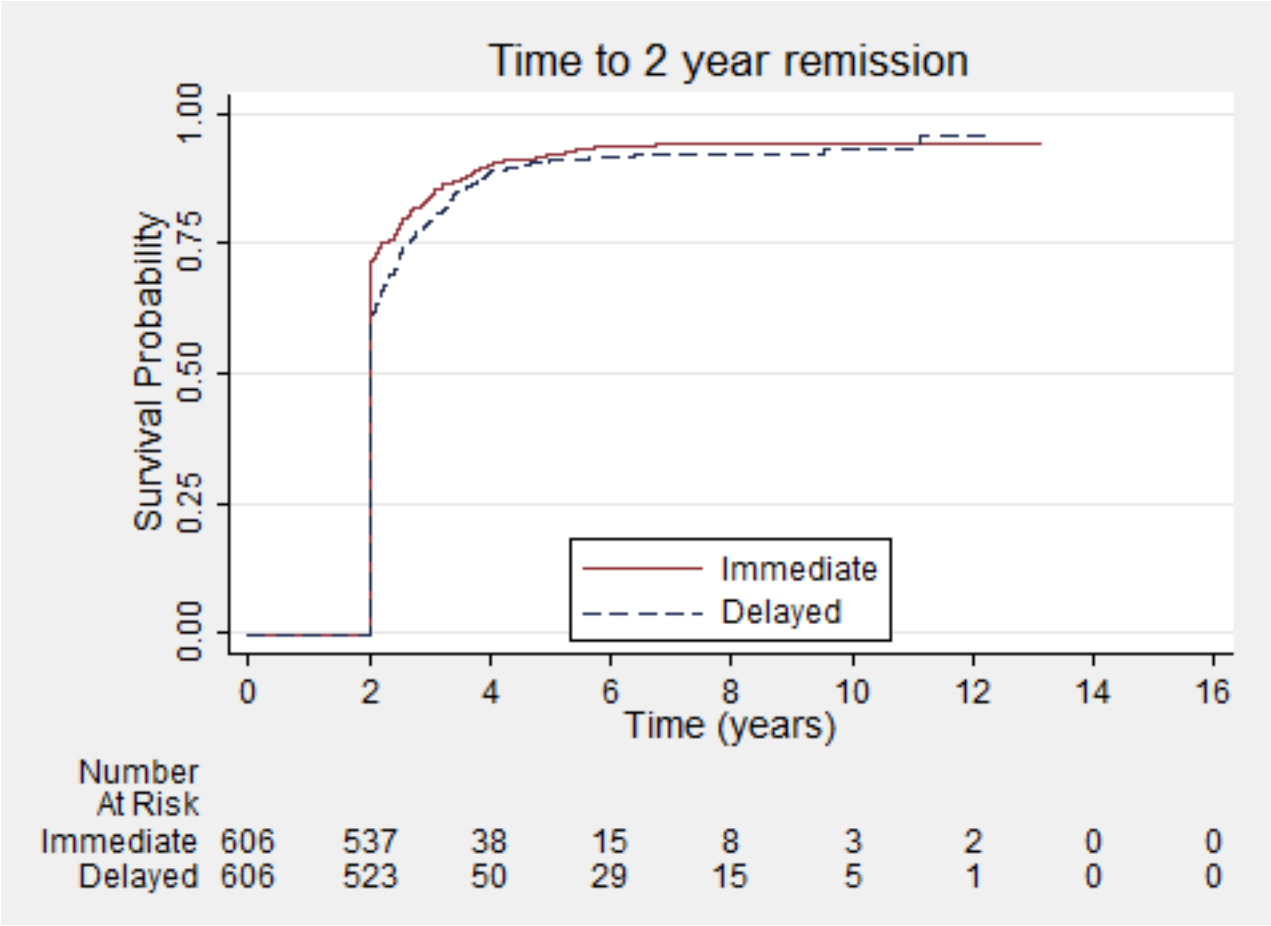
Time-to-two-year and five-year remission

The time-to-event analysis with FIRST 1993 and Marson 2005 showed that both two-year and five-year immediate remissions occurred significantly earlier for immediate treatment compared to delayed treatment (two-year immediate remission HR 1.29; 95% CI 1.10 to 1.52; P = 0.002; Analysis 2.5; five-year immediate remission HR 1.39; 95% CI 1.09 to 1.76; P = 0.007; Analysis 2.6).

Two-year remission at any time also occurred significantly earlier for immediate treatment compared to delayed treatment (HR 1.19; 95% CI 1.05 to 1.35; P = 0.007; Analysis 2.7), but there was no difference between the immediate and delayed treatment groups for five-year remission at any time (HR 1.14; 95% CI 0.93 to 1.39; P = 0.20; Analysis 2.8).

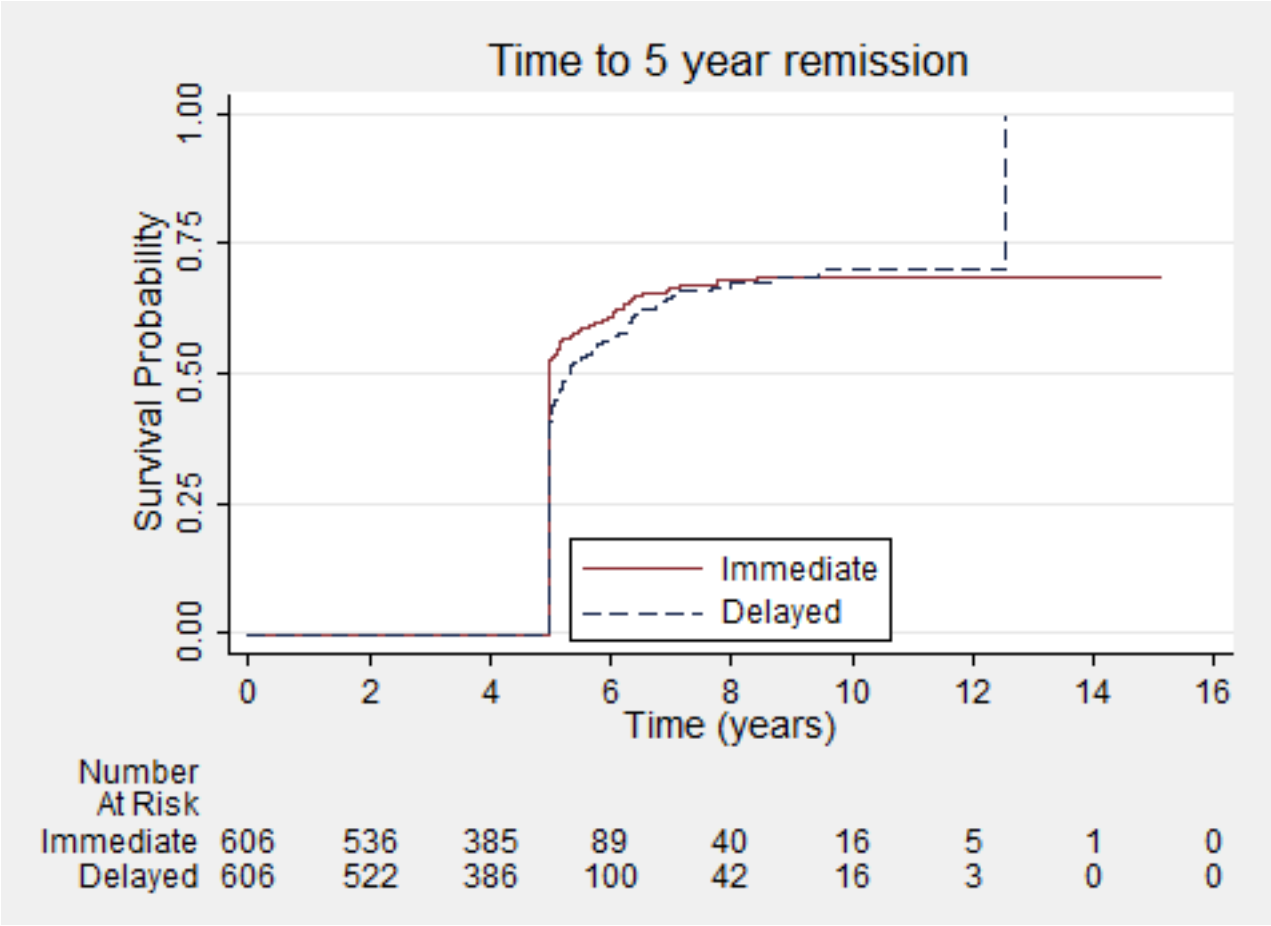
The cumulative time-dependent probability of achieving two-year remission was 70.1% in the immediate treatment group versus 59.1% in the control group at two years, and 92.2% versus 91.5% at five years, respectively (Figure 5). A log rank test showed no significant difference between the treatment groups across all follow-up (P = 0.06).

Figure 5. Cumulative incidence plot of time to 2-year remission



The cumulative time-dependent probability of achieving five-year remission was 52.7% in the immediate treatment group versus 41% in the control group at five years (Figure 6). A log rank test showed no significant difference between the treatment groups across all follow-up (P = 0.46).

Figure 6. Cumulative incidence plot of time to 5-year remission



Mortality during follow-up

Data on deaths during the follow-up (ranging from 8 to 21.5 years) were available for two studies, and showed no difference between the experimental and control groups (RR 1.16; 95% CI 0.69 to 1.95; P = 0.58; Analysis 3.1). Time-to-death was also not different between the immediate and delayed treatment groups (HR 1.14; 95% CI 0.67 to 1.95; P = 0.62; Analysis 3.2; FIRST 1993; Marson 2005).

Adverse events (AEs)

Five studies reported AEs (Camfield 1989; Chandra 1992; FIRST 1993; Gilad 1996; Marson 2005). The risk of having an AE during follow-up was significantly higher for those treated immediately (RR 1.64; 95% CI 1.37 to 1.97; P < 0.00001; Analysis 4.1). Since substantial heterogeneity was present between the trials (I^2= 71%), we recalculated the risk ratio using a random-effects model; RR 6.18; 95% CI 1.61 to 23.73; P = 0.02, indicating that when variation between trials was incorporated into analysis, AEs were still more frequent if treatment was started immediately after the first seizure. However, this analysis was influenced by low and zero event rates in four of the five trials and assessments of adverse events was not blinded and no checklist was used in most studies, therefore we are uncertain regarding the true magnitude of effect for this outcome.

We conducted a subgroup analysis by type of control group (deferred treatment, no treatment, or placebo; Analysis 4.2). The risk of AEs in the immediate treatment group was highest compared to no treatment (RR 14.50; 95% CI 1.93 to 108.76; two studies), followed by placebo control (RR 4.91; 95% CI 1.10 to 21.93; one study), and then the deferred treatment control (RR 1.49; 95% CI 1.23 to 1.79, two studies). However, the two studies with the deferred treatment control contributed the majority of the data (97.6% of events; FIRST 1993; Marson 2005). There was a statistically significant difference between subgroups (P = 0.03) and 72.3% of the variability in the analysis was due to the difference in control groups.

Only one trial reported a complete list of AEs in the intervention and control groups, although data for participants with first seizure and early epilepsy were not discernible (Marson 2005). The five leading AEs were tiredness or drowsiness, gastrointestinal symptoms, depression or anxiety, dizziness or unsteadiness, and headache in the intervention group; dizziness or unsteadiness, depression or anxiety, gastrointestinal symptoms, tiredness or drowsiness, and injury or scalds in the deferred treatment group.

DISCUSSION

Summary of main results

Six trials met our inclusion criteria for this review. Individual participant data were available for two of these trials (74% of participants) for all the outcomes of interest, except adverse events. The trials included in this review consistently found that treatment of the first seizure was followed by a significant reduction in the

risk of relapse during the next 24 months. Compared to controls, participants randomised to immediate treatment had lower risk of relapse at 12 months (risk ratio (RR) 0.49, 95% confidence interval (CI) 0.42 to 0.58), but in the pooled analysis of reports with prolonged follow-up, this advantage was reduced: RR 0.69 (95% CI 0.59 to 0.80) at two years and RR 0.78 (95% CI 0.68 to 0.89) at five years. The robustness of these findings was confirmed by the results of the individual studies, which consistently showed benefit of immediate treatment regardless of age, gender, or assigned drug. For two-year remission, the RR was 1.28, (95% CI 1.16 to 1.41), and for five-year remission, the RR was 1.25 (95% CI 1.02 to 1.54). However, when we considered remission at any time as a marker of impact on the long-term prognosis of epilepsy, no significant difference was observed for both time to two-year remission, RR 1.03 (95% CI 0.98 to 1.09) and time to five-year remission, RR 1.02 (95% CI 0.87 to 1.21). This result was confirmed by the consistency of the results of the two studies with prolonged follow-up (FIRST 1993; Marson 2005).

Antiepileptic drugs did not contribute to either an increase or a decrease in the overall mortality of epilepsy after the first seizure. The mortality rate among participants treated after the first seizure approximated the rate of untreated individuals (RR 1.16, 95% CI 0.69 to 1.95). As the risk of death in participants with unprovoked seizures was comparatively lower than that of acute symptomatic seizures (Hesdorffer 2009), first seizure trials may not have been sufficiently powered to address the effects of treatment on this outcome measure, even when pooled data were examined.

In contrast, immediate treatment of the first seizure was associated with a significantly higher risk of adverse events compared to deferred treatment (RR 1.64, 95% CI 1.37 to 1.97).

Overall completeness and applicability of evidence

The external validity of this review and meta-analysis can be contended on several grounds. First of all, the results obtained for long-term prognosis were mostly driven by the two largest studies (FIRST 1993; Marson 2005), as all the remaining trials (Camfield 1989; Chandra 1992; Das 2000; Gilad 1996) had very small samples, very short follow-up periods, or both. Second, the inclusion criteria were slightly different across studies and even the largest trials differed in seizure types. While participants included in the Marson 2005 study had both focal and generalised seizures, those enrolled in the FIRST 1993 study had only unprovoked (primarily or secondarily) generalised tonic-clonic seizures. Third, all the analyses in the original studies were performed in the intention-to-treat population, and in this regard, they did not consider the start of treatment at the time of seizure relapse among participants who were randomised to be untreated or to receive placebo. This may have diluted the long-term effects of immediate treatment of the first seizure. Fourth, all the examined studies were pragmatic trials which, by definition, have poor internal validity as, except for treatment assignment, virtually no control is exerted on the effects of treatment decisions. Last, in all the studies under review, only first-generation drugs (except for lamotrigine) were assessed. For this reason, we do not know whether similar results could be obtained with second- and third-generation drugs.

Quality of the evidence

Selection bias could not be entirely excluded because the random sequence generation was described in only three studies. However, the two largest studies exerted a satisfactory control of selection bias. Blinding was an issue because only one (small) trial used a double-blind design. The two largest studies were unblinded. However, most of the recurrences were generalised tonic-clonic seizures, a type of seizures that is easily recognizable. For this reason we did not downgrade the certainty of the evidence.
Attrition bias could not be excluded, especially in studies with the longest follow-up; however, the number of dropouts was reported in the largest studies. Reporting bias was difficult to ascertain because the studies were mostly conducted in years when the policy of protocol publication was not widespread.

Certainty of the evidence

Overall, the certainty of the evidence from the included studies was high for seizure recurrence, remission and mortality outcomes; with high-certainty evidence reported in the two large studies, we were able to analyse individual participant data. Certainty of the evidence for adverse events was moderate to low, with variable reporting across studies and imprecision in effect sizes due to small numbers of adverse events occurring.

Potential biases in the review process

The original protocol of the review was published in 2008 (Beghi 2008), however the work on the review did not begin for some time afterwards. With developments in methodology and clinical relevance, before screening eligible studies for inclusion in the review, we reflected upon and changed some of the methods described in our original protocol to more appropriate methods for the review question, including a change to analyse data on adverse events both combined and separately by type of controls. All changes from the methods are outlined in Differences between protocol and review.

Agreements and disagreements with other studies or reviews

Our findings partly overlap with the results of a previous meta-analysis that focused on the effects of immediate versus deferred treatment of the first seizure or seizure relapse, and provide explanatory evidence that the effects of the treatment of the first seizure are short-lasting and reflect a symptomatic rather than a curative action of antiepileptic drugs (Wiebe 2008). A demonstration of the symptomatic role of antiepileptic drugs comes from the results of meta-analyses of the prophylactic use of drugs following head trauma (Thompson 2015), brain tumours (Tremont-Lukats 2008), stroke (Kwan 2010), and craniotomy (Greenhalgh 2020). The results of clinical investigations are in keeping with animal studies and support the concept that none of the drugs currently in use can prevent the establishment of a chronic seizure disorder (Pitkänen 2002).

AUTHORS' CONCLUSIONS

Implications for practice

There is high-certainty evidence that antiepileptic drug treatment following a first unprovoked seizure reduces the risk of relapse but does not affect the proportion of patients achieving a five-year remission in the long term. There is moderate to low-certainty evidence that treatment is associated with adverse events. For these reasons, indiscriminate treatment following a first unprovoked seizure is not warranted, since the risk of

recurrence must be balanced against the likelihood of attaining five-year remission during the follow-up and the possible harm of drugs given for a long-lasting period. Adverse events associated with antiepileptic drugs are a particular concern for children, women considering pregnancy, pregnant women, and the elderly. Therefore, the decision to start antiepileptic drug treatment following a first unprovoked seizure should be individualised and based on patient preference, clinical, legal, and sociocultural factors.

Implications for research

Further research is required to identify patients most likely to benefit from AED treatment following a first seizure, and it is important to highlight that children and the elderly are under-represented in current trials, despite the higher incidence of first seizures in these age groups compared to other adults. One other approach in future trials might be to assess AED treatment in patients with specific epilepsy syndromes, although for many patients it is not possible to diagnose a specific syndrome following only one seizure. Prognostic models can help identify patients most (and least) likely to benefit from AED treatment (Bonnett 2012; Bonnett 2014; Kim 2006), and future trial data could contribute to the generation and validation of such models.

Given the findings of this review, for the majority of patients with a first seizure, it is unlikely that there will be equipoise about the need for AED treatment (versus no AED), but the presence (or absence) of equipoise requires evaluation in order to inform future trials. In the absence of equipoise, it would not be appropriate to undertake further trials where the control group receives placebo (blinded) or no AED treatment (unblinded). It is also important to highlight that it is not feasible to assess long-term outcomes using placebo-controlled designs.

For patients who choose to start AED treatment following a first seizure, current evidence does not reliably inform the choice of specific AED that should be prescribed. For patients with an identified epilepsy syndrome, choice of AED could be extrapolated using data from trials recruiting patients with the same syndrome and an accepted diagnosis of epilepsy. In addition, future head-to-head AED trials in patients with a first seizure are also required to better inform treatment choices. Such trials could recruit only patients with a first seizure, or could recruit patients with one or more seizures.

In this context, consideration must be given to the International League Against Epilepsy's (ILAE) most recent definition of epilepsy, which states that epilepsy can be diagnosed following a single unprovoked seizure, provided that a 60% or greater risk of relapse can be predicted (Fisher 2014). As, by definition, these participants have a higher risk of recurrence, they may be willing to participate in future randomised trials.

Current AEDs reduce the risk of seizure but have no disease-modifying effect, as evidenced by the results of this review; AEDs reduce short-term seizure recurrence risk but have no impact on long-term epilepsy prognosis. Work is ongoing to identify and develop drugs that are disease-modifying (anti-epileptogenic), and it is important to consider the population that might be willing to participate in randomised trials of such treatments, One option is to focus on patients with a brain insult (e.g. head injury) who have a high risk of developing epilepsy. Another option is to consider patients with a first seizure at high risk of recurrence and of developing drug-resistant epilepsy. Further research is required to enable the reliable prediction of outcome for such patients, to assess the acceptability of trials of such treatments that might have important adverse event risks, and to consider wider aspects of trial design.

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Wiebe 2008

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Camfield 1989

Study characteristics	
Methods	Randomised controlled trial
Participants	31 children (intervention 14; control 17) with a first afebrile unprovoked focal or generalised tonic-clonic seizure presenting at a regional population-based epilepsy service
Interventions	Intervention: Carbamazepine 10 to 20 mg/kg/day Control: No anticonvulsant treatment
Outcomes	Recurrent unprovoked afebrile seizure at 12 months Carbamazepine side effects leading to treatment stop or change Achievement of > 2-year remission
Notes	Study supported in part by Ciba-Geigy pharmaceutical company

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were stratified according to seizure type (focal versus generalised seizures), age (≤ 6 versus > 6 years) and neurological deficits (absent/present). Randomisation was in blocks of 6 for each factor
Allocation concealment (selection bias)	Low risk	Allocation by sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were aware of treatment allocation

Camfield 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators were aware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome at 12 months was reported for all included participants.
Selective reporting (reporting bias)	Low risk	No protocol mentioned. Ethical Committee mentioned. Clinical relevant outcomes reported
Other bias	Low risk	None

Chandra 1992

Study characteristics	
Methods	Randomised controlled trial
Participants	228 participants (113 intervention; 115 control) 16 years or older with a single focal or generalised unprovoked seizure; from public or private hospitals
Interventions	Intervention: valproate 1200 mg/day Control: placebo
Outcomes	Seizure recurrence at 12 months
Notes	Sources of funding not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation specified; although participants from several hospitals were included, there was no indication of separate randomisation lists
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was reported to be a double-blind placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was reported to be a double-blind placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information has been made available on the number of participants present at each follow-up visit

Chandra 1992 *(Continued)*

Selective reporting (reporting bias)	High risk	No mention of protocol and submission to Ethical Committee. Only seizure recurrence was reported
Other bias	Low risk	None

Das 2000

Study characteristics		
Methods	Randomised controlled trial	
Participants	76 participants (36 intervention; 40 control) with a single unprovoked idiopathic generalised seizure from a single tertiary centre	
Interventions	Intervention: treatment of seizure with antiepileptic drugs Control: no treatment	
Outcomes	Seizure recurrence at 3, 6, 9, 12, 18, and 24 months	
Notes	Sources of funding not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both participants and investigators were aware of treatment allocations
Blinding of outcome assessment (detection bias) All outcomes	High risk	Both participants and investigators were aware of treatment allocations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was available on the number of participants present at each follow-up visit
Selective reporting (reporting bias)	High risk	No mention of protocol and submission to Ethical Committee. Only seizure recurrence was reported
Other bias	Low risk	None

FIRST 1993

Study characteristics		

FIRST 1993 *(Continued)*

Methods	Multicentre, randomised controlled trial
Participants	419 participants (intervention (immediate treatment) 215; control (delayed treatment) 204) with a first unprovoked generalised tonic-clonic seizure (with or without focal onset)
Interventions	Intervention: treatment with carbamazepine, phenobarbital, valproate or phenytoin at a target dose selected according to physician's preference Control: No treatment until recurrence
Outcomes	Time to first relapse, to 1-year, 2-year, and 5-year remission. Time to death
Notes	Study funded by Ciba-Geigy (now Novartis) pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated separately for each centre with permuted blocks
Allocation concealment (selection bias)	Low risk	Random sequence generated by an independent centre (not involved in participants' recruitment)
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label study: participants were aware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators were aware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 419 randomised, follow-up ≥ 1 year was available for 394 (94%), follow-up ≥ 2 years was available for 370 participants (88%), and follow-up ≥ 5 years was available for 264 participants (63%). Length of follow-up and number lost to follow-up was balanced across groups; intention-to-treat approach was used in analyses in this review
Selective reporting (reporting bias)	Low risk	Protocol published; protocol violation mentioned. Ethical committee mentioned. IPD available
Other bias	Low risk	None

Gilad 1996

Study characteristics

Methods	Quasi-randomised controlled trial
Participants	91 participants (intervention 46; control 45) aged 18 to 50 years, with a generalised unprovoked seizure
Interventions	Intervention: carbamazepine or valproate Control: no treatment

Gilad 1996 *(Continued)*

Outcomes	Seizure recurrence at 12, 24, and 36 months
Notes	Sources of funding not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation on a sequential basis according to the admission number
Allocation concealment (selection bias)	High risk	Allocation not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Both participants and investigators were aware of treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome at 36 months was reported for all included participants
Selective reporting (reporting bias)	Low risk	No mention of protocol and submission to Ethical Committee. However, clinical relevant outcomes were reported
Other bias	Low risk	None

Marson 2005

Study characteristics

Methods	Multicentre randomised, controlled trial
Participants	793 participants; (intervention (immediate treatment) 413; control (delayed treatment) 421), aged at least 1 month, with a single focal or generalised unprovoked seizure, for which the clinician was in equipoise. Data available for analysis for 391 from immediate treatment group and 402 from delayed treatment group, with at least one follow-up visit
Interventions	Intervention: anticonvulsant treatment according to clinician's judgement; daily dose in accordance with clinician's usual practice Control: no anticonvulsant treatment until deemed necessary by the caring clinician
Outcomes	Time from randomisation to first seizure of any type; to first tonic-clonic seizure; to second and fifth seizures of any type; to 2-year remission of seizures; proportion of participants seizure-free for 2 years between 1 and 3 years, and between 3 and 5 years after randomisation; time to death
Notes	Study funded by the UK Medical Research Council

Risk of bias

Marson 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment was assigned by the minimisation method to balance across centre or region
Allocation concealment (selection bias)	Low risk	Random sequence generated by an independent centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label study: participants were aware of treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	High risk	Investigators were aware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 834 participants randomised, follow-up ≥ 1 year was available for 747 (90%), follow-up ≥ 2 years was available for 686 (82%), and follow-up ≥ 5 years was available for 336 (40%). Length of follow-up and number lost to follow-up was balanced across groups; intention-to-treat approach was used in analyses in this review
Selective reporting (reporting bias)	Low risk	No protocol mentioned. Ethical committee mentioned. However, all relevant outcomes were reported and IPD were available
Other bias	Low risk	None

IPD = independent patient data

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

Study	Reason for exclusion
Gupta 1993	Excluded as study design not in the inclusion criteria: controlled non-randomised study
Najafi 2008	Incomplete description of randomisation and therefore unclear that the study was randomised. Unbalanced groups after randomisation: 50 participants in the experimental group (immediate treatment) and 87 in the control group (no treatment)

DATA AND ANALYSES

Comparison 1. Seizure recurrence

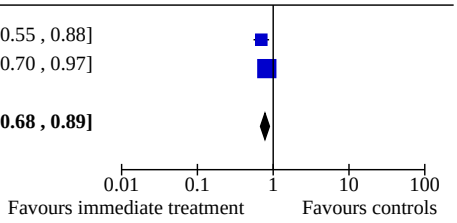
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Seizure recurrence at 5 years	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.68, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Seizure recurrence at 1 year	6	1634	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.42, 0.58]
1.3 Seizure recurrence at 1 year - subgroup analysis by control treatment	6	1634	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.42, 0.58]
1.3.1 Control - deferred treatment	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.57, 0.82]
1.3.2 Control - no treatment	3	194	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.43]
1.3.3 Control - placebo	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.03, 0.19]
1.4 Seizure recurrence at 2 years	3	1299	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.59, 0.80]
1.5 Seizure recurrence at any time	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.69, 0.90]
1.6 Time to relapse of seizures after randomisation	2	1212	Hazard Ratio (IV, Fixed, 95% CI)	0.70 [0.59, 0.83]

Analysis 1.1. Comparison 1: Seizure recurrence, Outcome 1: Seizure recurrence at 5 years

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	72	215	98	204	35.4%	0.70 [0.55 , 0.88]
Marson 2005	149	391	186	402	64.6%	0.82 [0.70 , 0.97]
Total (95% CI)		**606**		**606**	**100.0%**	**0.78 [0.68 , 0.89]**
Total events:	221		284			

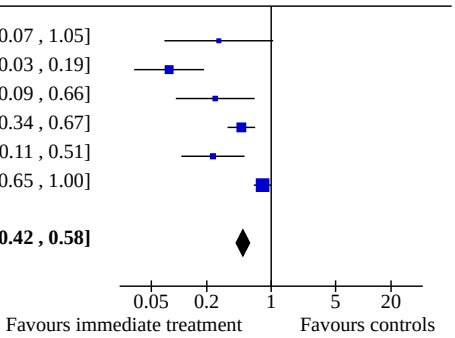
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 3.63 (P = 0.0003)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Seizure recurrence, Outcome 2: Seizure recurrence at 1 year

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Camfield 1989	2	14	9	17	2.6%	0.27 [0.07 , 1.05]
Chandra 1992	5	115	63	113	20.0%	0.08 [0.03 , 0.19]
Das 2000	4	36	18	40	5.4%	0.25 [0.09 , 0.66]
FIRST 1993	37	215	74	204	23.9%	0.47 [0.34 , 0.67]
Gilad 1996	6	45	24	42	7.8%	0.23 [0.11 , 0.51]
Marson 2005	102	391	130	402	40.4%	0.81 [0.65 , 1.00]
Total (95% CI)		**816**		**818**	**100.0%**	**0.49 [0.42 , 0.58]**
Total events:	156		318			

Heterogeneity: Chi² = 42.77, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 8.29 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Seizure recurrence, Outcome 3: Seizure recurrence at 1 year - subgroup analysis by control treatment

Study or Subgroup	Immediate Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Control - deferred treatment						
FIRST 1993	37	215	74	204	23.9%	0.47 [0.34 , 0.67]
Marson 2005	102	391	130	402	40.4%	0.81 [0.65 , 1.00]
Subtotal (95% CI)		**606**		**606**	**64.3%**	**0.68 [0.57 , 0.82]**
Total events:	139		204			

Heterogeneity: Chi² = 6.51, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 4.07 (P < 0.0001)

1.3.2 Control - no treatment						
Camfield 1989	2	14	9	17	2.6%	0.27 [0.07 , 1.05]
Das 2000	4	36	18	40	5.4%	0.25 [0.09 , 0.66]
Gilad 1996	6	45	24	42	7.8%	0.23 [0.11 , 0.51]
Subtotal (95% CI)		**95**		**99**	**15.7%**	**0.24 [0.14 , 0.43]**
Total events:	12		51			

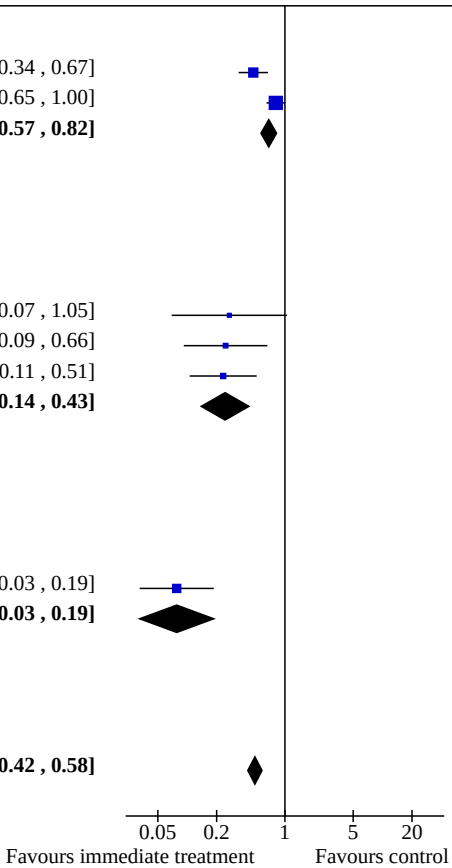
Heterogeneity: Chi² = 0.03, df = 2 (P = 0.98); I² = 0%
Test for overall effect: Z = 4.92 (P < 0.00001)

1.3.3 Control - placebo						
Chandra 1992	5	115	63	113	20.0%	0.08 [0.03 , 0.19]
Subtotal (95% CI)		**115**		**113**	**20.0%**	**0.08 [0.03 , 0.19]**
Total events:	5		63			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.73 (P < 0.00001)

Total (95% CI)		**816**		**818**	**100.0%**	**0.49 [0.42 , 0.58]**
Total events:	156		318			

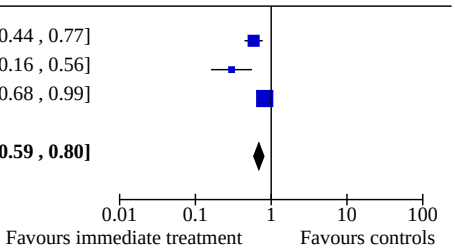
Heterogeneity: Chi² = 42.77, df = 5 (P < 0.00001); I² = 88%
Test for overall effect: Z = 8.29 (P < 0.00001)
Test for subgroup differences: Chi² = 32.46, df = 2 (P < 0.00001), I² = 93.8%



Analysis 1.4. Comparison 1: Seizure recurrence, Outcome 4: Seizure recurrence at 2 years

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	55	215	89	204	33.6%	0.59 [0.44 , 0.77]
Gilad 1996	9	45	28	42	10.6%	0.30 [0.16 , 0.56]
Marson 2005	123	391	154	402	55.8%	0.82 [0.68 , 0.99]
Total (95% CI)		**651**		**648**	**100.0%**	**0.69 [0.59 , 0.80]**
Total events:	187		271			

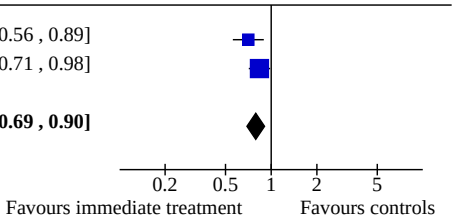
Heterogeneity: Chi² = 11.40, df = 2 (P = 0.003); I² = 82%
Test for overall effect: Z = 4.86 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Seizure recurrence, Outcome 5: Seizure recurrence at any time

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	73	215	98	204	35.2%	0.71 [0.56 , 0.89]
Marson 2005	153	391	188	402	64.8%	0.84 [0.71 , 0.98]
Total (95% CI)		**606**		**606**	**100.0%**	**0.79 [0.69 , 0.90]**
Total events:	226		286			

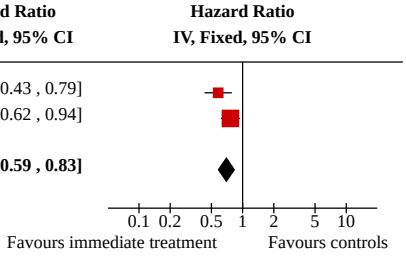
Heterogeneity: Chi² = 1.35, df = 1 (P = 0.25); I² = 26%
Test for overall effect: Z = 3.45 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Seizure recurrence, Outcome 6: Time to relapse of seizures after randomisation

Study or Subgroup	log[Hazard Ratio]	SE	Immediate treatment Total	Controls Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FIRST 1993	-0.54269	0.1549	215	204	33.1%	0.58 [0.43 , 0.79]
Marson 2005	-0.27075	0.10893	391	402	66.9%	0.76 [0.62 , 0.94]
Total (95% CI)			**606**	**606**	**100.0%**	**0.70 [0.59 , 0.83]**

Heterogeneity: Chi² = 2.06, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 4.05 (P < 0.0001)
Test for subgroup differences: Not applicable



Comparison 2. Remission

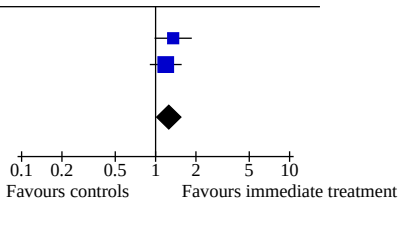
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 5-year immediate remission	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.02, 1.54]
2.2 2-year immediate remission	3	1299	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.16, 1.41]
2.3 2-year remission at any time	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
2.4 5-year remission at any time	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Time to immediate 2-year remission	2	1212	Hazard Ratio (IV, Fixed, 95% CI)	1.29 [1.10, 1.52]
2.6 Time to immediate 5-year remission	2	1212	Hazard Ratio (IV, Fixed, 95% CI)	1.39 [1.09, 1.76]
2.7 Time to 2-year remission	2	1212	Hazard Ratio (IV, Fixed, 95% CI)	1.19 [1.05, 1.35]
2.8 Time to 5-year remission	2	1212	Hazard Ratio (IV, Fixed, 95% CI)	1.14 [0.93, 1.39]

Analysis 2.1. Comparison 2: Remission, Outcome 1: 5-year immediate remission

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	67	215	47	204	39.2%	1.35 [0.98 , 1.86]
Marson 2005	88	391	76	402	60.8%	1.19 [0.91 , 1.56]
Total (95% CI)		**606**		**606**	**100.0%**	**1.25 [1.02 , 1.54]**
Total events:	155		123			

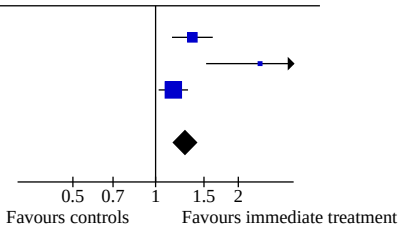
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Remission, Outcome 2: 2-year immediate remission

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	142	215	99	204	31.4%	1.36 [1.15 , 1.61]
Gilad 1996	36	45	14	42	4.5%	2.40 [1.53 , 3.77]
Marson 2005	237	391	210	402	64.1%	1.16 [1.03 , 1.31]
Total (95% CI)		**651**		**648**	**100.0%**	**1.28 [1.16 , 1.41]**
Total events:	415		323			

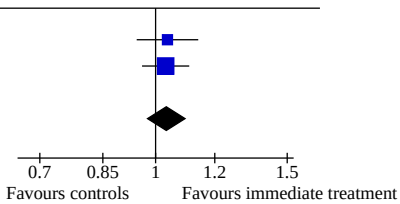
Heterogeneity: Chi² = 10.37, df = 2 (P = 0.006); I² = 81%
Test for overall effect: Z = 4.96 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Remission, Outcome 3: 2-year remission at any time

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	176	215	161	204	35.0%	1.04 [0.94 , 1.14]
Marson 2005	312	391	311	402	65.0%	1.03 [0.96 , 1.11]
Total (95% CI)		**606**		**606**	**100.0%**	**1.03 [0.98 , 1.09]**
Total events:	488		472			

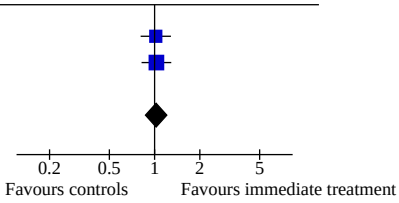
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Remission, Outcome 4: 5-year remission at any time

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	88	215	82	204	44.1%	1.02 [0.81 , 1.28]
Marson 2005	108	391	108	402	55.9%	1.03 [0.82 , 1.29]
Total (95% CI)		**606**		**606**	**100.0%**	**1.02 [0.87 , 1.21]**
Total events:	196		190			

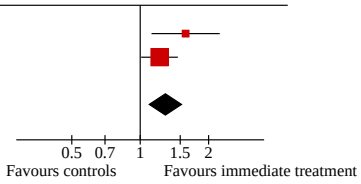
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Remission, Outcome 5: Time to immediate 2-year remission

Study or Subgroup	log[Hazard Ratio]	SE	Immediate treatment Total	Controls Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FIRST 1993	0.46021	0.17632	215	204	22.4%	1.58 [1.12 , 2.24]
Marson 2005	0.19568	0.09481	391	402	77.6%	1.22 [1.01 , 1.46]
Total (95% CI)			**606**	**606**	**100.0%**	**1.29 [1.10 , 1.52]**

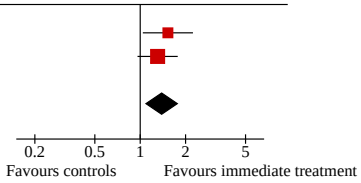
Heterogeneity: Chi² = 1.75, df = 1 (P = 0.19); I² = 43%
Test for overall effect: Z = 3.05 (P = 0.002)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Remission, Outcome 6: Time to immediate 5-year remission

Study or Subgroup	log[Hazard Ratio]	SE	Immediate treatment Total	Controls Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FIRST 1993	0.42308	0.19532	215	204	39.1%	1.53 [1.04 , 2.24]
Marson 2005	0.26611	0.15665	391	402	60.9%	1.30 [0.96 , 1.77]
Total (95% CI)			**606**	**606**	**100.0%**	**1.39 [1.09 , 1.76]**

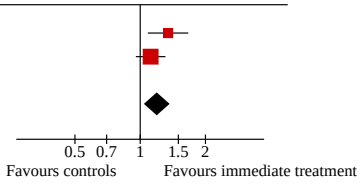
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Remission, Outcome 7: Time to 2-year remission

Study or Subgroup	log[Hazard Ratio]	SE	Immediate treatment Total	Controls Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FIRST 1993	0.29595	0.10958	215	204	34.9%	1.34 [1.08 , 1.67]
Marson 2005	0.11089	0.08021	391	402	65.1%	1.12 [0.95 , 1.31]
Total (95% CI)			**606**	**606**	**100.0%**	**1.19 [1.05 , 1.35]**

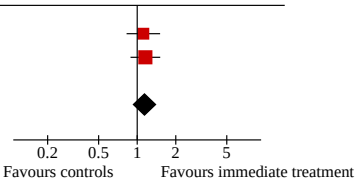
Heterogeneity: Chi² = 1.86, df = 1 (P = 0.17); I² = 46%
Test for overall effect: Z = 2.71 (P = 0.007)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Remission, Outcome 8: Time to 5-year remission

Study or Subgroup	log[Hazard Ratio]	SE	Immediate treatment Total	Controls Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FIRST 1993	0.11035	0.15365	215	204	44.0%	1.12 [0.83 , 1.51]
Marson 2005	0.14672	0.13619	391	402	56.0%	1.16 [0.89 , 1.51]
Total (95% CI)			**606**	**606**	**100.0%**	**1.14 [0.93 , 1.39]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



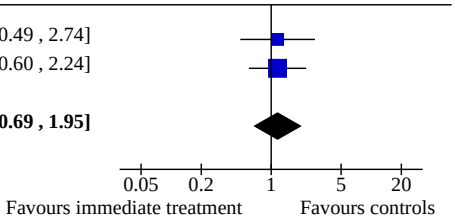
Comparison 3. Mortality at the end of the follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mortality at the end of the follow-up	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.69, 1.95]
3.2 Time to death	2	1212	Hazard Ratio (IV, Fixed, 95% CI)	1.14 [0.67, 1.95]

Analysis 3.1. Comparison 3: Mortality at the end of the follow-up, Outcome 1: Mortality at the end of the follow-up

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
FIRST 1993	11	215	9	204	36.9%	1.16 [0.49 , 2.74]
Marson 2005	18	391	16	402	63.1%	1.16 [0.60 , 2.24]
Total (95% CI)		**606**		**606**	**100.0%**	**1.16 [0.69 , 1.95]**
Total events:	29		25			

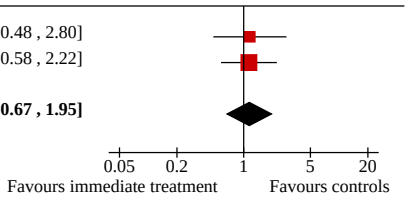
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Mortality at the end of the follow-up, Outcome 2: Time to death

Study or Subgroup	log[Hazard Ratio]	SE	immediate treatment Total	controls Total	Weight	Hazard Ratio IV, Fixed, 95% CI
FIRST 1993	0.14963	0.44966	215	204	36.9%	1.16 [0.48 , 2.80]
Marson 2005	0.12595	0.34361	391	402	63.1%	1.13 [0.58 , 2.22]
Total (95% CI)			**606**	**606**	**100.0%**	**1.14 [0.67 , 1.95]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



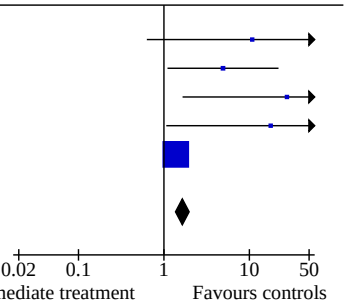
Comparison 4. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Adverse events	5	1558	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.37, 1.97]
4.2 Adverse events - subgroup analysis by control treatment	5	1558	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.37, 1.97]
4.2.1 Control - deferred treatment	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.23, 1.79]
4.2.2 Control - no treatment	2	118	Risk Ratio (M-H, Fixed, 95% CI)	14.50 [1.93, 108.76]
4.2.3 Control - placebo	1	228	Risk Ratio (M-H, Fixed, 95% CI)	4.91 [1.10, 21.93]

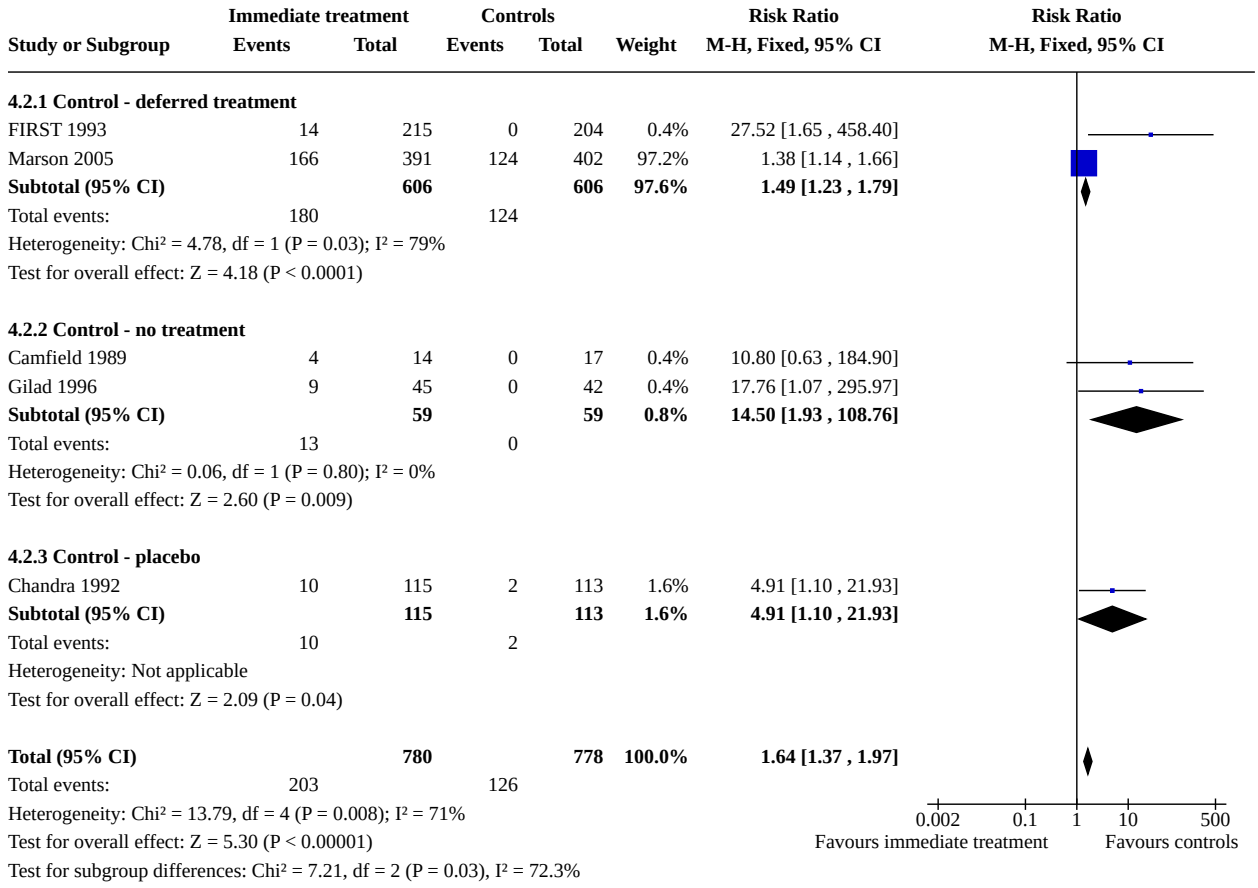
Analysis 4.1. Comparison 4: Adverse events, Outcome 1: Adverse events

Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Camfield 1989	4	14	0	17	0.4%	10.80 [0.63 , 184.90]
Chandra 1992	10	115	2	113	1.6%	4.91 [1.10 , 21.93]
FIRST 1993	14	215	0	204	0.4%	27.52 [1.65 , 458.40]
Gilad 1996	9	45	0	42	0.4%	17.76 [1.07 , 295.97]
Marson 2005	166	391	124	402	97.2%	1.38 [1.14 , 1.66]
Total (95% CI)		**780**		**778**	**100.0%**	**1.64 [1.37 , 1.97]**
Total events:	203		126			

Heterogeneity: Chi² = 13.79, df = 4 (P = 0.008); I² = 71%
Test for overall effect: Z = 5.30 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Adverse events, Outcome 2: Adverse events - subgroup analysis by control treatment



Study or Subgroup	Immediate treatment Events	Total	Controls Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Control - deferred treatment						
FIRST 1993	14	215	0	204	0.4%	27.52 [1.65 , 458.40]
Marson 2005	166	391	124	402	97.2%	1.38 [1.14 , 1.66]
Subtotal (95% CI)		**606**		**606**	**97.6%**	**1.49 [1.23 , 1.79]**
Total events:	180		124			
Heterogeneity: Chi² = 4.78, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 4.18 (P < 0.0001)						
4.2.2 Control - no treatment						
Camfield 1989	4	14	0	17	0.4%	10.80 [0.63 , 184.90]
Gilad 1996	9	45	0	42	0.4%	17.76 [1.07 , 295.97]
Subtotal (95% CI)		**59**		**59**	**0.8%**	**14.50 [1.93 , 108.76]**
Total events:	13		0			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 2.60 (P = 0.009)						
4.2.3 Control - placebo						
Chandra 1992	10	115	2	113	1.6%	4.91 [1.10 , 21.93]
Subtotal (95% CI)		**115**		**113**	**1.6%**	**4.91 [1.10 , 21.93]**
Total events:	10		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**780**		**778**	**100.0%**	**1.64 [1.37 , 1.97]**
Total events:	203		126			
Heterogeneity: Chi² = 13.79, df = 4 (P = 0.008); I² = 71%						
Test for overall effect: Z = 5.30 (P < 0.00001)						
Test for subgroup differences: Chi² = 7.21, df = 2 (P = 0.03), I² = 72.3%						

APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web)

1. ((first OR single OR initial) NEXT (seizure* OR epileptic OR unprovoked OR generali* OR tonic OR idiopathic OR focal OR partial)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

2. MeSH DESCRIPTOR Epilepsy Explode All WITH QUALIFIER DT AND CENTRAL:TARGET

3. MESH DESCRIPTOR Seizures EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET

4. MeSH DESCRIPTOR Anticonvulsants Explode All AND CENTRAL:TARGET

5. MeSH DESCRIPTOR Midazolam Explode All AND CENTRAL:TARGET

6. MeSH DESCRIPTOR Methazolamide Explode All AND CENTRAL:TARGET

7. MeSH DESCRIPTOR Propofol Explode All AND CENTRAL:TARGET

8. MeSH DESCRIPTOR Temazepam Explode All AND CENTRAL:TARGET

9. MeSH DESCRIPTOR Thiopental Explode All AND CENTRAL:TARGET

10. (antiepilep* or anti-epilep* or anticonvulsant* or anti-convulsant* or AED or AEDs):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

11. (Acetazolamid* or Aedon or Aethosuximide or Alodorm or Amizepin* or Antelepsin or Anxirloc or Arem or Ativan or Atretol or Avugane):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

12. (Baceca or Barbexaclon* or Beclamid* or Biston or Bomathal or Brivaracetam or Bromid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

13. (Calepsin or Carbagen or Carbamazepen* 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,KY,MC,MH,TI AND CENTRAL:TARGET

14. (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 Diphenylhydatanoin* or Distraneurin or Divalpr* or Dormicum or DPA or Dwufenylohydantoin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

15. (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,KY,MC,MH,TI AND CENTRAL:TARGET

16. (Fanatrex or Felbam* or Felbatol or Fenitoin* or Fenytoin* or Fenobarbit* or Finlepsin or Fosphenytoin or Frisium or Fycompa):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

17. (Gabapentin* or Gabapetin* or Gabarone or Gabitril or Gabrene or Ganaxolone or Garene or Gralise or Grifoclobam):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

18. (Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

19. (Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

20. (Lacosamid* or Lamict* or Lamitor or Lamitrin or Lamogine or Lamotrigin* or Lamotrine or Landsen or Levanxol or Levetiracetam* or Lexin or Liskantin or Loraz or Lorazepam* or Losigamon* or Lucium or Luminal or Lyrica):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

21. (Magnesium sulfat* or Magnesium sulphat* or Mebaral or Medazepam or Mephenytoin or Mephobarbit* or Mephyltaletten 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,KY,MC,MH,TI AND CENTRAL:TARGET

22. (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,KY,MC,MH,TI AND CENTRAL:TARGET

23. (OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or Oxcarbamazepin* or Oxcarbazepin* or Oxydiazepam):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

24. (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,KY,MC,MH,TI AND CENTRAL:TARGET

25. (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,KY,MC,MH,TI AND CENTRAL:TARGET

26. (Sabril or Seclar or Sederlona or Selenica or Seletracetam 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,KY,MC,MH,TI AND CENTRAL:TARGET

27. (Talampanel or Taloxa or Tasedan or Tegretal or Tegretol or Telesmin or Temaze or Temazep* or Temesta or Temtabs or Tenox or Teril or Thiomebumal 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,KY,MC,MH,TI AND CENTRAL:TARGET

28. (Urbadan or Urbanil or Urbanyl):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

29. (Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro* or Versed or Vigabatrin* or Vimpat or Visano or VPA):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

30. (Xilep or "YKP 509" or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

31. #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 OR #30 AND CENTRAL:TARGET

32. #1 AND #31 AND CENTRAL:TARGET

Appendix 2. MEDLINE (Ovid) 1946-

1. ((first or single or initial) adj (seizure$ or epileptic or unprovoked or generali$ or tonic or idiopathic or focal or partial)).tw.

2. exp *Epilepsy/dt [Drug Therapy]

3. exp Seizures/dt [Drug Therapy]

4. exp Anticonvulsants/

5. exp Midazolam/

6. exp Methazolamide/

7. exp Propofol/

8. exp Temazepam/

9. exp Thiopental/

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

11. (Acetazolamid$ or Aedon or Aethosuximide or Alodorm or Amizepin$ or Ant?lepsin or Anxirloc or Arem or Ativan or Atretol or Avugane).tw.

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

13. (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.

14. (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 Diphenylhydatanoin$ or Distraneurin or Divalpr$ or Dormicum or DPA or Dwufenylohydantoin$).tw.

15. (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).tw.

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

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

18. (Halogabide or Halogenide or Harkoseride or Hibicon or Hydroxydiazepam or Hypnovel).tw.

19. (Iktorivil or Inovelon or Insoma or Intensl or Karbamazepin or Karidium or Keppra or Klonopin or Kriadex).tw.

20. (Lacosamid$ or Lamict$ or Lamitor or Lamitrin or Lamogine or Lamotrigin$ or Lamotrine or Landsen or Levanxol or Levetiracetam$ or Lexin or Liskantin or Loraz or Lorazepam$ or Losigamon$ or Lucium or Luminal or Lyrica).tw.

21. (Magnesium sulfat$ or Magnesium sulphat$ or Mebaral or Medazepam or Mephenytoin or Mephobarbit$ or Mephyltaletten 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.

22. (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).tw.

23. (OCBZ or Onfi or Orfiril or Orlept or Ormodon or Ospolot or Oxcarbamazepin$ or Oxcarbazepin$ or Oxydiazepam).tw.

24. (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).tw.

25. (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.

26. (Sabril or Seclar or Sederlona or Selenica or Seletracetam 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.

27. (Talampanel or Taloxa or Tasedan or Tegret?l or Telesmin or Temaze or Temazep$ or Temesta or Temtabs or Tenox or Teril or Thiomebumal 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.

28. (Urbadan or Urban?l).tw.

29. (Valance or Valcote or Valium or Valnoctamide or Valparin or Valpro$ or Versed or Vigabatrin$ or Vimpat or Visano or VPA).tw.

30. (Xilep or "YKP 509" or Zalkote or Zarontin or Zebinix or Zonegran or Zonisamid$).tw.

31. or/2-30

32. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

33. clinical trials as topic.sh.

34. trial.ti.

35. 32 or 33 or 34

36. exp animals/ not humans.sh.

37. 35 not 36

38. 1 and 31 and 37

39. remove duplicates from 38

WHAT'S NEW

Date	Event	Description
28 May 2019	New citation required but conclusions have not changed	Conclusions are unchanged. In accordance with the latest classification of epilepsies released by the International League Against Epilepsy (ILAE) (Scheffer 2017) any previous mention of "partial epilepsy" or "refractory epilepsy" throughout this review has been changed to "focal epilepsy" and "drug-resistant epilepsy", respectively.
28 May 2019	New search has been performed	Searches updated 28 May 2019; no new relevant studies were identified for inclusion.

HISTORY

Protocol first published: Issue 2, 2008
Review first published: Issue 5, 2016

CONTRIBUTIONS OF AUTHORS

MAL assessed studies for inclusion, assessed risk of bias in all* included studies, extracted data, added a 'Summary of findings' table, and wrote the first draft of the review.

GG independently assessed studies for inclusion, added a 'Summary of findings' table, extracted data, and revised the draft of the review.

SN performed analyses in SAS version 9.3 and Stata version 11.2, added a 'Summary of findings' table, and revised the draft of the review.

AGM obtained individual participant data, provided guidance with the clinical interpretation of results, and revised the draft of the review.

EB independently assessed risk of bias in all* included studies, obtained individual participant data, provided guidance with the clinical interpretation of results, and revised the draft of the review.

*Review authors who were investigators on an included study did not participate in data extraction or quality assessment for that study.

DECLARATIONS OF INTEREST

MAL: none known*

GG: none known

SN: none known

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EB: none known*

*Three authors (EB, MAL and AGM) declare that they were among the authors of the two major randomised trials of the treatment of the first unprovoked seizure (FIRST 1993; Marson 2005).

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Internal sources

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External sources

- National Institute for Health Research (NIHR), UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol of this review was published in 2008 (Beghi 2008) but the work on the review did not start until 2011. Some changes were made to the review methods (outlined below) following re-review of the original methods described. All changes were made before eligible studies for the review were identified.

The title has been changed from "*Treatment for first epileptic seizure"* to " *Immediate antiepileptic drug treatment, versus placebo, deferred, or no treatment for first unprovoked seizure* " to better reflect the main aim of review.

Types of studies were amended to include quasi-RCTs in agreement with other Cochrane reviews on antiepileptic drugs in epilepsy.

Types of controls were changed from "*No immediate antiepileptic treatment or placebo"* to *"deferred treatment, were given placebo, or were left untreated"* to better clarify the therapeutic approach in the control arm.

Health-related quality of life and health economics were included in the protocol as secondary outcomes, but they were not included in the review.

The primary outcome listed in the protocol was the time from randomisation to first seizure in each group but was changed to: 1. Seizure recurrence five years after randomisation and 2. Five-year immediate remission after randomisation, as we judged these outcomes to be more clinically relevant on re-review.

Subgroup analyses were performed according to type of control group (deferred treatment, no treatment, or placebo). These subgroup analyses were not mentioned in the protocol but were suggested by a peer reviewer.

In accordance with the latest classification of epilepsies released by the International League Against Epilepsy (ILAE) (Scheffer 2017), any previous mention of "partial epilepsy" or "refractory epilepsy" throughout this review has been changed to "focal epilepsy" and "drug-resistant epilepsy", respectively.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Bias; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Remission Induction; Risk; Secondary Prevention; Seizures [complications] [*drug therapy] [mortality]; Time Factors; *Time-to-Treatment; Watchful Waiting

MeSH check words

Adult; Child; Female; Humans; Male