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

Leone MA, Giussani G, Nolan SJ, Marson AG, Beghi E

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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

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, in children and adults.

Search methods

We searched the following databases: Cochrane Epilepsy Group Specialized Register (accessed 13 October 2015), Cochrane Central Register of Controlled Trials (*The Cochrane Library* September 2015, issue 9, accessed 13 October 2015), PUBMED (accessed 22 April 2015), MEDLINE (Ovid, 1946 to 13 October 2015), EMBASE (accessed 22 April 2015), ClinicalTrials.gov (accessed 15 October 2015), and the [WHO International Clinical Trials Registry Platform](http://www.who.int/ictrp/) (ICTRP; accessed 13 October 2015). There were no language restrictions.

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 quality of the evidence 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 generalized tonic-clonic seizures, a major type of seizures that is easily recognised, which should reduce the risk of outcome reporting bias.

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

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Main results

After exclusion of uninformative papers, only six studies (nine reports) were selected for inclusion. For the two largest studies data were available for individual participant meta-analysis. 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, high quality evidence), at five years (RR 0.78; 95% CI 0.68 to 0.89; high quality evidence) and a higher probability of an immediate five-year remission (RR 1.25; 95% CI 1.02 to 1.54, high quality 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, high quality evidence). Antiepileptic drugs did not affect overall mortality after a first seizure (RR 1.16; 95% CI 0.69 to 1.95, high quality evidence). Compared to deferred treatment (RR 1.49, 95% CI 1.23 to 1.79, moderate quality evidence), treatment of the first seizure was associated with a significantly higher risk of adverse events. Moderate to low quality imprecise evidence was available for the association of treatment of the first seizure compared to no treatment or placebo (RR 14.50, 95% CI 1.93 to 108.76) and (RR 4.91, 95% CI 1.10 to 21.93) 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 individualized and based on patient preference, clinical, legal, and socio-cultural 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 on seizure recurrence, seizure remission, side effects and mortality (death). The evidence is current to 13 October 2015.

Methods

Our literature search found six studies (nine reports) that included children, adults, or both, with a first unprovoked seizure of any type (partial, generalised or unclassified). They compared antiepileptic treatment given immediately after the first seizure versus deferred (delayed) treatment, placebo or no treatment.

Results

Compared to controls, participants randomised to immediate treatment had a lower probability of seizure recurrence at one year and at five years (high quality evidence) and a higher probability of five-year remission of seizures (high quality evidence).

Immediate treatment did not contribute to the overall mortality of epilepsy after the first seizure (high quality evidence), but treatment of the first seizure was associated with a significantly higher risk of adverse events. The quality of the evidence for side effects was moderate to low with variable reporting of the outcome in the included studies; there is moderate quality evidence that immediate treatment may result in more side effects than delayed treatment, but it is 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 individualized and based on clinical, legal, and socio-cultural factors.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Immediate treatment compared to controls for first unprovoked seizure						
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)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (see comments)	com- 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	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

months						
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	0 per 1000 (see comment)	0 per 1000 (see comment)	RR 14.50 (1.93 to 108.76)	118 (1 study)	⊕⊕○○ low ⁵	There were no adverse events in the control group and 13 adverse events in the immediate treatment group.
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 quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

¹ Although outcome assessment was not blinded in all studies, most of the seizure recurrences were generalized 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).

²Point estimates vary widely across studies; however, all studies favour immediate treatment and confidence limits largely overlap. For this reason, inconsistency may not be important.

³Although 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.

⁴Downgraded 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](#))

⁵Downgraded twice due to very wide confidence intervals and low number of events, we are uncertain about this estimate

⁶Downgraded once due to wide confidence intervals and low number of events

BACKGROUND

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 antiepileptic drugs assessed in this review include carbamazepine, lamotrigine, phenobarbital, phenytoin, and valproate.

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 in people with epilepsy are shown in a number of published Cochrane reviews ([Brigo 2015](#); [Gamble 2006](#); [Hemming 2013](#); [Koch 2009](#); [Marson 2000](#); [Marson 2001](#); [Nolan 2013a](#); [Nolan 2013b](#), [Nolan 2013c](#); [Pulman 2014](#)).

Why it is important to do this review

A decision to start antiepileptic drug treatment following a first seizure should be informed 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. 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 immediate AED treatment compared to controls in children and adults with a first seizure.

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 (partial, generalized, 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
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

Electronic databases

We searched the following databases:

- Cochrane Epilepsy Group Specialized Register (accessed 13 October 2015), using the search strategy shown in [Appendix 1](#).
- Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* September 2015, issue 9,

accessed 13 October 2015), using the search strategy shown in [Appendix 2](#).

- PUBMED (accessed 22 April 2015), using the search strategy shown in [Appendix 3](#). This search was updated by searching MEDLINE (Ovid) for items added after the PUBMED search - see below.
- MEDLINE (Ovid, 1946 to 13 October 2015), using the search strategy shown in [Appendix 4](#).
- EMBASE (accessed 22 April 2015), using the search strategy shown in [Appendix 5](#). This search was not updated because randomised and quasi-randomised controlled trials in EMBASE are now included in CENTRAL.
- [ClinicalTrials.gov](#) (accessed 15 October 2015), using the search strategy shown in [Appendix 6](#).
- [WHO International Clinical Trials Registry Platform](#) (ICTRP, accessed 13 October 2015), using the search strategy shown in [Appendix 7](#).

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.

Data extraction and management

The review authors extracted the following information:

Trial methods:

- (a) method of generation of random list;
- (b) method of concealment of randomisation;
- (c) methods of blinding;
- (d) completeness of the follow-up;
- (e) whether protocol was mentioned or published.

Participant characteristics:

- (a) total number of participants allocated to each group (treatment or control);

- (b) age and gender;
- (c) seizure type (partial or generalized seizure);
- (d) number of seizures at baseline and after randomisation period;
- (e) adverse events;
- (e) the reason for participants' exclusion.

Intervention types:

- (a) types and doses of drugs tested;
- (b) duration of pre-randomisation baseline period;
- (c) duration of treatment period.

Outcomes:

- (a) number of participants experiencing each outcome (see [Types of outcome measures](#));
- (b) time at which recurrence was reported;
- (c) 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 AM). 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.

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 crossed 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 Chi² test (P value threshold for heterogeneity was 0.10). We also calculated the I² 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 (I² > 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-effect model (see [Assessment of heterogeneity](#)). We calculated overall estimates of Hazard ratios (HR) with 95% CIs using the generic inverse-variance method.

Summary of Findings and quality of the evidence

The GRADE approach was employed to interpret findings and the GRADE profiler (GRADEPRO) allowed us to import data from Review Manager to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality 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' tables: 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 quality of the evidence in four categories according to the GRADE approach. We provided the results of the GRADE assessment in the 'Summary of findings' tables ([Summary of findings for the main comparison](#); Summary of findings table 2; Summary of findings table 3; Summary of findings table 4).

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.

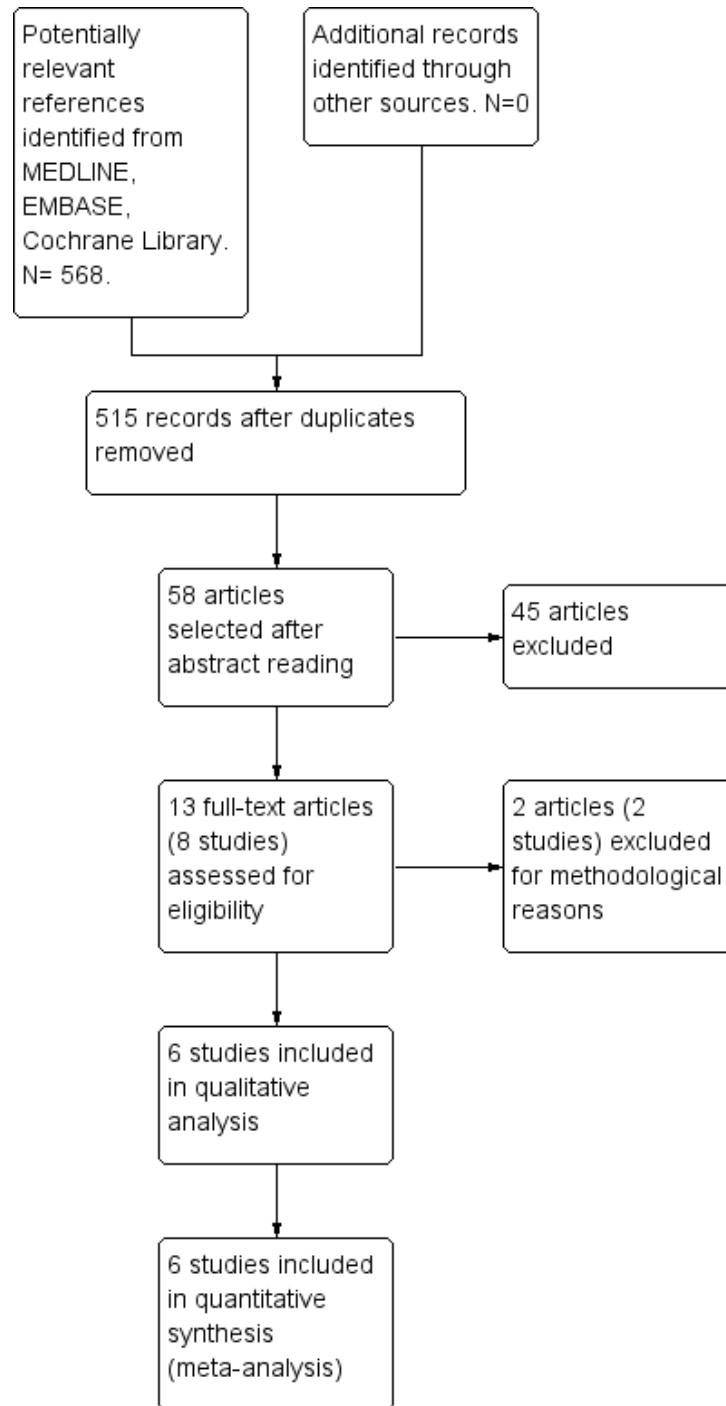
RESULTS

Description of studies

Results of the search

Our search strategy, including handsearching of the reference lists, identified a total of 568 articles. The abstract of all reports were independently evaluated by two reviewer authors (GG and ML): 457 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 (nine 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 multi-centred (FIRST 1993, Marson 2005), one recruited participants in hospitals where the author was a consultant (Chandra 1992), 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 generalized tonic-clonic seizures (Das 2000; FIRST 1993; Gilad 1996), the others included both generalized and partial 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 controlled randomised study was excluded because of incomplete description of randomisation and unbalanced groups after randomisation (Najafi 2008).

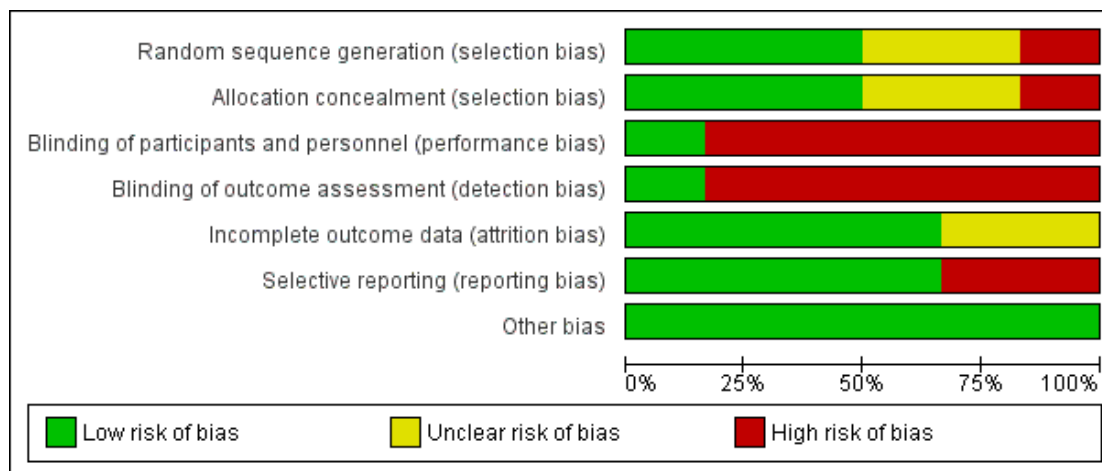
Risk of bias in included studies

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Camfield 1989	+	+	-	-	+	+	+
Chandra 1992	?	?	+	+	?	-	+
Das 2000	?	?	-	-	?	-	+
FIRST 1993	+	+	-	-	+	+	+
Gilad 1996	-	-	-	-	+	+	+
Marson 2005	+	+	-	-	+	+	+

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 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 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 at high risk of bias (Chandra 1992; Das 2000).

Other potential sources of bias

No other potential source of bias was found.

Effects of interventions

See: [Summary of findings for the main comparison Immediate treatment compared to controls for first unprovoked seizure](#)

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

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

1. 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 vary widely across studies; however all studies favoured immediate treatment and confidence limits largely overlap but for two year seizure recurrence, one study ([Gilad 1996](#)) had very 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.

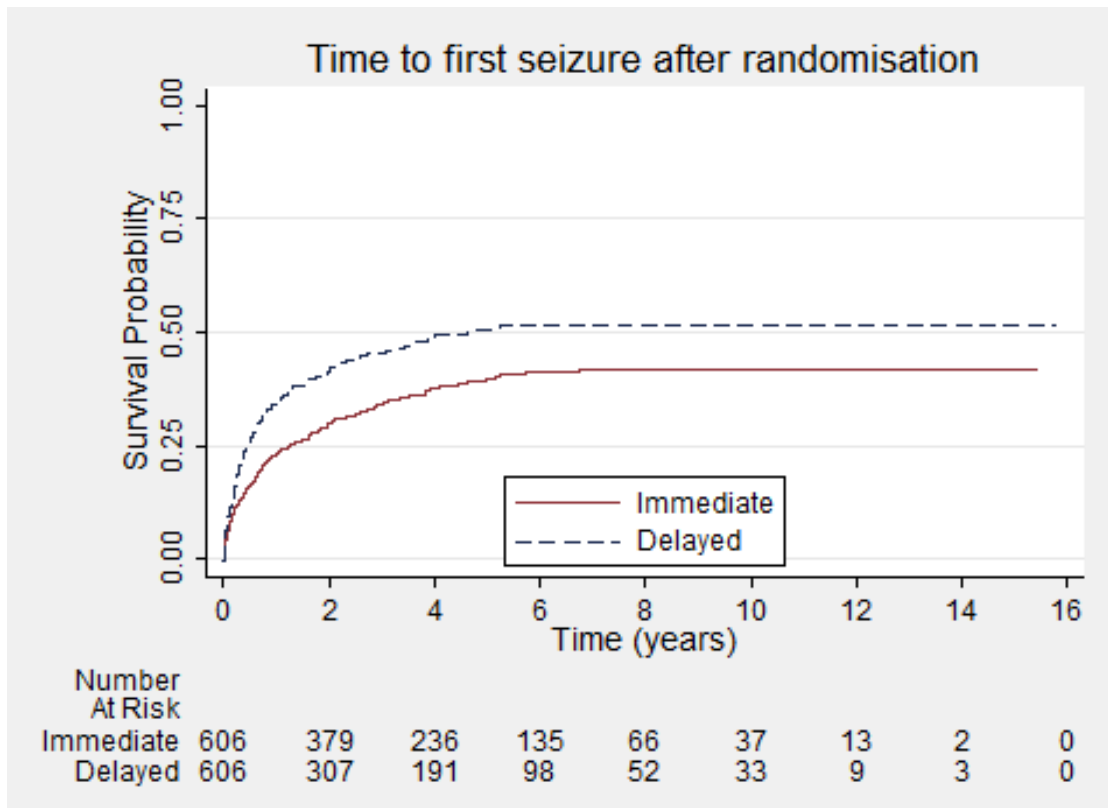
We did not perform subgroup analyses for other outcomes, as the two studies with the deferred treatment control groups contributed 90% to 100% of the data ([FIRST 1993](#), [Marson 2005](#)).

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](#)).

2. 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



3. 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 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).

4. 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).

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

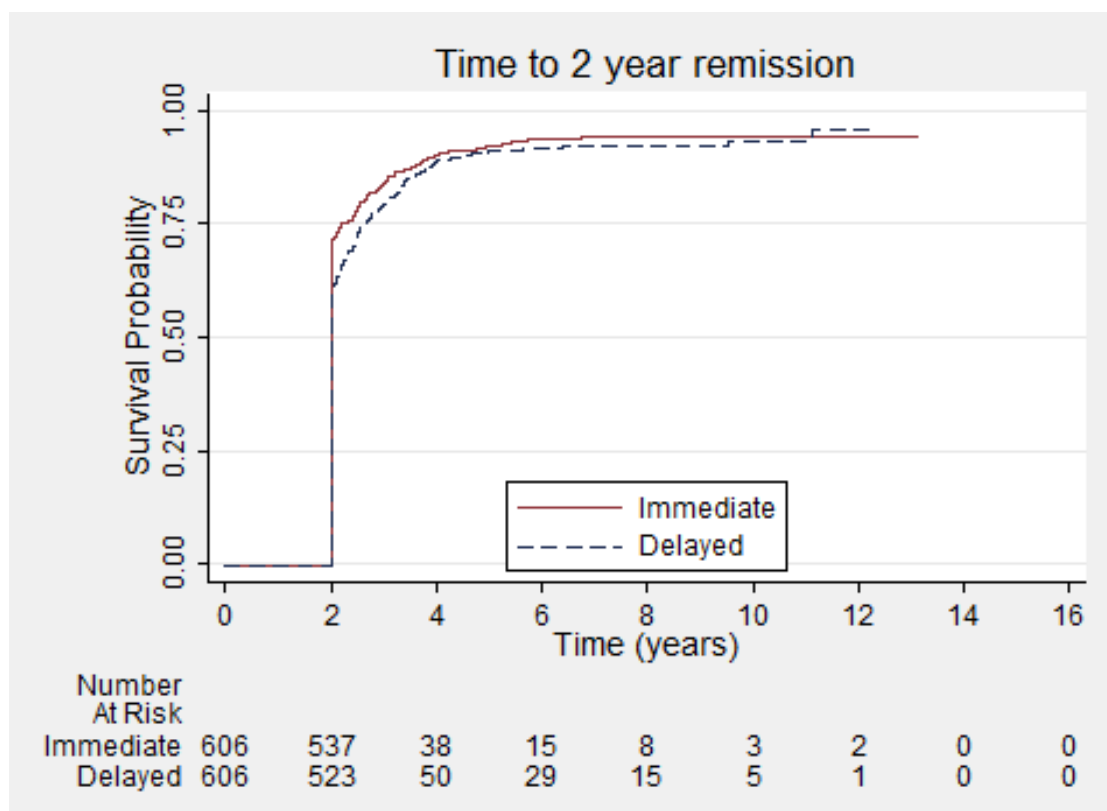
The time-to-event analysis with FIRST 1993 and Marson 2005 showed that both two-year and five-year immediate remissions occurred significantly earlier for immediate treatment compared

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](#)).

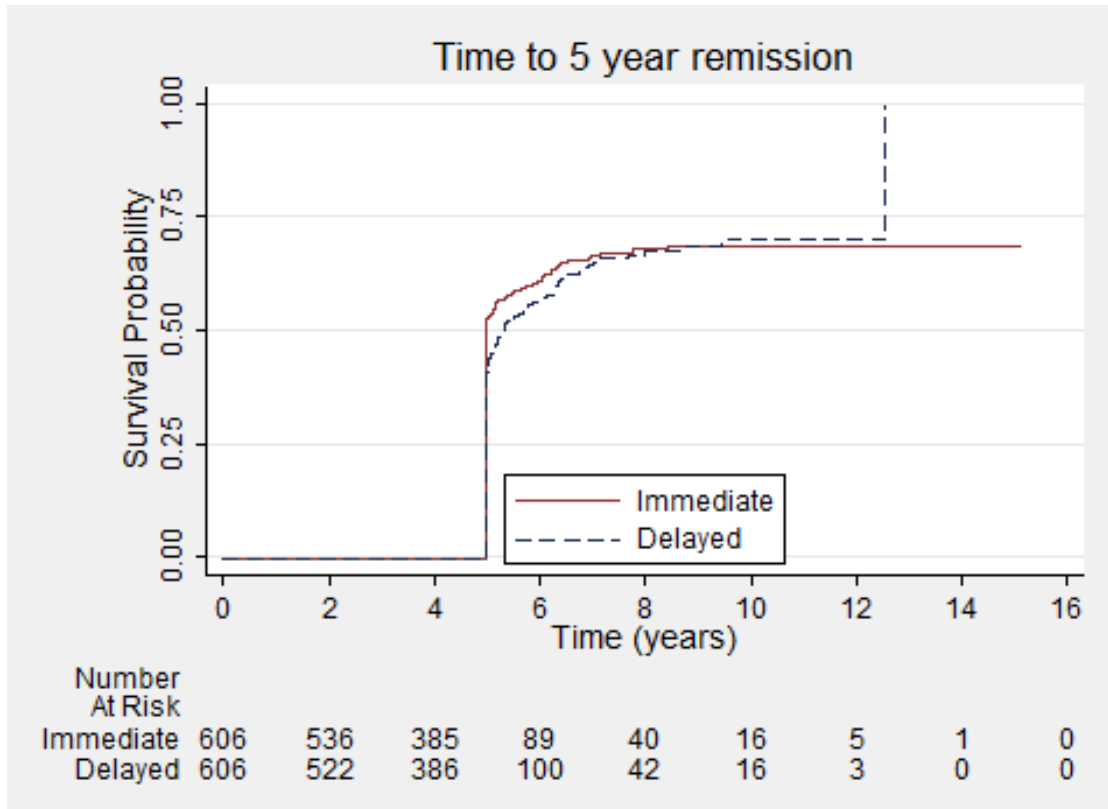
The cumulative time-dependent probability of achieving two-year remission was 70.1% in the immediate treatment group versus 59.1% in the control group at two years, and 92.2% versus 91.5% at five years respectively ([Figure 5](#)). A log rank test showed no significant difference between the treatment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

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



The cumulative time-dependent probability of achieving two-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 ($P = 0.46$).

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



6. 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](#)).

7. 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 group, 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 interests, 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 a 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, treatment of the first seizure was associated with a significantly higher risk of adverse events (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 considered on several grounds. First of all, the results obtained for long-term prognosis was 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 partial and generalised seizures, those enrolled in the FIRST 1993 study had only unprovoked (primarily or secondarily) generalized 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

Overall, the quality of the evidence from the included studies was high for seizure recurrence, remission and mortality outcomes; with high quality evidence reported in the two large studies we were able to analyse individual participant data. Quality 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.

Selection bias cannot 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 generalized tonic-clonic seizures, a type of seizures that is easily recognizable. For this reason we did not downgrade the quality of the evidence.

Attrition bias could not be excluded, especially in studies with the longest follow-up; however, the number of drop-outs 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.

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 (Schierhout 2001), brain tumours (Tremont-Lukats 2008), stroke (Kwan 2010), and craniotomy (Weston 2015). 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 quality 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 5-year remission in the long-term. There is moderate to low quality 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 to attain 5-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 individualized and based on patient preference, clinical, legal, and socio-cultural 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 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 (Kim 2006; Bonnett 2012; Bonnett 2014), 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 not feasible to assess long term outcomes using placebo controlled designs.

For patients that 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 refractory 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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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Camfield 1989

Methods	Randomised controlled trial
Participants	31 children (intervention 14; control 17) with a first afebrile unprovoked partial or generalized 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 generalized seizures), age (≤ 6 versus > 6) 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
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

Methods	Randomised controlled trial
Participants	228 participants (113 intervention; control 115) 16 years or older with a single partial or generalized 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 are included, there is 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 is reported to be a double-blind placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study is 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
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

Methods	Randomised controlled trial
Participants	76 participants (36 intervention; 40 control) with a single unprovoked idiopathic generalized 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

Das 2000 (Continued)

Notes	Sources of funding not stated	
<i>Risk of bias</i>		
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

Methods	Multicentre, randomised controlled trial	
Participants	419 participants (intervention (immediate treatment) 215; control (delayed treatment) 204) with a first unprovoked generalized tonic-clonic seizure (with or without partial 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	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

FIRST 1993 (Continued)

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

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

Risk of bias

Bias	Authors' judgement	Support for judgement
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Gilad 1996 (Continued)

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 are reported
Other bias	Low risk	None

Marson 2005

Methods	Multicentre randomised, controlled trial
Participants	793 participants; (intervention (immediate treatment) 413; control (delayed treatment) 421), aged at least 1 month, with a single partial 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 judgment; 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

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

Marson 2005 (Continued)

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 are 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 randomization. Unbalanced groups after randomization: 50 participants in the control group (immediate treatment) and 87 in the experimental group (deferred treatment)

DATA AND ANALYSES

Comparison 1. Seizure recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure recurrence at 5 years	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.68, 0.89]
2 Seizure recurrence at 1 year	6	1634	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.42, 0.58]
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]
3.1 Control - deferred treatment	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.57, 0.82]
3.2 Control - no treatment	3	194	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.14, 0.43]
3.3 Control - placebo	1	228	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.03, 0.19]
4 Seizure recurrence at 2 years	3	1299	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.59, 0.80]
5 Seizure recurrence at any time	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.69, 0.90]
6 Time to relapse of seizures after randomisation	2	1212	Hazard Ratio (Fixed, 95% CI)	0.70 [0.59, 0.83]

Comparison 2. Remission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 5-year immediate remission	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.02, 1.54]
2 2-year immediate remission	3	1299	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.16, 1.41]
3 2-year remission at any time	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
4 5-year remission at any time	2	1212	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.87, 1.21]
5 Time to immediate 2-year remission	2	1212	Hazard Ratio (Fixed, 95% CI)	1.29 [1.10, 1.52]
6 Time to immediate 5-year remission	2	1212	Hazard Ratio (Fixed, 95% CI)	1.39 [1.09, 1.76]
7 Time to 2-year remission	2	1212	Hazard Ratio (Fixed, 95% CI)	1.19 [1.05, 1.35]
8 Time to 5-year remission	2	1212	Hazard Ratio (Fixed, 95% CI)	1.14 [0.93, 1.39]

Comparison 3. Mortality at the end of the follow up

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

Comparison 4. Adverse events

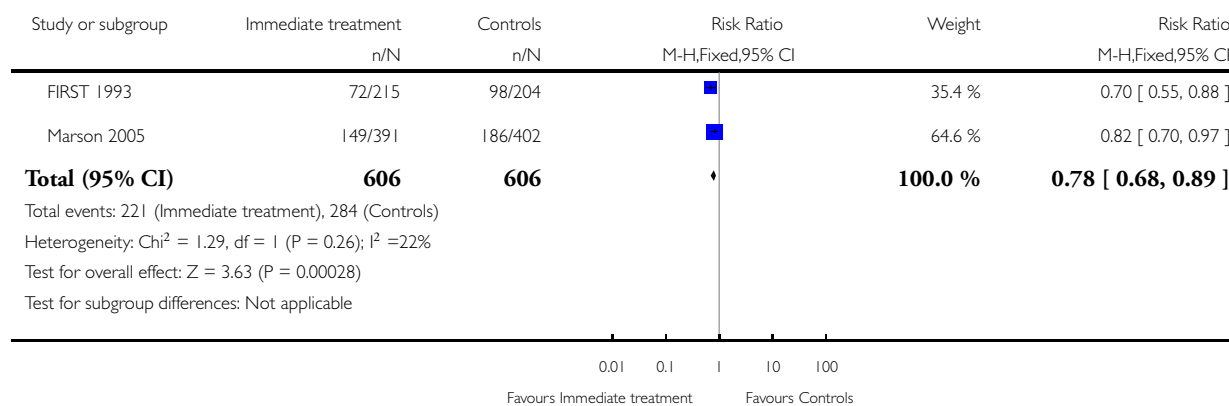
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	5	1558	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.37, 1.97]
2 Adverse events - subgroup analysis by control treatment	5	1558	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.37, 1.97]
2.1 Control - deferred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

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

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

Comparison: 1 Seizure recurrence

Outcome: 1 Seizure recurrence at 5 years

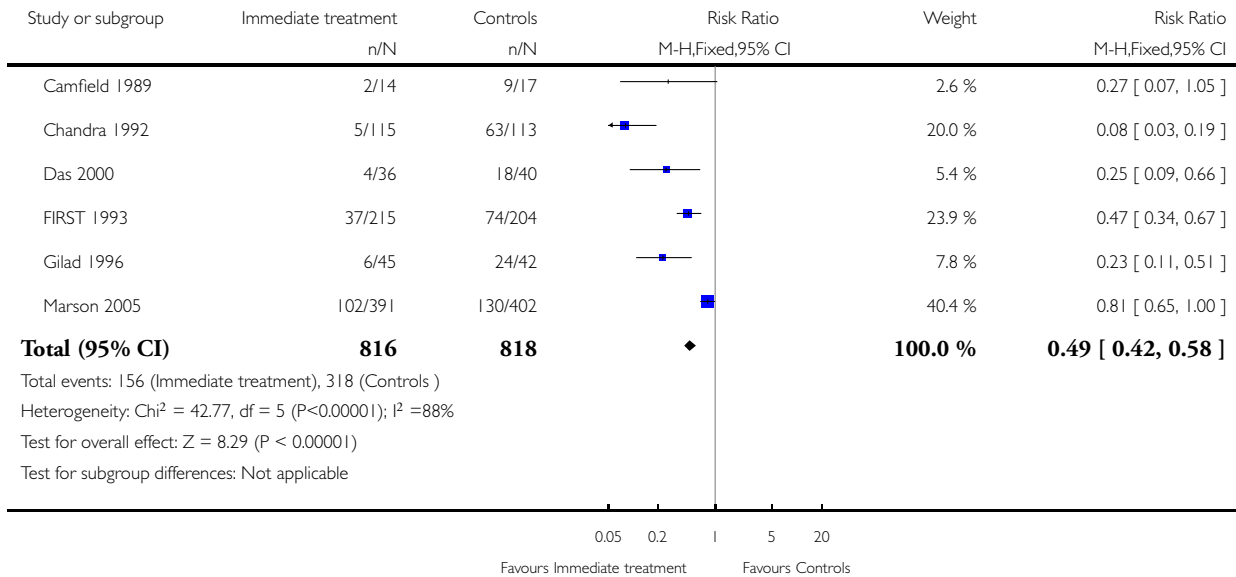


Analysis 1.2. Comparison 1 Seizure recurrence, Outcome 2 Seizure recurrence at 1 year.

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

Comparison: 1 Seizure recurrence

Outcome: 2 Seizure recurrence at 1 year

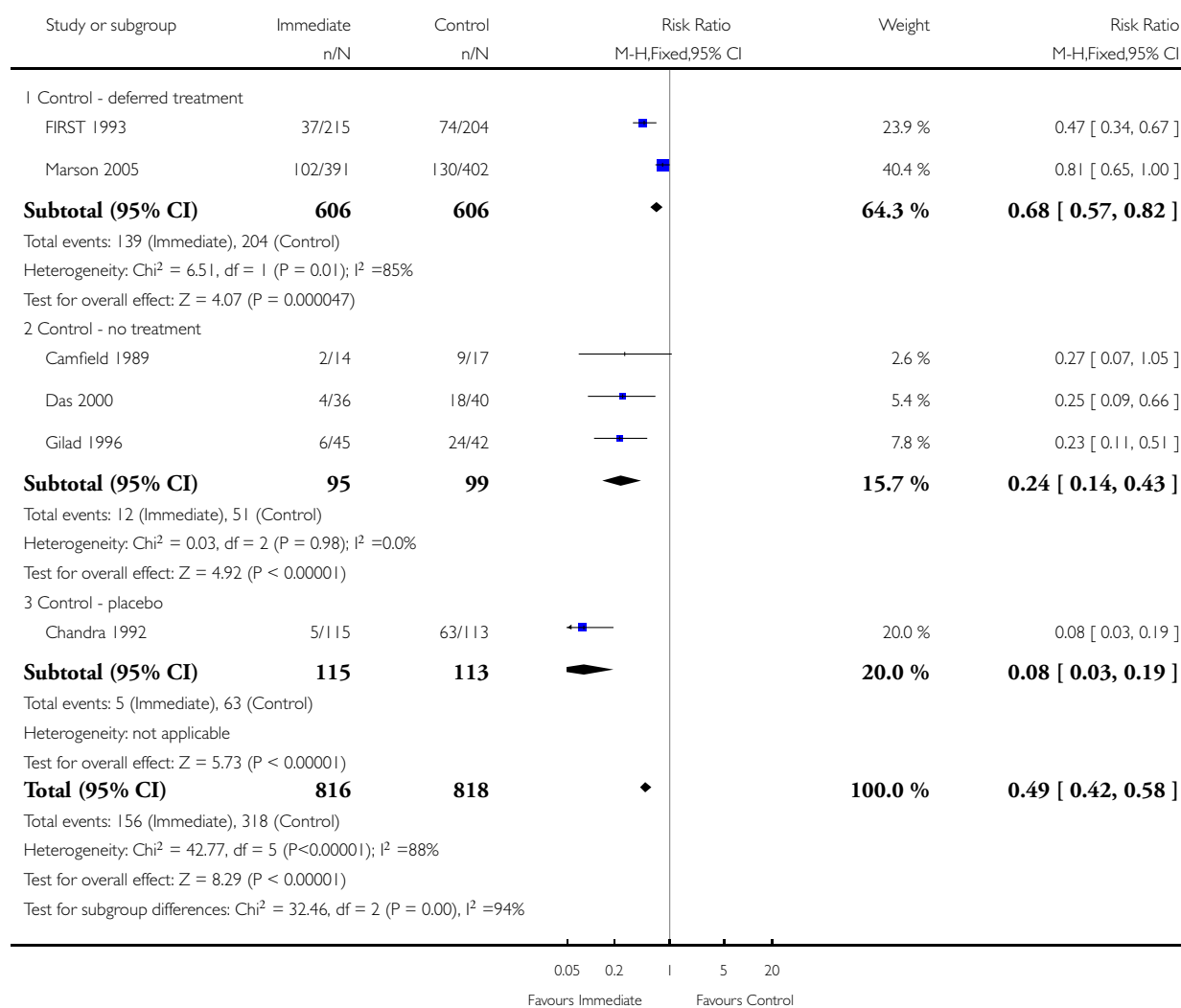


Analysis I.3. Comparison I Seizure recurrence, Outcome 3 Seizure recurrence at 1 year - subgroup analysis by control treatment.

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

Comparison: I Seizure recurrence

Outcome: 3 Seizure recurrence at 1 year - subgroup analysis by control treatment

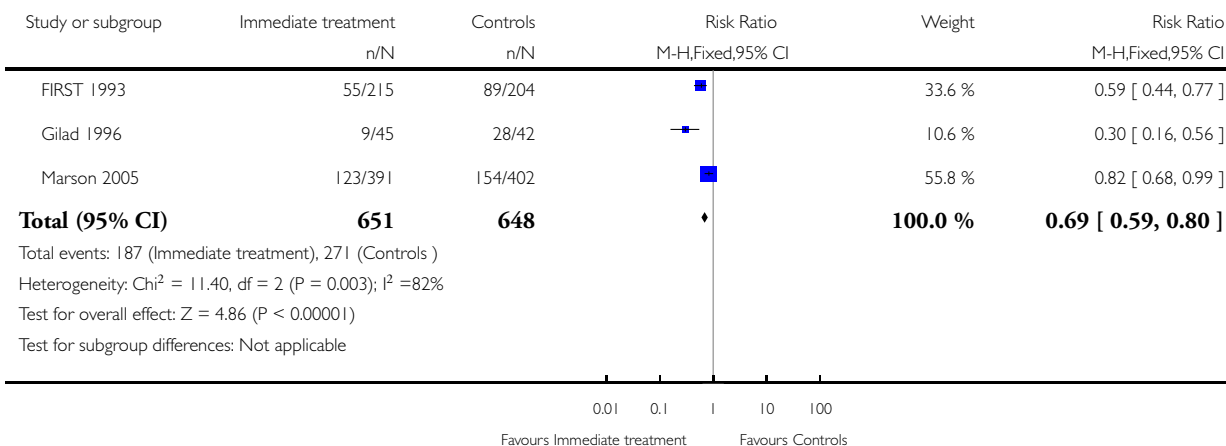


Analysis 1.4. Comparison 1 Seizure recurrence, Outcome 4 Seizure recurrence at 2 years.

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

Comparison: 1 Seizure recurrence

Outcome: 4 Seizure recurrence at 2 years

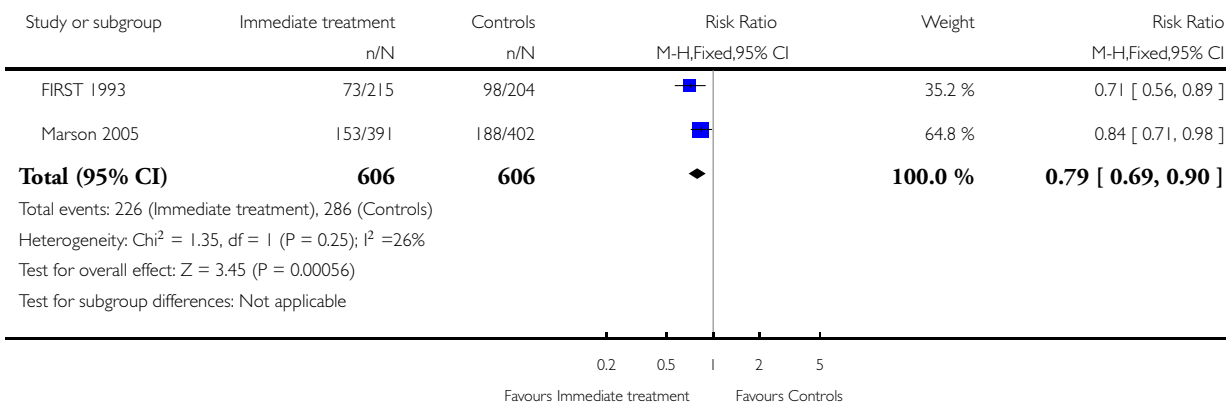


Analysis 1.5. Comparison 1 Seizure recurrence, Outcome 5 Seizure recurrence at any time.

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

Comparison: 1 Seizure recurrence

Outcome: 5 Seizure recurrence at any time

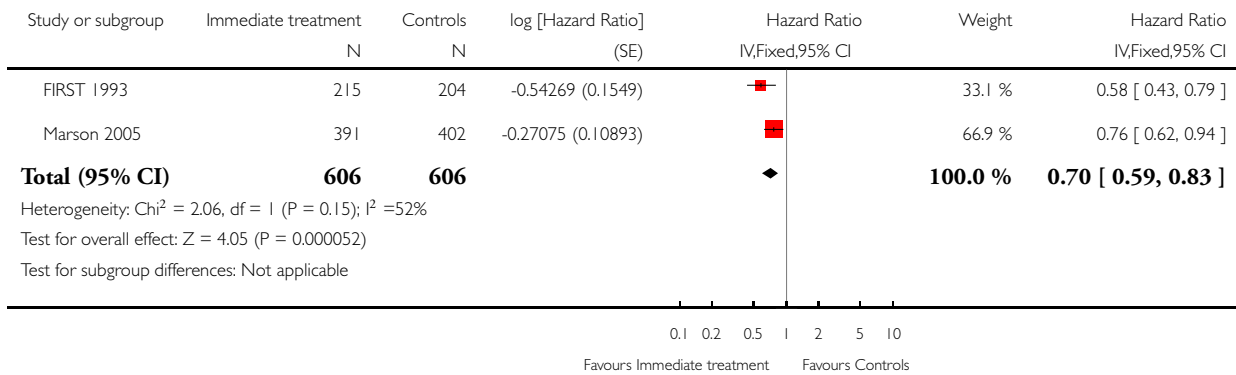


Analysis 1.6. Comparison 1 Seizure recurrence, Outcome 6 Time to relapse of seizures after randomisation.

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

Comparison: 1 Seizure recurrence

Outcome: 6 Time to relapse of seizures after randomisation

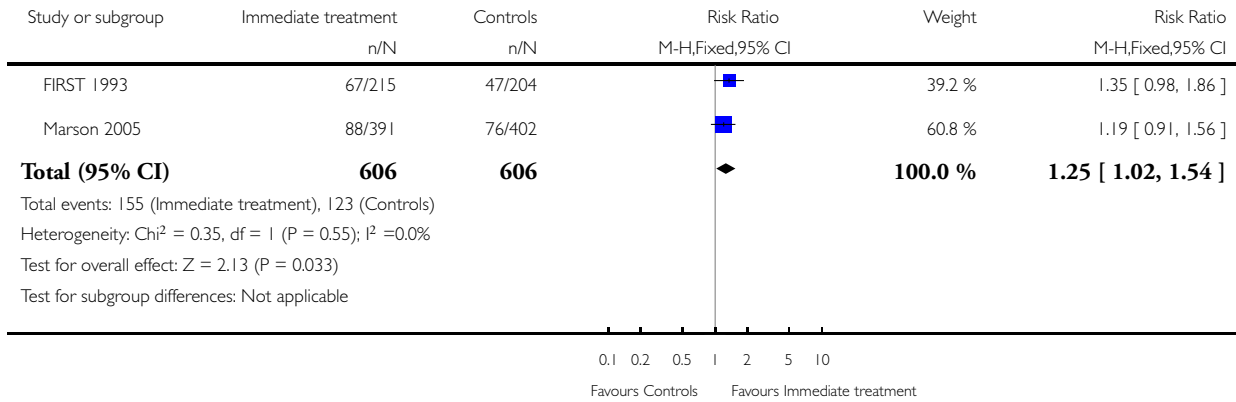


Analysis 2.1. Comparison 2 Remission, Outcome 1 5-year immediate remission.

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

Comparison: 2 Remission

Outcome: 1 5-year immediate remission

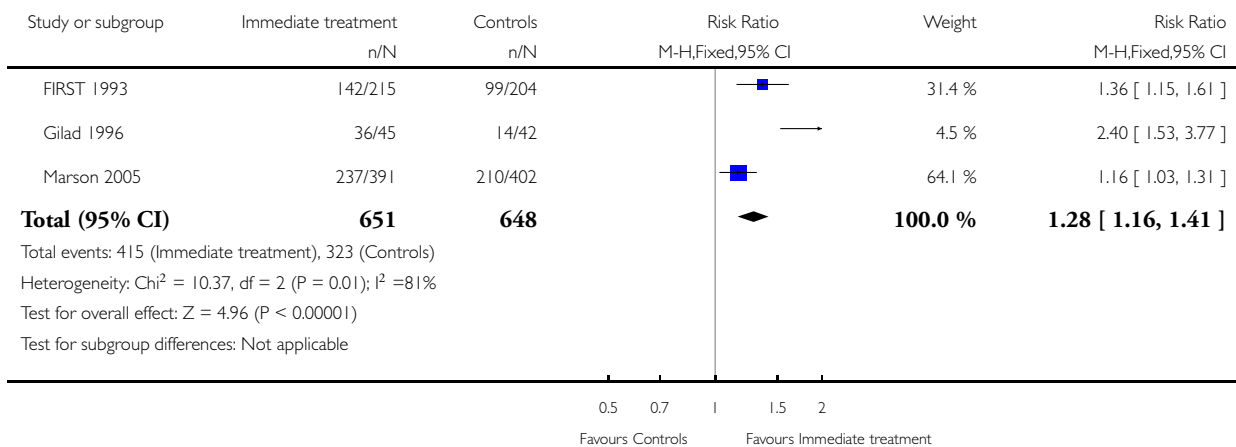


Analysis 2.2. Comparison 2 Remission, Outcome 2 2-year immediate remission.

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

Comparison: 2 Remission

Outcome: 2 2-year immediate remission

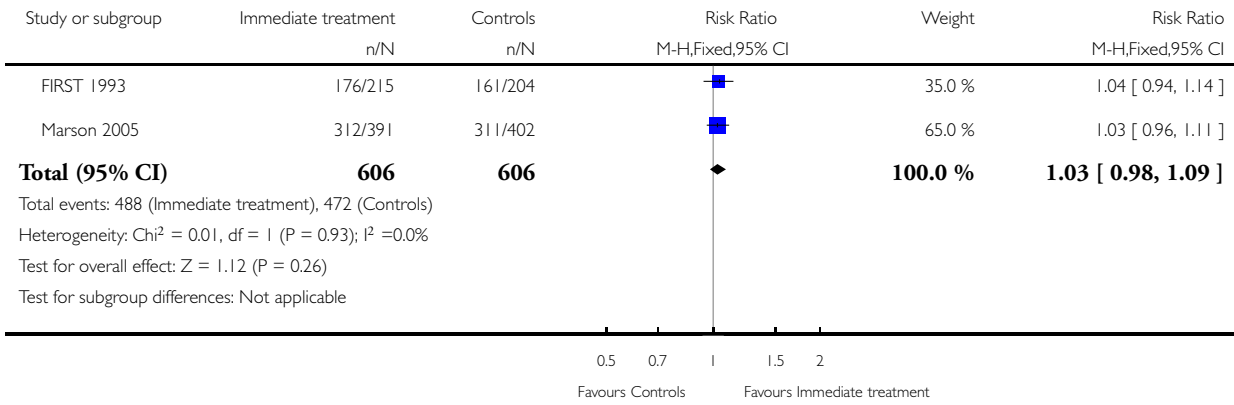


Analysis 2.3. Comparison 2 Remission, Outcome 3 2-year remission at any time.

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

Comparison: 2 Remission

Outcome: 3 2-year remission at any time

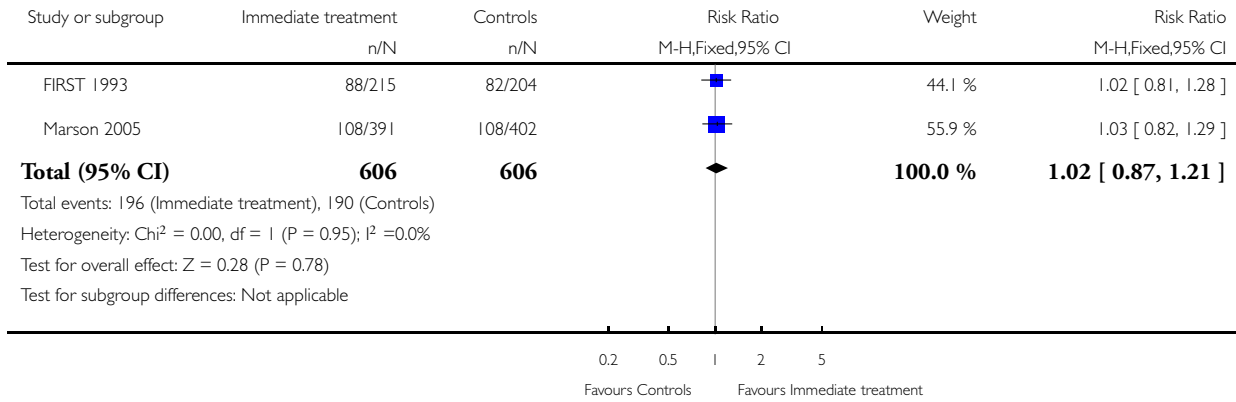


Analysis 2.4. Comparison 2 Remission, Outcome 4 5-year remission at any time.

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

Comparison: 2 Remission

Outcome: 4 5-year remission at any time

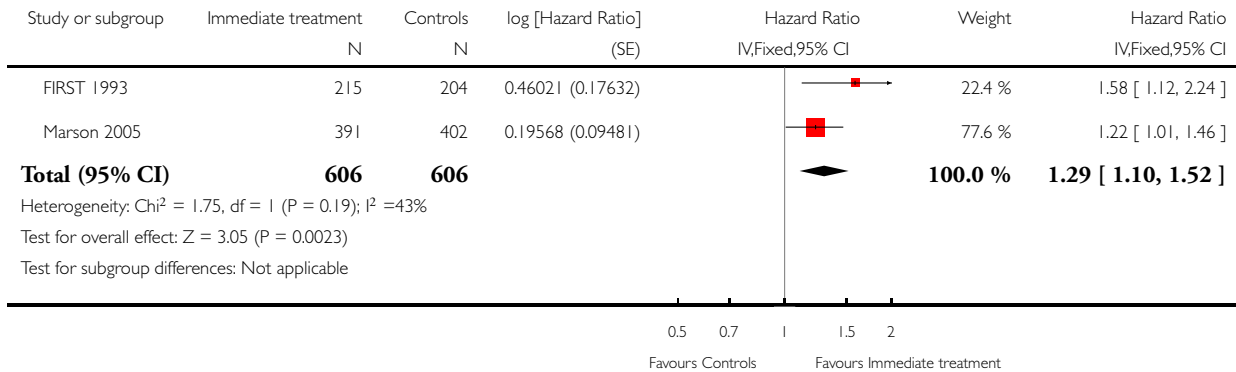


Analysis 2.5. Comparison 2 Remission, Outcome 5 Time to immediate 2-year remission.

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

Comparison: 2 Remission

Outcome: 5 Time to immediate 2-year remission

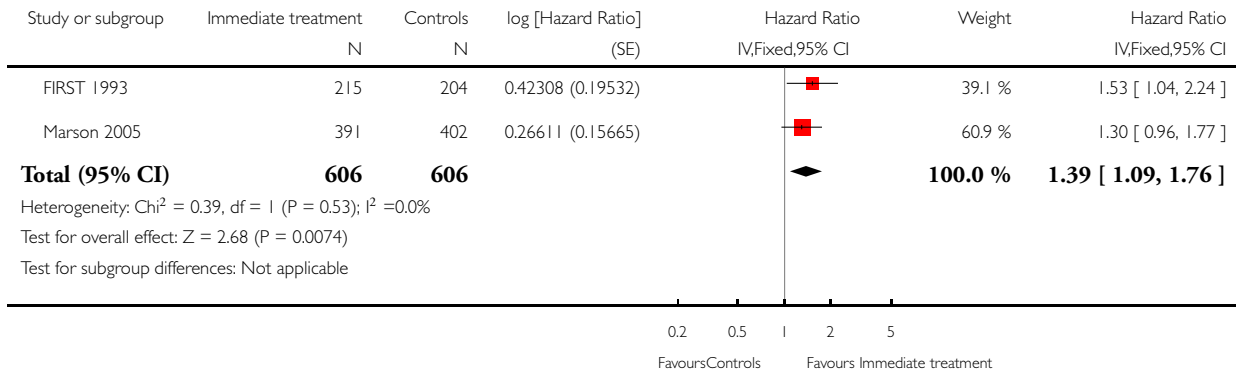


Analysis 2.6. Comparison 2 Remission, Outcome 6 Time to immediate 5-year remission.

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

Comparison: 2 Remission

Outcome: 6 Time to immediate 5-year remission

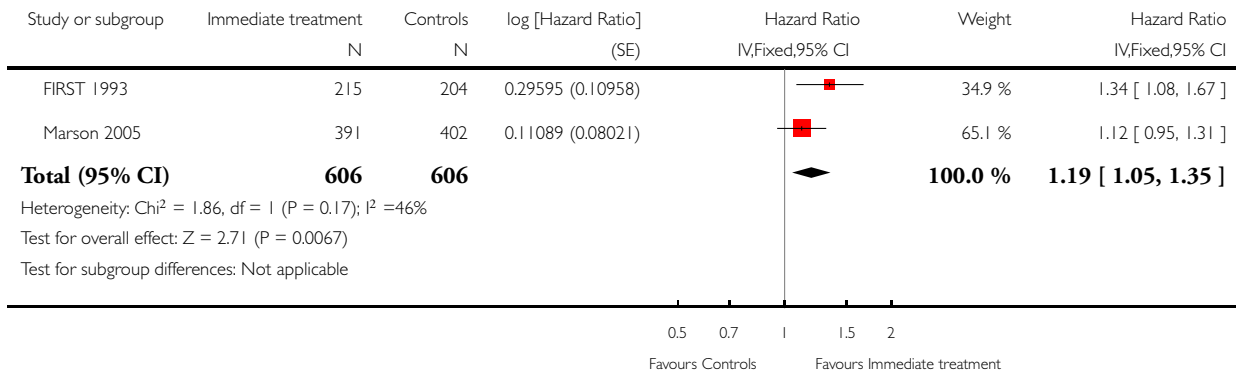


Analysis 2.7. Comparison 2 Remission, Outcome 7 Time to 2-year remission.

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

Comparison: 2 Remission

Outcome: 7 Time to 2-year remission

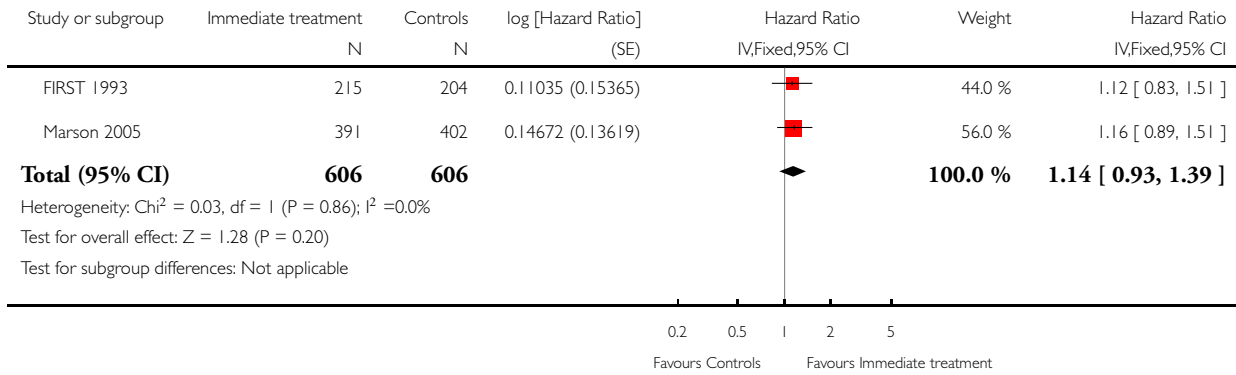


Analysis 2.8. Comparison 2 Remission, Outcome 8 Time to 5-year remission.

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

Comparison: 2 Remission

Outcome: 8 Time to 5-year remission

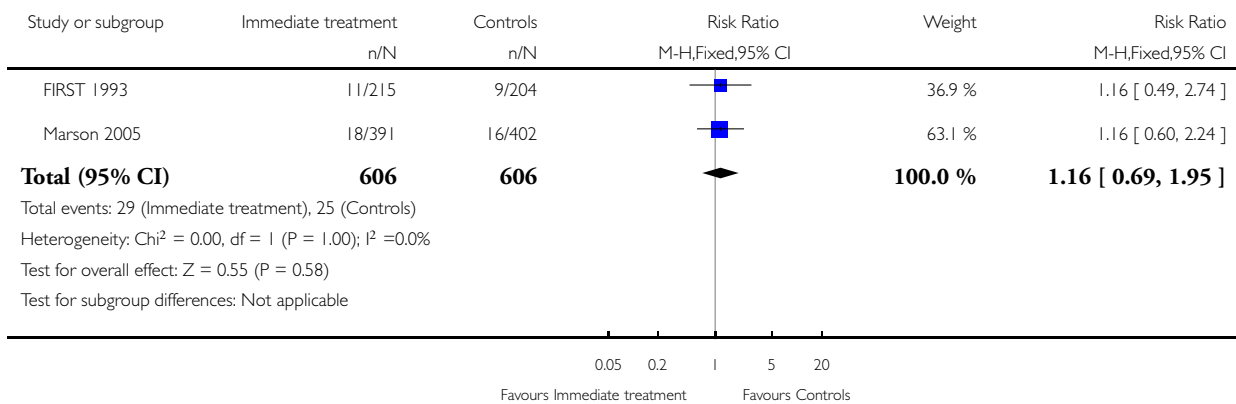


Analysis 3.1. Comparison 3 Mortality at the end of the follow up, Outcome 1 Mortality at the end of the follow-up.

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

Comparison: 3 Mortality at the end of the follow up

Outcome: 1 Mortality at the end of the follow-up

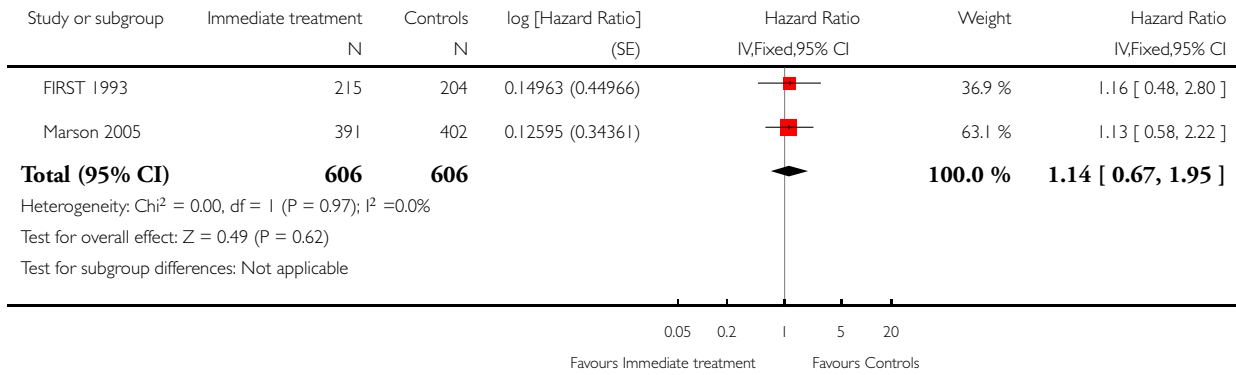


Analysis 3.2. Comparison 3 Mortality at the end of the follow up, Outcome 2 Time to death.

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

Comparison: 3 Mortality at the end of the follow up

Outcome: 2 Time to death

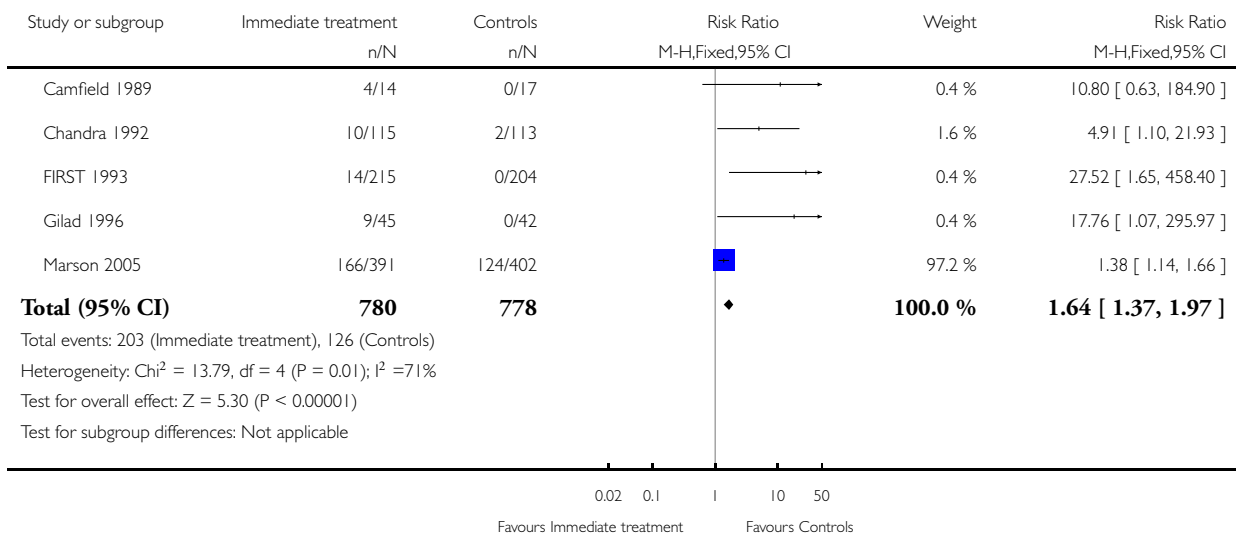


Analysis 4.1. Comparison 4 Adverse events, Outcome 1 Adverse events.

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

Comparison: 4 Adverse events

Outcome: 1 Adverse events

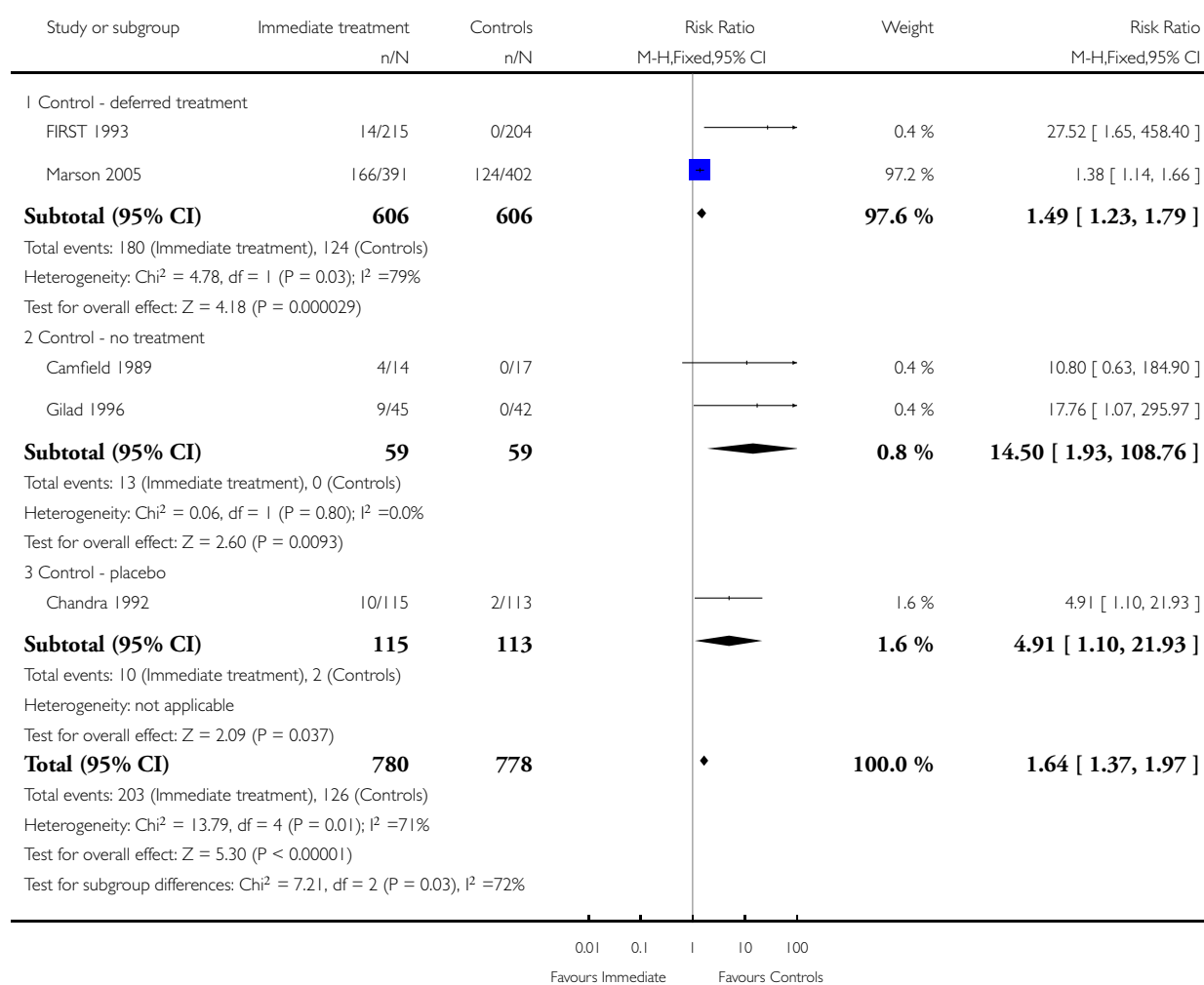


Analysis 4.2. Comparison 4 Adverse events, Outcome 2 Adverse events - subgroup analysis by control treatment.

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

Comparison: 4 Adverse events

Outcome: 2 Adverse events - subgroup analysis by control treatment



APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

("first seizure*" or "single seizure*") AND (INREGISTER)

Appendix 2. CENTRAL search strategy

#1 (first next seizure* or (single next seizure*):ti,ab,kw (Word variations have been searched)

#2 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Epilepsy] explode all trees

#4 MeSH descriptor: [Seizures] explode all trees

#5 (#2 or #3 or #4) in Trials

#6 #1 and #5

Appendix 3. PubMed search strategy

Cochrane Highly Sensitive Search Strategy to identify randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); PubMed format:

#1 Search randomized controlled trial [pt]

#2 Search controlled clinical trial [pt]

#3 Search randomized [tiab]

#4 Search placebo [tiab]

#5 Search drug therapy [sh]

#6 Search randomly [tiab]

#7 Search trial [tiab]

#8 Search groups [tiab]

#9 Search ((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8

#10 Search "Epilepsy" [Mesh]

#11 Search "Seizures" [Mesh]

#12 Search epilepsy[tiab]

#13 Search epilep*[tiab]

#14 Search seizure*[tiab]

#15 Search convulsion*[tiab]

#16 Search ((((((#10) OR #11) OR #12) OR #13) OR #14) OR #15

#17 Search (#9) AND #16

#18 Search "Animals"[Mesh]

#19 Search "Humans"[Mesh]

#20 Search (#18) NOT #19

#21 Search first seizure*[tiab] OR single seizure*[tiab]

#22 Search (#17) NOT #20

#23 Search (#22) AND #21

Appendix 4. MEDLINE (Ovid) search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011).

1. (first seizure* or single seizure*).ti,ab.
2. exp Epilepsy/
3. exp Seizures/
4. (epilep\$ or seizure\$ or convuls\$).tw.
5. 2 or 3 or 4
6. exp *Pre-Eclampsia/ or exp *Eclampsia/
7. 5 not 6
8. (randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
9. clinical trials as topic.sh.
10. trial.ti.
11. 8 or 9 or 10
12. exp animals/ not humans.sh.
13. 11 not 12
14. 1 and 7 and 13
15. remove duplicates from 14
16. limit 15 to ed=20150401-20151013

Appendix 5. EMBASE search strategy

- #1 epilep*:ab,ti OR seizure*:ab,ti OR convulsion*:ab,ti AND [humans]/lim AND [embase]/lim
- #2 'epilepsy'/exp AND [humans]/lim AND [embase]/lim
- #3 'seizure'/exp AND [humans]/lim AND [embase]/lim
- #4 'convulsion'/exp AND [humans]/lim AND [embase]/lim
- #5 #1 OR #2 OR #3 OR #4
- #6 'single blind procedure'/exp AND [humans]/lim AND [embase]/lim
- #7 'randomized controlled trial'/exp AND [humans]/lim AND [embase]/lim
- #8 'double blind procedure'/exp AND [humans]/lim AND [embase]/lim
- #9 'crossover procedure'/exp AND [humans]/lim AND [embase]/lim
- #10 random*:ab,ti OR factorial*:ab,ti OR crossover:ab,ti OR 'cross over':ab,ti OR placebo*:ab,ti OR 'double blinding':ab,ti OR 'single blinding':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti AND [humans]/lim AND [embase]/lim
- #11 #6 OR #7 OR #8 OR #9 OR #10
- #12 #5 AND #11
- #13 'first seizure':ab,ti OR 'first seizures':ab,ti OR 'single seizures':ab,ti OR 'single seizure':ab,ti AND [humans]/lim AND [embase]/lim
- #14 #12 AND #13

Appendix 6. ClinicalTrials.gov search strategy

(first OR single) AND seizure | Interventional Studies | epilepsy | antiepileptic drugs AND (immediate OR early) NOT "immediate release"

Appendix 7. ICTRP search strategy

first seizure OR single seizure

CONTRIBUTIONS OF AUTHORS

MA Leone assessed studies for inclusion, assessed risk of bias in all included studies, extracted data, added summary of findings tables, and wrote the first draft of the review.

G Giussani independently assessed studies for inclusion, added 'Summary of findings' tables, extracted data, and revised the draft of the review.

S Nolan performed analyses in SAS version 9.3 and Stata version 11.2, added 'Summary of findings' tables, and revised the draft of the review.

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

E Beghi 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.

DECLARATIONS OF INTEREST

None known. However, three authors (EB, MAL and AM) 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.

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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 reflection upon the original methods described. All changes were made before eligible studies for the review were identified.

The title has been changed from genetic title "*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.

Type 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 reflection.

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.