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Antiepileptic drugs for seizure control in people with neurocysticercosis (Review)

Frackowiak M, Sharma M, Singh T, Mathew A, Michael BD

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[Intervention Review]

Antiepileptic drugs for seizure control in people with neurocysticercosis

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ABSTRACT

Background

Neurocysticercosis is the most common parasitic infection of the brain. Epilepsy is the most common clinical presentation, though it may also present with headache, symptoms of raised intracranial pressure, hydrocephalus and ocular symptoms depending upon the localisation of the parasitic cysts. Anthelmintic drugs, anti-oedema drugs, such as steroids, and antiepileptic drugs (AEDs) form the mainstay of treatment.

This is an updated version of the original Cochrane Review published in 2015, Issue 10.

Objectives

To assess the effects (benefits and harms) of AEDs for the primary and secondary prevention of seizures in people with neurocysticercosis.

For the question of primary prevention, we examined whether AEDs reduce the likelihood of seizures in patients who have neurocysticercosis but have not had a seizure.

For the question of secondary prevention, we examined whether AEDs reduce the likelihood of further seizures in patients who have had at least one seizure due to neurocysticercosis.

As part of primary prevention studies, we also aimed to examine which AED has been found to be beneficial in people with neurocysticercosis in terms of duration, dose and side-effect profile.

Search methods

For the latest update of this review, we searched the following databases on 8 July 2019: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to July 05, 2019) and LILACS (1982-). CRS Web includes the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised or quasi-randomised, controlled trials from Embase, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP). We also checked the references lists of identified studies, and contacted experts in the field and colleagues to search for additional studies and for information about ongoing studies.

Selection criteria

Randomised and quasi-randomised controlled trials.

Single-blind, double-blind or unblinded studies were eligible for inclusion.

Data collection and analysis

Two review authors screened all citations for eligibility (MS screened the initially identified 180 citations, MF and BDM screened the 48 citations identified for the purpose of this update).Two review authors independently extracted data and evaluated each study for risk of bias.

Main results

We did not find any trials that investigated the role of AEDs in preventing seizures among people with neurocysticercosis, presenting with symptoms other than seizures.

We did not find any trials that evaluated evaluating individual AEDs in people with neurocysticercosis.

We found one trial, comparing two AEDs in people with solitary neurocysticercosis with seizures. However, we excluded this study from the review as it was of poor quality.

We found four trials that compared the efficacy of short term versus longer term AED treatment for people with solitary neurocysticercosis (identified on computed tomography (CT) scan) presenting with seizures. In total, 466 people were enrolled. These studies compared various AED treatment durations, six, 12 and 24 months. The risk of seizure recurrence with six months treatment compared with 12 to 24 months treatment was not statistically significant (odds ratio (OR) 1.34 (95% confidence interval (CI) 0.73 to 2.47; three studies, 360 participants; low-certainty evidence)). The risk of seizure recurrence with six to 12 months compared with 24 months treatment was not statistically significant (OR 1.36 (95% CI 0.72 to 2.57; three studies, 385 participants; low-certainty evidence)).

Two studies co-related seizure recurrence with CT findings and suggested that persistent and calcified lesions had a higher recurrence risk and suggest longer duration of treatment with AEDs. One study reported no side effects, while the rest did not comment on side effects of drugs. None of the studies addressed the quality of life of the participants.These studies had certain methodological deficiencies such as a small sample size and a possibility of bias due to lack of blinding, which affect the results of this review.

Authors' conclusions

Despite neurocysticercosis being the most common cause of epilepsy worldwide, there is currently no evidence available regarding the use of AEDs as seizure prophylaxis among people presenting with symptoms other than seizures. For those presenting with seizures, there is no reliable evidence regarding the duration of treatment required. There is therefore a need for large scale randomised controlled trials to address these questions.

PLAIN LANGUAGE SUMMARY

Treatment of epilepsy in people with neurocysticercosis

Background

Neurocysticercosis is a common infection of the brain caused by the larvae of the pork tapeworm, migrating to the brain. Seizures are the most common symptom, although some people may present with headache, vomiting or other symptoms of brain swelling.

This review investigates the usefulness of antiepileptic drugs (AEDs) in preventing seizures in people who did not have seizures but presented with these other symptoms. We also examined the usefulness of the AEDs in people with epilepsy due to neurocysticercosis in terms of choice of drug, dosage, duration of treatment, cost, side effects and the quality of life.

Study characteristics

Four trials with a total of 466 participants were reviewed, focusing on the comparison of 'short duration' and 'long duration' of AEDs drugs in people with a single cerebral lesion. These trials compared various durations of AED therapy: six to 12 months as short duration and 12 to 24 months as long-duration therapy.

Key results

No statistically significant benefit of one duration of AED over the other (six, 12 or 24 months) could be demonstrated. In people with calcified cysts, longer duration of therapy may be preferable.

All four included trials, enrolled people with a single brain lesion. The findings of our review cannot be extrapolated to people with multiple cysts or with cysts in unusual parts of the brain.

The evidence is current to July 2019.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Short-duration AED treatment (six months) compared with long-duration AED treatment (12 to 24 months) for people with neurocysticercosis

Short duration AEDs (six months) compared with long duration AEDs (12 to 24 months) for seizure control in people with neurocysticercosis

Patient or population: people with neurocysticercosis
Settings: outpatients, in India
Intervention: short duration AEDs (6 months)
Comparison: long duration AEDS (12 to 24 months)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Long duration AEDs (12 to 24 months)	Short duration AEDs (6 months)				
Seizure control Seizure recurrence Follow-up: median 12 months	**Study population**		OR 1.34 (95% CI 0.73 to 2.47)	360 (3 studies)	⊕⊕⊖⊖ **low**[1]	OR > 1 indicates seizure recurrence is more likely on short duration AEDs (6 months)
	121 per 1000	**162 per 1000** (88 to 299 per 1000)				

Assumed Risk: The event rate in the long duration AEDs group multiplied by 1000. The event rate is the proportion of the total, in which the event occurred.

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; **OR:** Odds 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] Down-graded twice due to lack of blinding of participants and researchers in all the included studies, unclear risk of bias in patient concealment, and lack of applicability.

Summary of findings 2. Six to 12 months AED treatment compared with 24 months AED treatment for seizure control in neurocysticercosis

Six to 12 months AED treatment compared with 24 months AED treatment for seizure control in people with neurocysticercosis

Patient or population: people with neurocysticercosis

Settings: outpatients, in India
Intervention: 6 to 12 months AED treatment
Comparison: 24 months AED treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	24 months AED treatment	6 to 12 months AED treatment				
Seizure control Seizure recurrence Follow-up: 18 months	**Study population**		OR 1.36 (95% CI 0.72 to 2.57)	385 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	OR > 1 indicates seizure recurrence is more likely on 6 to 12 months AED treatment
	103 per 1000	**140 per 1000** (74 to 264 per 1000)				

Assumed Risk: The event rate in the long duration AEDs group multiplied by 1000. The event rate is the proportion of the total, in which the event occurred.

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; **OR:** Odds 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] Down-graded twice due to lack of blinding of participants and researchers in all the included studies, unclear risk of bias in patient concealment, and lack of applicability.
[2] Inconsistency in report of withdrawals and reasons for them

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews (2015, Issue 10; Sharma 2015) on *Antiepileptic drugs for seizure control in people with neurocysticercosis*.

Description of the condition

Neurocysticercosis is an infection of the central nervous system by *Taenia solium cysticerci*. *Taenia solium* is an intestinal parasite that infests animals such as pigs and has a secondary life cycle in human beings. Ingestion of the parasite eggs, excreted in the faeces of the pig or an infested human host, can result in cysticercosis. After ingestion, the eggs can migrate from the gut to lodge in various tissues of the body, where they form cysts. Cysticercosis is usually asymptomatic. When symptoms of cysticercosis do develop it is usually due to cysticercal invasion of the central nervous system and eyes.

Neurocysticercosis is the most common parasitic infection of the brain. The prevalence of neurocysticercosis is high in low- and middle-income countries where there is close proximity between humans and pigs. It is common in much of South and Central America, China, the Indian subcontinent, South-East Asia, and sub-Saharan Africa. It affects around 50 million people worldwide (Dhawan 2011), with men and women equally affected, and has a peak incidence at ages 30 to 40 years (Zafar 2013). However, migration of populations has changed the epidemiology of the disease and the prevalence of the disease in developed countries is now increasing.

The presentation of neurocysticercosis is related to the site of invasion by the cyst, the stage of the parasite and the host immune response. Cysts in the cerebral parenchyma are noted to have four stages - vesicular stage, colloidal stage, granulomatous stage and calcified stage (DeGiorgio 2004; García 2002). The vesicular stage is the viable cyst which is associated with a minimal immune response and hence shows limited enhancement after intravenous contrast in neuroimaging. Although an eccentric scolex may be seen with magnetic resonance imaging (MRI) within the cyst at this stage. The second stage is where the viable cyst ruptures to release its fluid in the surrounding parenchyma. This fluid stimulates an intense immune response in the host and results in perilesional oedema which is associated with contrast enhancement on MRI. This is the most common clinically evident stage of neurocysticercosis. Cellular response to this stage results in the next granulomatous (or nodular) stage during which some perilesional oedema may still be visible. The final stage of destruction and calcification may result in permanent calcific lesions in the parenchyma. There may also be a conglomeration of cysts in the basal cisterns (termed racemose cysts). Single cysts are usually up to 20 mm in diameter. Giant cysts more than 50 mm in diameter may produce space-occupying effects. Cysts may also occur within the ventricles or in the spinal cord.

Epilepsy is an important neurological condition characterised by recurrent seizures, and has an estimated annual incidence of 50/100,000 and a prevalence of five to 10/1000 in the developed world (Sander 1996). Approximately three per cent of the population will suffer from seizures at some point in their lives (Hauser 1992). Epilepsy can have several causes, for example, head injury, infections of the brain, tumours, infarcts and haemorrhage. Neurocysticercosis is an important cause of symptomatic seizures or secondary epilepsy among children and adults in many low- and middle-income countries. In some countries neurocysticercosis has been reported to be the cause of 20% to 70% of cases of symptomatic epilepsy (Daniels 2006; Del Brutto 2005; Palacio 1998; Rajshekhar 2006). In some Asian countries, neurocysticercosis causes up to 50% cases of epilepsy Rajshekhar 2003), and up to 90% of cases of symptomatic seizures in children (Singhi 2000).

Seizures are the most common first presenting feature of neurocysticercosis, occurring in nearly 70% to 90% of patients (DeGiorgio 2004). The seizures are usually partial seizures, with or without secondary generalisation (Del Brutto 1992; Singhi 2000). Host immune response (resulting in oedema and/or gliosis surrounding the cysts) and calcification are the reasons for epileptogenesis (the gradual process during which a previously normal brain develops epilepsy) in neurocysticercosis (Pradhan 2000). Multiple parenchymal cysts are associated with more frequent seizures (Ferreira 2002). A smaller but significant number of patients may present with severe and recurrent headaches. Localisation in the ventricles or in the basal cisterns may result in development of hydrocephalus causing severe headache and features of raised intracranial pressure. In addition, cysticercostic encephalitis is a rare clinical presentation of neurocysticercosis (García 2002).

The diagnosis of neurocysticercosis is established on the basis of clinical presentation and computed tomography (CT) scan or MRI. Diagnostic criteria proposed by Rajshekhar and Brutto (Del Brutto 2001; Rajshekhar 2003) includes these features and can be used to define the disease The clinical and radiological diagnosis can be supported by serological tests such as enzyme-linked immunosorbent assay (ELISA) and enzyme-linked immuno transfer blot test (ELITB), which have been found to be highly specific for the diagnosis (Dhawan 2011).

Description of the intervention

As seizures are the most common presentation of neurocysticercosis, antiepileptic drugs (AEDs) are often used. The duration of AED therapy has been based on expert opinions or consensus. Most experts recommend that AEDs be continued until the epileptogenic focus, in the form of the oedema or the degenerating cyst, resolves completely. This may be a variable period of up to six months. However, as some of the lesions may resolve as a calcified lesion in the parenchyma, they may continue to be a focus for seizures. The benefit of longer-term AED therapy on seizure frequency has not been established (Gupta 2002; Thussu 2002; Verma 2006). Seizure recurrence in people with neurocysticercosis is usually associated with the presence of multiple parenchymal cysts, frequent seizures before the start of treatment with AEDs, and persistent calcification (Del Brutto 1996; Gupta 2002; Rajshekhar 2004; Thussu 2002). Monotherapy with carbamazepine or phenytoin is the common choice for seizure control. A small proportion may require polytherapy (Rajshekhar 2004).

How the intervention might work

AEDs are important in the control of seizures, which are the most common presentation of neurocysticercosis. These drugs help to prevent the recurrence of seizures in patients with symptomatic epilepsy secondary to neurocysticercosis and may have a role in

primary prevention of seizures in people with neurocysticercosis who present with features other than seizures, such as headache or altered behavior.

Why it is important to do this review

The management of an individual with neurocysticercosis imposes a great burden on the economy of the world, costing an estimated 0.0037% of the gross national product for one treatment of all the neurocysticercosis patients in one country (Murthy 2007; Pal 2000). Solitary neurocysticercosis is essentially self-limiting and presents clinically when the viable cysts actually start degenerating to produce an immune response. The use of anthelmintic treatment has been a subject of debate and is the topic of another Cochrane Review (Abba 2010). Short courses of steroids (oral prednisolone) are used to control the host response and pericystic oedema.

For people with symptomatic epilepsy secondary to neurocysticercosis, there are no systematic reviews on which AED to use, what dosage to prescribe, or how long to treat for. In addition, for those with neurocysticercosis who present with symptoms other than seizures, there are no systematic reviews on the use of AEDs to prevent seizures occurring. Hence, we undertook a systematic review of the role of AEDs in the treatment of people with neurocysticercosis presenting with or without seizures.

OBJECTIVES

To assess the effects (benefits and harms) of antiepileptic drugs (AEDs) for the primary and secondary prevention of seizures in people with neurocysticercosis.

1. For the question of primary prevention, we examined whether AEDs reduce the likelihood of seizures in patients who have neurocysticercosis but have not had a seizure.
2. For the question of secondary prevention, we examined whether AEDs reduce the likelihood of further seizures in patients who have had at least one seizure due to neurocysticercosis.
3. As part of primary prevention studies, we also aimed to examine which AED has been found to be beneficial in people with neurocysticercosis in terms of duration, dose and side-effect profile.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials.

Single-blind, double-blind or unblinded studies were eligible for inclusion.

For studying primary prevention, we planned to include studies where individuals with neurocysticercosis presented with symptoms other than seizures, such as headache or behavioural changes.

For secondary prevention, we planned to include studies where the participants had neurocysticercosis with seizures prior to randomisation.

Types of participants

We included studies of people with neurocysticercosis, diagnosed on the basis of neuroimaging findings, with or without additional serological or histopathological confirmation.

We excluded studies on neurocysticercosis at extracerebral sites.

The participants were of all age groups (children and adults) and both genders. The participants may have had any type of seizures associated with neurocysticercosis or presented with symptoms other than seizures.

Types of interventions

The intervention group may have received any of the currently marketed AEDs, in addition to the usual treatment for neurocysticercosis (anthelmintics or steroids, or both). The controls may have received placebo or only the usual treatment for neurocysticercosis without AEDs. The AEDs may have been a single drug (monotherapy) or in combination. The duration of treatment may have been short (a few weeks or months) or prolonged (years).

Types of outcome measures

Primary outcomes

1. Proportion of individuals experiencing seizures.
2. Time to first seizure post randomisation.

Secondary outcomes

1. Proportion of individuals who were seizure free for a specific time period (12 or 24 months).
2. Proportion of individuals who withdrew from treatment.
3. Proportion of individuals who developed drug-related side effects or complications.
4. For studies comparing short versus long duration of treatment, proportion of individuals who were seizure free with each treatment policy.
5. Quality of life (measured by validated scales).
6. Cost of therapy.
7. Requirement for hospitalisation, need for intensive care treatment and length of hospitalisation.
8. Mortality.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published or unpublished, in press, or in progress).

Electronic searches

Searches for the original review were run in April 2014. Subsequent searches were run in May 2015, December 2016, and June 2018. For the latest update, we searched the following databases on 8 July 2019.

1. Cochrane Register of Studies (CRS Web), using the search strategy outlined in Appendix 1.
2. MEDLINE (Ovid, 1946 to July 05, 2019), using the search strategy outlined in Appendix 2.
3. LILACS (1982-), using the search strategy outlined in Appendix 3.

CRS Web includes the Cochrane Epilepsy Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), and randomised or quasi-randomised, controlled trials from Embase, ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP).

Searching other resources

We also checked the references list in the selected studies and tried to contact researchers in the field to look at unpublished data. We contacted experts in the field and colleagues and asked if they were aware of any studies which we may have missed in our searches. We also tried to identify any ongoing studies from registries of clinical trials.

Data collection and analysis

We analysed the data using Cochrane's Review Manager software,RevMan 5.3 (RevMan 2014). The primary analysis was intention-to-treat analysis. We calculated odds ratio (OR) for dichotomous data (proportion of individuals experiencing seizures, seizure free for a specific time period (12 or 24 months), withdrew from treatment, developed drug-related side effects or complications, were seizure-free with each treatment policy, mortality), and planned to use mean difference (MD) for continuous data, if any continuous data were identified (quality of life, cost of treatment). We intended to evaluate time to first seizure after randomisation by hazard ratios (HRs). We assessed precision using 95% confidence intervals (CIs).

We stratified the analysis by treatment comparison. We also considered the duration of the drugs used, co-medications used and the length of follow-up.

Selection of studies

The review authors (MS, MF and BDM) independently screened all citations and abstracts and evaluated the eligibility of each study for the review. MS screened the initially identified 180 citations, MF and BDM screened the 48 citations identified for the purpose of this update. We included studies on the basis of the criteria earlier described in Criteria for considering studies for this review. We excluded studies that were not eligible and documented the reasons for exclusion.

Data extraction and management

Two review authors (MS, AM) independently extracted data using a tailored data extraction form. We summarised and coded data on study design, participant characteristics, interventions, and outcomes and entered them into RevMan (RevMan 2014). We resolved any discrepancies between data extracted by the two authors by discussion and by referring to the third review author.

We extracted the following data.

1. Trial factors:
   a. study setting, country and year of study;
   b. study design;
   c. randomisation method;
   d. blinding;
   e. duration of study;
   f. duration of follow-up.
2. Participants:
   a. number in each group;
   b. age and sex distribution per randomised group;
   c. seizure type and frequency per randomised group;
   d. number of seizures before randomisation in each group;
   e. other neurologic deficits;
   f. neuroimaging data: location of lesion; number of lesions-solitary or multiple, nature of cyst - live or dying or calcified.
3. Type of intervention:
   a. AED studied;
   b. number of drugs used;
   c. duration of AED;
   d. adjunctive medications used in each group.
4. Outcome measures (as described earlier).
5. Withdrawals from study.

Assessment of risk of bias in included studies

Two review authors (MS, AM) assessed each trial independently. We resolved any disagreements by consensus, or with consultation of a third party (TS) in case of disagreement. We assessed risk of bias using Cochrane's 'Risk of bias' tool (Higgins 2011).

We used the following criteria.

1. Was the allocation sequence adequately generated?
2. Was the allocation adequately concealed?
3. Was knowledge of the allocated intervention adequately prevented during the study?
4. Were incomplete outcome data adequately addressed?
5. Are reports of the study free of suggestion of selective outcome reporting?
6. Was the study apparently free of other problems that could put it at a high risk of bias?

We used individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A 'Risk of bias' graph figure and 'Risk of bias' summary figure can be accessed here (Figure 1; Figure 2).

We planned to explore the influence of individual 'Risk of bias' criteria in a sensitivity analysis.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

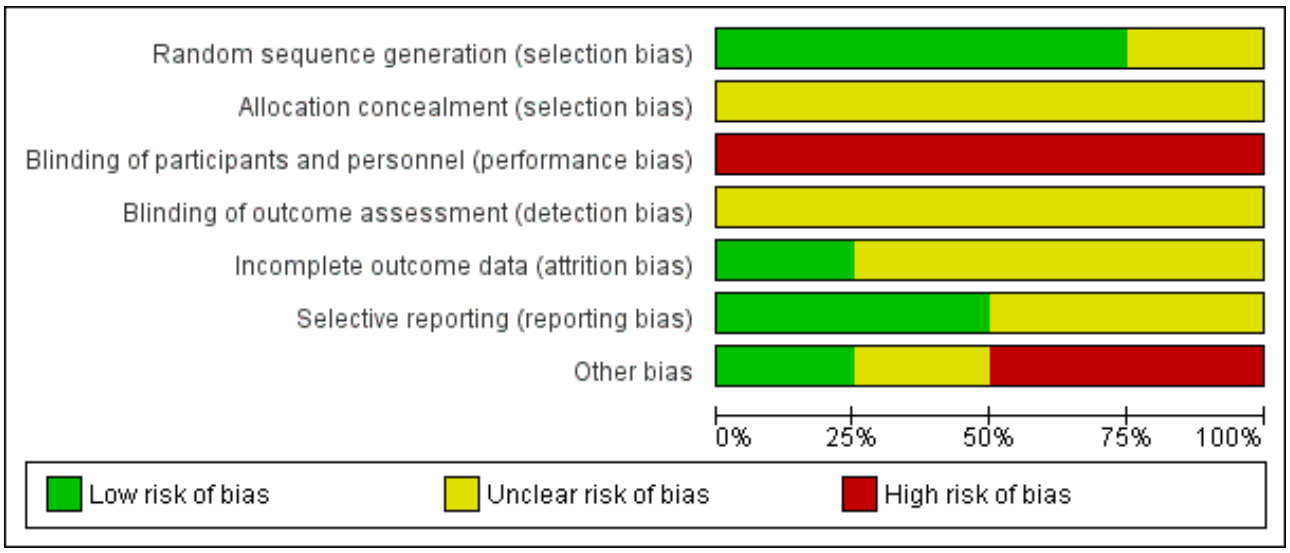
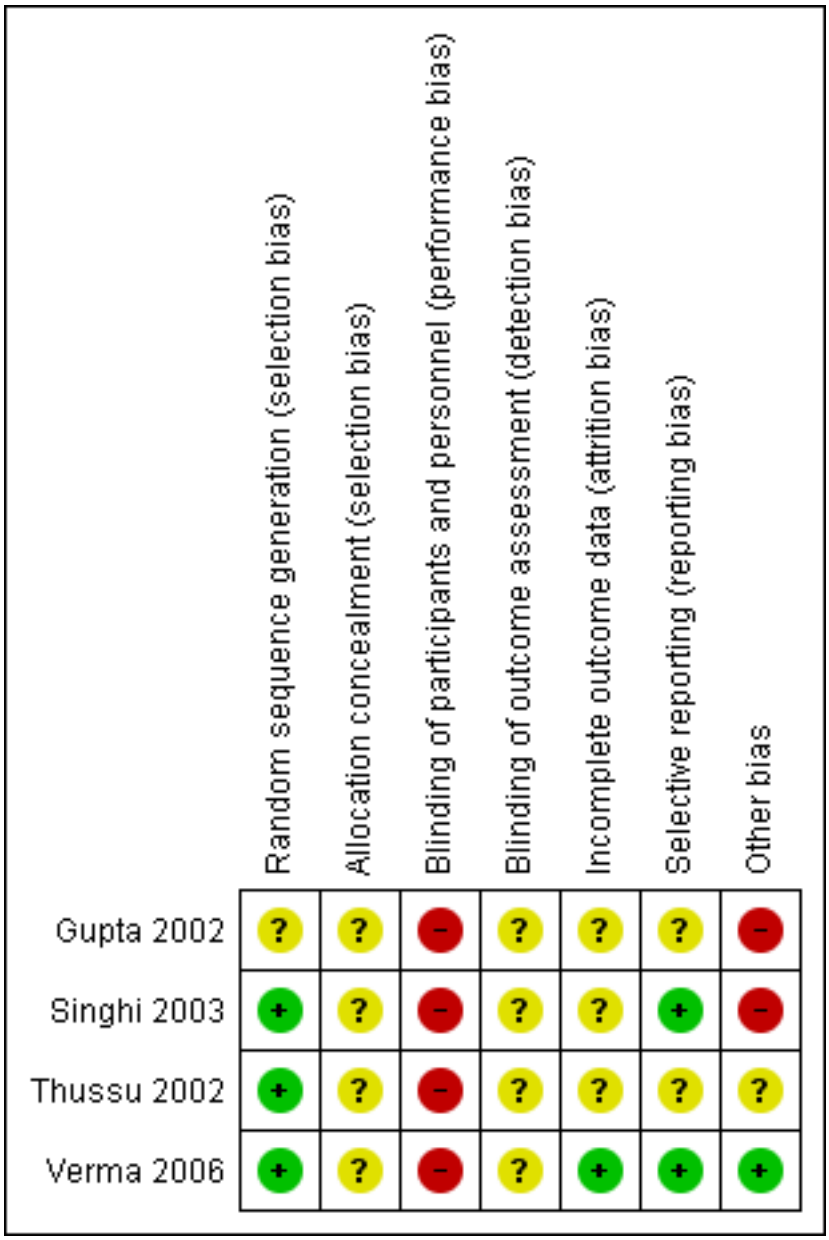


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We measured treatment effect as the proportion of individuals in each group who were seizure free for a specific time period (six,12 or 24 months). We calculated ORs for dichotomous data and planned to use MD for continuous data. We assessed precision using 95% CIs.

We planned to measure the adverse effect of treatment as the proportion of individuals withdrawn from the study due to adverse effects of the drugs. We also planned to try to measure and compare the adverse effects between short and long duration of treatment in studies that compared short and long duration of treatment.

We carried out an analysis of three studies comparing six months AED with 12 to 24 months AED and of three studies comparing six to 12 months versus 24 months AED therapy.

Unit of analysis issues

We intended to take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome. However, none of the studies included in the review are cross-over or cluster-randomised trials.

Dealing with missing data

We procured the complete article for collection of data. In case of missing data (number of patients excluded, reasons), we contacted the principal investigator of the study by email. Up until the time of writing the review, we had not received any replies.

Assessment of heterogeneity

We assessed heterogeneity between trials by examining the forest plot, and using the I^2 statistic for heterogeneity, where an I^2 greater than 50% indicates substantial heterogeneity

We assessed clinical heterogeneity by comparing the differences in demographics, type and number of seizures, type of AED used, dosages and duration of treatment and radiological data in the various studies.

Assessment of reporting biases

We assessed the included studies for reporting bias by evaluating the exclusion criteria in the study and also by evaluating the dropout rate and noting the reasons for it. We also assessed the probability of publication bias by examining a funnel plot for asymmetry.

Data synthesis

We combined dichotomous data by the method of Mantel Haenzsel using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We had planned to undertake subgroup analysis for the following subgroups:

1. individuals with a single granuloma and those with multiple cerebral granulomas;
2. individuals with neurocysticercosis treated with monotherapy and polytherapy;

We did not find any studies comparing treatment in people with single and multiple granulomas or that compared monotherapy versus polytherapy.

Sensitivity analysis

We carried out a sensitivity analysis to test the robustness of meta-analysis.

Summarising and interpreting results

Two 'Summary of findings' tables have been created; one table for each comparison (six months AED treatment versus 12 to 24 months AED treatment and six to 12 months AED treatment versus 24 months AED treatment), including the primary outcome of proportion of individuals experiencing seizure recurrence (Summary of findings for the main comparison, Summary of findings 2). The other primary outcome of the review, time to first seizure after randomisation was not reported in any of the included studies. If this outcome is reported in included studies in future updates of the review, it will be added to the 'Summary of findings' tables. The certainty of the evidence was determined using the GRADE approach (GRADEPro 2004); where evidence was downgraded in the presence of high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. Evidence was downgraded by one level if the limitation was considered serious and two levels if considered very serious; as judged by the review authors.

RESULTS

Description of studies

The review authors (MS, MF, BDM) independently reviewed the results of the electronic search to identify relevant trials for the complete review.

Results of the search

A total of 228 records were identified through database searching, including 48 newly identified trials and a further three records were identified through other sources. We removed duplicate citations and obviously irrelevant items (i.e. not reports of trials), trials studying the use of albendazole, praziquantel and their combinations and trials studying various protocols of steroids for people with neurocysticercosis. Of the 85 remaining records, 78 were excluded as they were studies addressing laboratory diagnosis of neurocysticercosis or trials for which the outcomes reported were an assessment of the impact of non-AED medicines such as anthelmintics and/or steroids.

We found seven potentially relevant studies for the review. Full published texts of the articles of these seven publications were reviewed. Three were excluded and we finally included four studies. The review authors decided which studies should be included for the review after discussion. The inclusion, exclusion criteria and methodological quality were graded on a pre designed format. The review authors were not blinded to the study authors names, institute of the studies and the journal of publication. The search results are shown in Figure 3.

Figure 3. Study flow diagram.

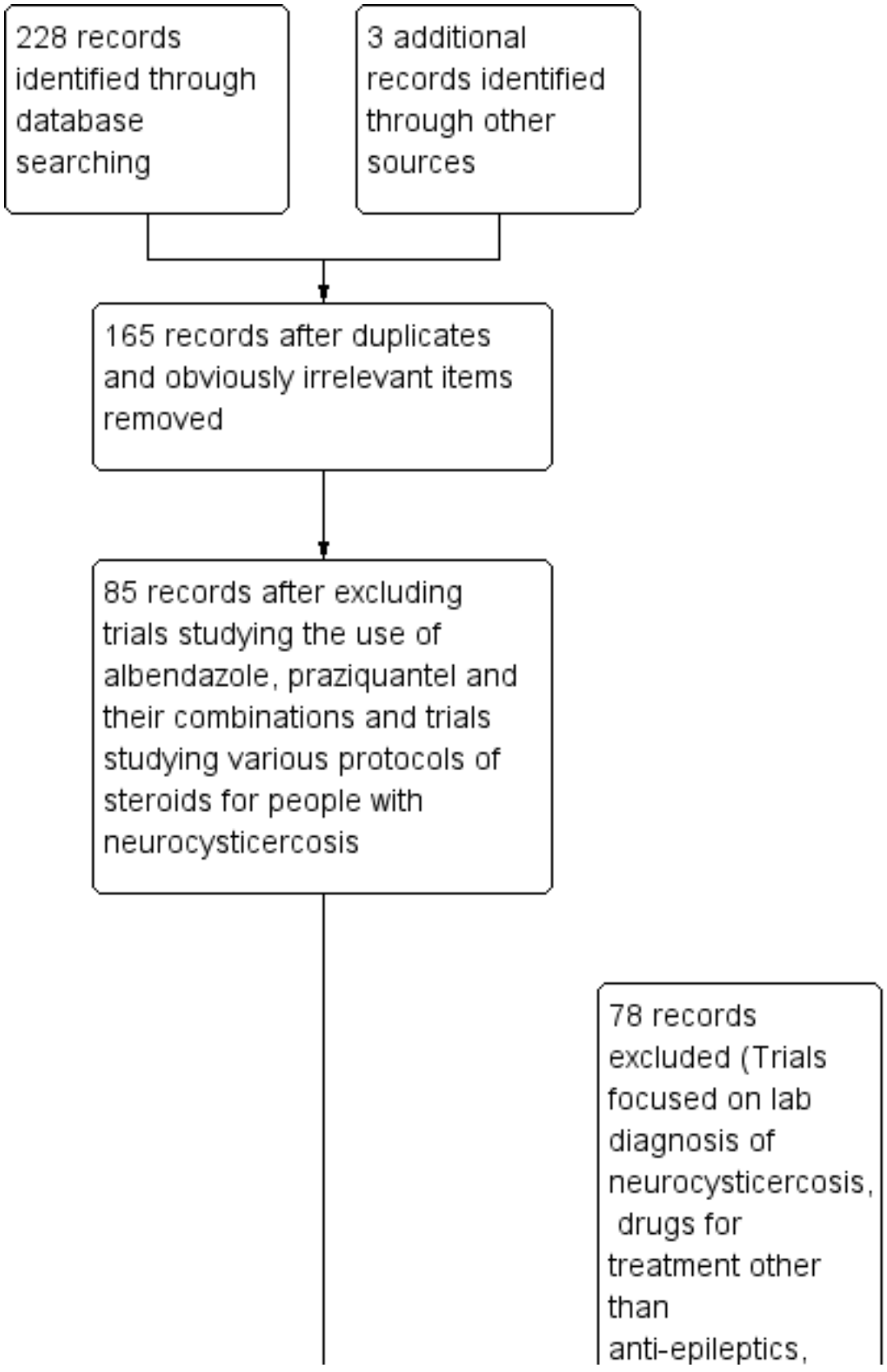
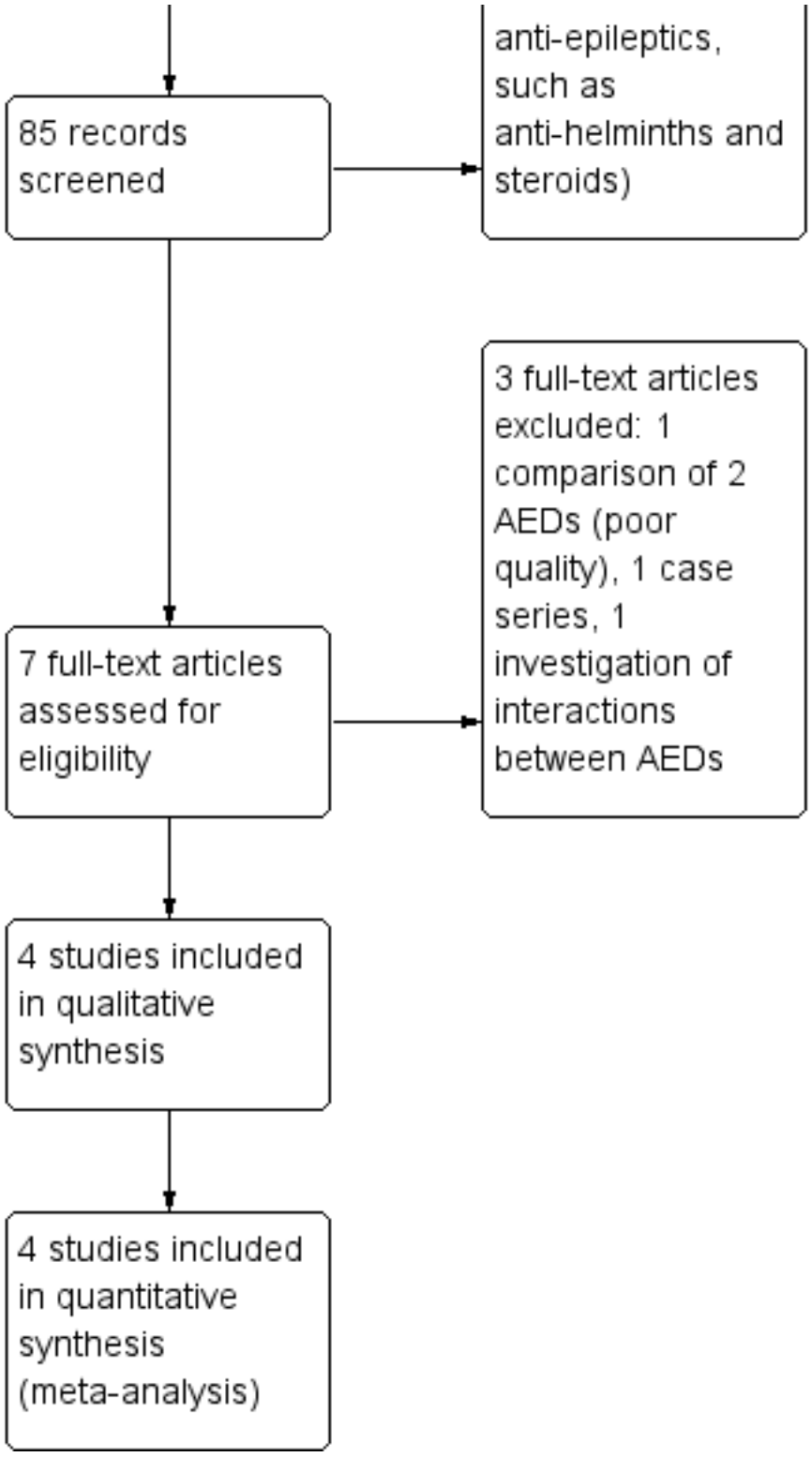


Figure 3. (Continued)



Included studies

We identified four studies, which together enrolled 466 patients with neurocysticercosis. One study (Singhi 2003) included children between the ages of three and 14 years; one study (Verma 2006) included adults (age not specified); one study (Thussu 2002) included both children and adults, ages varying from four to 52 years; and one study (Gupta 2002) did not clearly mention the age range of patients included in the study. Three studies (Singhi 2003; Thussu 2002; Verma 2006) enrolled patients from outpatient clinics whereas Gupta 2002 did not mention the source of patients.

Of the 466 people involved, the gender of 81 people included in one study (Gupta 2002) was not specified. Of the rest, 237 were male and 148 were female participants. Partial seizures were the commonest form of seizures. Forty-two people had primary generalised seizures and 343 people had partial seizures. One study (Gupta 2002) did not elaborate on the type of seizures and drugs given. In the other three studies, 299 people were given carbamazepine and 105 people received phenytoin.

All the studies included were single-centre studies carried out at various centres in India. A total of 466 people were included in the trials. These studies compared efficacy of various durations (six, 12 and 24 months) of AED therapy. Three studies (Gupta 2002; Thussu 2002; Verma 2006) considered six months AED treatment as short duration and one study (Singhi 2003) considered 12 months treatment as short duration. Twelve months was considered as long duration of treatment in Gupta 2002 and three studies (Singhi 2003; Thussu 2002 Verma 2006) considered 24 months as long duration of treatment. One hundred and eight-six people in three studies (Gupta 2002; Thussu 2002; Verma 2006) received six months of AED and 55 people in one study (Singhi 2003) received 12 months AED as short duration. One hundred and eighty-five people in three studies (Singhi 2003; Thussu 2002 Verma 2006) received 24 months AED as long duration and 40 people in one study (Gupta 2002) received 12 months AED as long duration of treatment.

Patients were followed up for a period of 12 months in three studies (Gupta 2002; Singhi 2003; Thussu 2002) and for 18 months in one (Verma 2006) after randomisation. Repeat neuroimaging was performed in three studies; at three or six months in two studies (Gupta 2002; Verma 2006) and at 12 months in one study (Singhi 2003) after an initial scan at randomisation.

The common AEDs used were carbamazepine or phenytoin. Two studies (Singhi 2003; Verma 2006) stated that choice of drug was decided by the treating physician and possibly affected by cost of treatment. One study (Thussu 2002) did not state the reason, if any, for choice of a particular AED. The fourth study (Gupta 2002) focused on the comparison of the duration of AED given and did not state which drug was given. This adds an element of bias in choice of therapy and affects outcome and we judged it as high risk of other bias.

Details of each of the included studies are further described in Characteristics of included studies.

Excluded studies

We excluded three studies. One study (Chang 1998) was a small case series of add-on treatment with tiagabine in adults with neurocysticercosis receiving AEDs for seizure control. The second study (Kaushal 2006) compared the tolerability and efficacy and safety of clobazam with phenytoin sodium. We excluded this study as the participants in this open-label pilot study were only observed for six months and the authors do not provide 12 months follow-up data on the outcome measures required in this review. The third study (Lanchote 2002) investigated the pharmacokinetic interactions between AEDs and serum albendazole enantiomer concentrations.

Risk of bias in included studies

The risk of bias is demonstrated in Figure 1 and Figure 2 and detailed below.

Allocation

The method used for randomisation was stated in three studies (Singhi 2003; Thussu 2002; Verma 2006), whereas Gupta 2002 did not state the method of randomisation. Methods used for randomisation included a lottery system (Thussu 2002), coin toss (Verma 2006) and random number tables (Singhi 2003). We assumed that randomisation was done appropriately and thus there was a low risk of allocation bias.

There is an unclear risk of allocation concealment bias in all four studies (Gupta 2002; Singhi 2003; Thussu 2002; Verma 2006) as concealment has not been mentioned.

Blinding

None of the studies mention blinding of participants or treating physicians to the study arm or to the antiepileptic agent being used. In two studies (Singhi 2003; Verma 2006) the choice of drug used depended upon the physician and affordability of the agent. We report a high risk of performance bias and an unclear risk of detection bias in all four studies (Gupta 2002; Singhi 2003; Thussu 2002; Verma 2006).

Incomplete outcome data

One study (Verma 2006) detailed the number of patients excluded from the study due to loss to follow-up and fulfilment of exclusion criteria. We judged a low attrition bias in this study. The other three studies (Gupta 2002; Singhi 2003; Thussu 2002), mentioned exclusion criteria but did not detail the number of patients excluded in the final analysis. We judged a unclear attrition bias in these studies.

Selective reporting

The protocols of the selected studies were not available for comparison with the final conduct of the studies. We judged two studies (Singhi 2003, Verma 2006) to have a low risk of reporting bias as evident from the reported results in the studies. We judged two studies (Gupta 2002, Thussu 2002) to have an unclear risk of reporting bias.

Effects of interventions

See: **Summary of findings for the main comparison** Short-duration AED treatment (six months) compared with long-duration AED treatment (12 to 24 months) for people with neurocysticercosis; **Summary of findings 2** Six to 12 months AED treatment compared with 24 months AED treatment for seizure control in neurocysticercosis

All four studies included in the review compared the effectiveness of short-term versus long-term antiepileptic drugs (AED) treatment in seizure control in people with neurocysticercosis. All included studies recruited patients with seizures prior to AED treatment therefore analyses are of secondary prevention as opposed to primary prevention.

Primary Outcomes

None of the identified studies randomised individuals to specific AEDs and none compared the proportion of individuals experiencing seizures between the AEDs prescribed.

Secondary Outcomes

Three studies (Gupta 2002; Thussu 2002; Verma 2006) considered six months as short-term treatment, whereas Singhi 2003 considered patients treated for 12 months as the short-term group. Gupta 2002 considered 12 months as the long-duration treatment arm and the other three studies (Singhi 2003; Thussu 2002; Verma 2006) considered 24 months treatment as the long-duration arm. Three studies (Gupta 2002; Singhi 2003; Thussu 2002) followed up patients for 12 months after stopping AED while one study (Verma 2006), followed up patients for 18 months. The outcome seizure recurrence was recorded from patient reports on follow-up visits every two or three months after randomisation.

We analysed data comparing six months AED treatment versus 12 to 24 months AED treatment (data from three studies (Gupta 2002; Thussu 2002; Verma 2006)) and data comparing six to 12 months AED treatment versus 24 months AED treatment (data from three studies (Singhi 2003; Thussu 2002; Verma 2006)).

The odds ratio (OR) of seizure recurrence with six months AED treatment compared with 12 to 24 months AED treatment was not statistically significant (OR 1.34, 95% CI 0.73 to 2.47; three studies; 360 participants; low-certainty evidence; (Figure 4, Analysis 1.1)). The risk of seizure recurrence with six to 12 months AED treatment compared with 24 months AED treatment was also not statistically significant (OR 1.36, 95% CI 0.72 to 2.57; three studies, 385 participants; low-certainty evidence; (Figure 5; Analysis 2.1)).

Figure 4. Forest plot of comparison: 2. 6 months AED treatment versus 12-24 months AED treatment, outcome: 2.1 Seizure recurrence.

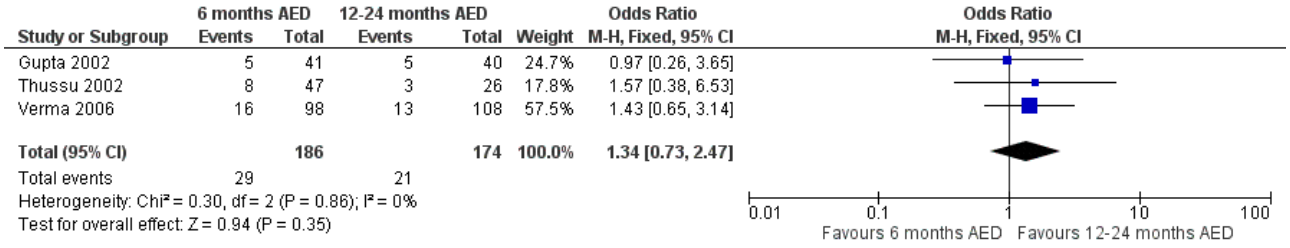
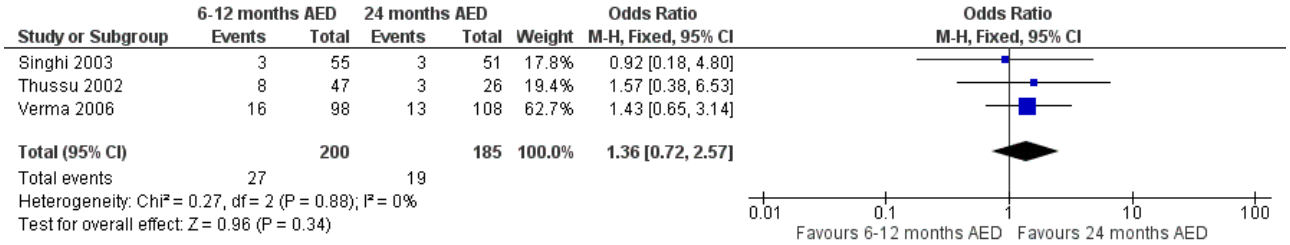


Figure 5. Forest plot of comparison: 2. 6-12 months AED treatment versus 24 months AED treatment, outcome: 2.1 Seizure recurrence.



Two studies (Singhi 2003; Verma 2006) correlated seizure recurrence with CT findings. Both studies suggest that prolonged AED treatment may be required for patients with persistent lesions or calcification, based on seizure recurrence and follow-up CT scanning.

Only one study (Verma 2006) mentioned that no side effects occurred in any patient. The other three studies (Gupta 2002; Singhi 2003; Thussu 2002) did not comment on side effects of AEDs in their patients.

The cost of treatment, quality of life, mortality, and requirement for hospitalisations were not evaluated in any of the studies.

The dosage of drug used was mentioned in one study (Verma 2006); no information was provided on drug doses in the other three studies. Therefore, we did not carry out subgrouping of drug given or dosage for this review.

DISCUSSION

We intended to look at trials evaluating the efficacy of various antiepileptic drugs (AEDs) for seizure control in people with neurocysticercosis. For primary prevention, we intended to look at patients with neurocysticercosis presenting with problems other than seizures for example, headache, diplopia (double vision) etc. However, in our electronic search we did not find trials addressing the above. This finding indicates a gap in our knowledge base and the need for randomised controlled trials to address this issue.

For secondary prevention, we aimed to look at studies that considered whether AEDs decrease the likelihood of further seizures in patients who have experienced at least one seizure.

Summary of main results

We found seven trials of apparent relevance. One study (Chang 1998) was excluded as it was a description of four cases. One study (Kaushal 2006) compared the safety and efficacy of clobazam versus phenytoin sodium in seizure control in people

with a single neurocysticercosis. This study was excluded as it was of poor quality. The third excluded study (Lanchote 2002) investigated the pharmacokinetic interactions between AEDs and serum albendazole enantiomer concentrations.

The four studies included in the review compared the use of short duration and long duration AED treatment in control of seizures in people with a single cerebral cysticercal cyst.

Four hundred and sixty-six people with neurocysticercosis participated in the four included studies (Gupta 2002; Singhi 2003; Thussu 2002; Verma 2006). These studies examined seizure recurrence with varying durations of AED treatment (six or 12 or 24 months).

The odds ratio (OR) of seizure recurrence with six months AED treatment compared with 12 to 24 months treatment was not statistically significant (OR 1.34; 95% CI 0.73 to 2.47; three studies, 360 participants (186 participants for six months treatment and 174 participants for 12 to 24 months treatment) (Analysis 1.1)). The risk of seizure recurrence with six to 12 months AED treatment compared with 24 months treatment was also not statistically significant (OR 1.36; 95% CI 0.72 to 2.57; three studies, 385 participants (200 participants randomised to six to 12 months treatment and 185 participants to 24 months treatment) (Analysis 2.1)).

Two studies (Singhi 2003; Verma 2006) indicated that in cases where a persistence of lesion or calcification is found on review computed tomography (CT) scans, prolongation of AED treatment may be effective in optimal seizure control.

Overall completeness and applicability of evidence

A major drawback of the four studies included in the review, comparing short-duration and long-duration treatments, is that none of the studies sought to establish the effectiveness of the specific AED being given, with respect to choice of drug, dosage, compliance or side-effect profiles. All four studies solely focused on comparison of duration of drugs being given. The results thus have limited applicability to choice of AED for physicians.

With the exception of Verma 2006, where exclusions and losses are detailed, none of the included studies mentioned the exact number of people excluded from the trial and why.

Most studies mentioned that neurocysticercosis is a benign and often a self-limiting condition. Thus patient selection may affect the final outcome of the studies. Two studies (Thussu 2002; Verma 2006) excluded patients who had a persistence of lesion, which is actually a high risk for seizure recurrence, implying that patients selected for the study had a low risk of seizure recurrence in the first place.

Most of the studies included in the review excluded patients with persistent lesions and those needing albendazole therapy, some of whom may have actually been potential candidates for seizure recurrence. As a result, the study inferences prevent generalisation to all patients will neurocysticercosis and rather focuses on patients with inactive parasitic cysts.

Also, all of the included studies focused on people with a solitary cerebral lesion. These factors limit the applicability and generalisation of the study results as evidence for future use in people with neurocysticercosis who may have multiple cysts or the lesion is situated in unusual locations for example, intra ventricular cysts, brainstem cysts etc .

Three of the studies (Gupta 2002; Singhi 2003; Verma 2006) correlated seizure recurrence and the need for prolonged therapy with the presence of a calcified lesion. They suggest that people with calcified lesions would benefit with a longer duration of AEDs and additionally helped by repeated neuroimaging to check the status of the lesion. This suggestion is useful in practice.

Certainty of the evidence

The studies that compared short-duration and long-duration AEDs included in this review have methodological deficiencies, such as lack of blinding, small sample sizes, reporting biases, lack of description of withdrawals from the study. We graded the level of evidence as low. All the included studies had an inherent bias in patient allocation and blinding. Though not clearly mentioned, it can be assumed that the treating physicians and patients were not blinded to the study drug and study arm being studied. This also adds a possibility of a reporting bias, all of which together affect the quality of evidence provided by the study results.

We evaluated the included studies for heterogeneity using the I^2 statistic (I^2 = 0%). The studies included in the meta-analysis, were homogenous with respect to diagnostic criteria used, method of sampling, method of observation, follow-up and analysis of results. The forest plot of comparison shows a trend (not statistically significant) in favour of a longer duration of AED treatment over a short duration of treatment for seizure recurrence (OR 1.34; 95% CI 0.73 to 2.47) for six months versus 12 to 24 months AED treatment (Analysis 1.1) and (OR 1.36; 95% CI 0.72 to 2.57) for six to 12 months versus 24 months AED treatment (Analysis 2.1).

An analysis of the findings is shown in the Summary of findings for the main comparison and Summary of findings 2. We graded the level of evidence as low.

Potential biases in the review process

Potentially, studies may have been missed by the search strategy if smaller studies were presented at clinical conferences, but not in the literature identified through the search engines employed.

None of the identified studies reported the primary outcome measures of the proportion of individuals experiencing seizures or the time to first seizure between AED treatment groups. We contacted the authors to attempt to obtain these data but did not receive these data to undertake these analyses. Nevertheless, had these data been made available, there would potentially be significant bias as the prescription of AEDS was not randomised but rather determined by the clinician, which reflects clinical and potentially financial bias.

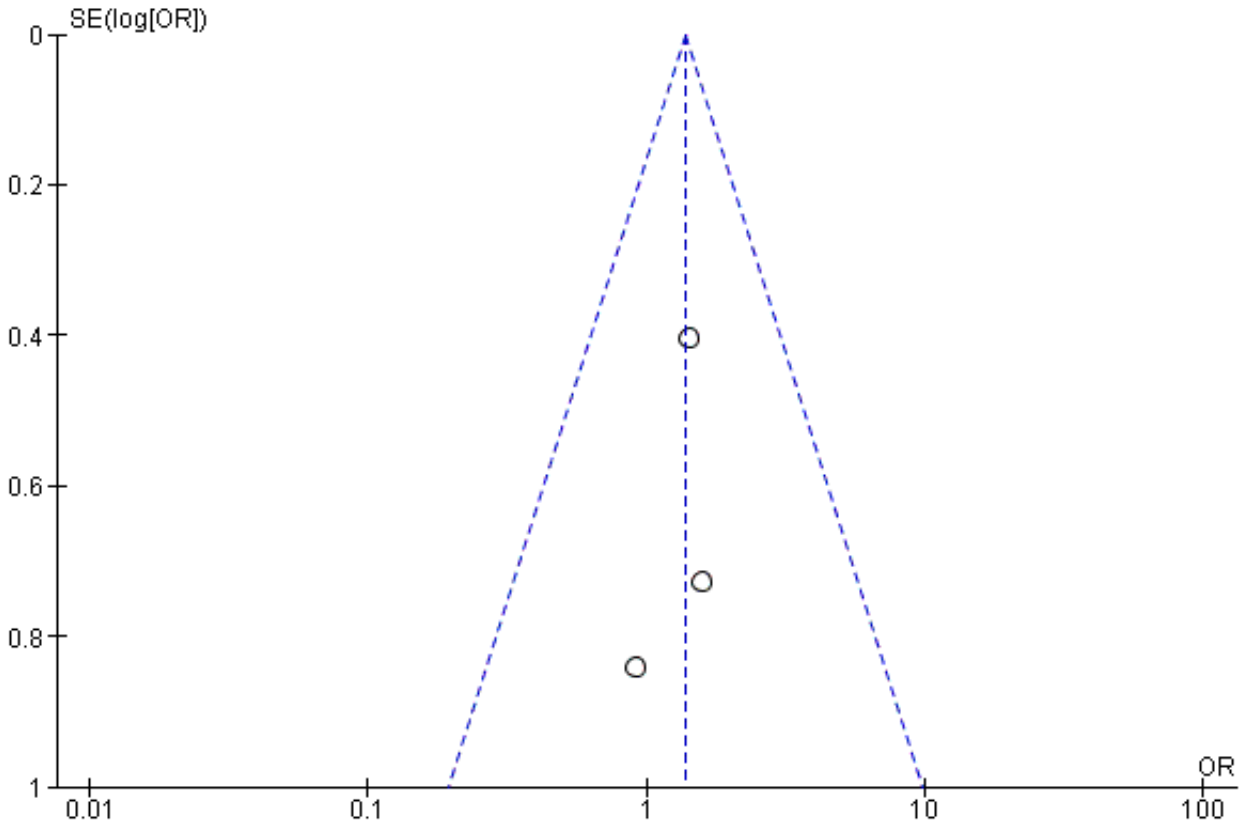
Study selection potentially could have introduced bias as in the protocol we limited our inclusion to studies with at least 12 months of data, therefore we are unable to comment on the efficacy of AEDs in the first six months of therapy.

All four included studies were single-centre studies from various parts of India. The geographic location and disease behaviour outcomes may be different in the subcontinent versus other regions

of the world where neurocysticercosis is equally rampant. We cannot rule out a regional bias in this review.

We generated a funnel plot indicating a publication bias in the included studies Figure 6. The quality of the trials included is not uniform, in terms of study design. For example, one study enrolled children only (Singhi 2003), one study included only adults (Verma 2006), while one included people of all age ranges (Thussu 2002). The mean age of people in the latter study (Thussu 2002) was in the adult range. The fourth study (Gupta 2002),did not specify details of the enrolled patients, such as age, gender or type of seizures. This factor affects the result of this review.

Figure 6. Funnel plot of comparison: 2. 6-12 months AED treatment versus 24 months AED treatment, outcome: 2.1 Seizure recurrence.



Agreements and disagreements with other studies or reviews

So far, there have been reviews on treatment of people with neurocysticercosis, highlighting anthelmintic therapy, anti-oedema measures such as steroids and various combinations of these measures with respect to seizure control (Abba 2010; García 2002; Zafar 2013). While most of these reviews mention the need for AEDs in patients presenting with seizures, there are no reviews dedicated to the use of AEDs with respect to drug choices, duration of treatment, side-effect profiles etc.

AUTHORS' CONCLUSIONS

Implications for practice

The initial research question for this review was: 'Do antiepileptic drugs (AEDs) influence seizure control in people with neurocysticercosis with respect to the drug used, dose and duration?' We also intended to look at primary prevention in people with symptoms other than seizures. We do not know whether prophylactic AED therapy is useful in preventing seizures in people with neurocysticercosis presenting with symptoms other than seizures, since no randomised controlled trials are available at present.

We found only one study that compared two AEDs in people with solitary cerebral cysticercosis. We excluded this study as it was of poor quality and had a limited follow-up period of only six months. We cannot suggest superiority of one AED over another.

We found four studies that addressed duration of AED for seizure control in people with a single cerebral cyst. Our analysis does not suggest a clear benefit of short (six to 12 months) or longer duration of AED (12 to 24 months). In people with persistent cysts or calcification, we found low-certainty evidence that a longer duration of AED treatment may reduce seizures compared to a shorter duration of AED treatment.

Implications for research

Further studies are needed to determine which AED is more suitable for persons with seizures (or epilepsy) due to neurocysticercosis and what is the optimal dose range and duration of treatment.

Studies are also needed to address the issue whether prophylactic treatment with AEDs reduce the occurrence of seizures. The effect of AED treatment on quality of life for people with neurocysticercosis also needs to be investigated.

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CHARACTERISTICS OF STUDIES

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

Gupta 2002

Methods	Randomised trial. Method of randomisation not stated. Single centre in New Delhi, India. Total duration of trial 1.5 to 2 years in both study groups. Ethical approval/consents not stated.
Participants	81 participants, 41 people with NCC treated for 6 months in group A, 40 people with NCC treated for a period of 12 months in group B.

Gupta 2002 *(Continued)*

	Diagnostic criteria based on CT Scan findings. Age and sex distribution not stated. Inclusion criteria: all patients with epilepsy and diagnostic CT findings, only patients with a single lesion. Exclusion criteria: suspected tuberculoma and NCC patients treated with albendazole. Follow-up: 12 months after drug withdrawal.
Interventions	AED treatment for seizure control for 6 months in group A and 12 months in group B. Details of drug used, dosage in either groups not stated.
Outcomes	Seizure recurrence after stoppage of treatment.
Notes	Single outcome studied. Withdrawls and exact number of excluded patients not stated. Choice of AED not mentioned. Dosage, side effects, cost and impact on quality of life not studied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not detailed
Allocation concealment (selection bias)	Unclear risk	Exact methodology not detailed in the article
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned in article, probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method of outcome recording not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals, exclusions and reasons (if any) not stated
Selective reporting (reporting bias)	Unclear risk	Protocol not available. Insufficient information to comment on reporting
Other bias	High risk	AED used, formulation and dosage not stated in the article

Singhi 2003

Methods	Randomised controlled trial. Single centre in India. Total duration of trial 2-3 years in both comparison groups.
Participants	Children with NCC.

Singhi 2003 *(Continued)*

	Diagnostic criteria based on CT Scan findings, only single lesions included. 55 children treated with AEDs for 1 year as group A, 51 children treated for 2 years as group B. Age range: 3 to 14 years, 61 boys, 45 girls. Demographically comparable groups. Inclusion criteria: children with seizures and CT scan diagnosis of NCC. Exclusion criteria: children with multiple or calcified CT lesions, static or progressive neurological disorder, any systemic or chronic illness, any clinical or ancillary evidence of tuberculosis; 55% also received albendazole within 3 months of presentation. Follow-up: 12 months after drug withdrawal.
Interventions	AEDs for 12 months in group A and 24 months in group B. All children received monotherapy. 80% received carbamazepine, 18% received dilantin. Formulations, dosage, group-wise distribution not stated.
Outcomes	Seizure recurrence during and after drug withdrawal. Association of seizure recurrence with clinical variables (type and frequency of seizures). Association of seizure recurrence with CT and EEG abnormalities.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence tables used for randomisation Demographic variables of children in both groups comparable Type and frequency of seizures, AEDs given, EEG and CT Scan observations detailed and comparable
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to the intervention. Hence, we assume here that they were also not blinded to short or long duration treatment arms.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and reasons not stated
Selective reporting (reporting bias)	Low risk	Study protocol not available, all expected outcomes suitably detailed in the results section

Singhi 2003 *(Continued)*

Other bias	High risk	Dosage of AEDs given not stated

Thussu 2002

Methods	Randomised clinical trial. Single centre in India. Duration of trial 1.5-3 years in two groups.
Participants	People with seizures and CT scan suggestive of NCC Age range: 4 to 52 years, Mean ages in group A and B 19.5 ± -8.79 years and 25.6 ± 12.5 years, respectively. 53% of patients were males. Total: 73 people, 47 in group A treated with AEDs for 6 months, 26 in group B treated for 24 months. Follow-up: every 2 months for 12 months after withdrawal of drugs. Exclusion criteria: people with persistent lesions requiring albendazole therapy.
Interventions	AEDs for 6 months in group A, 24 months in group B. Group A 25 received carbamazepine, 22 received phenytoin. Group B 13 each received carbamazepine and phenytoin. Exact dosage and formulations not stated. Mentioned to have received quote: "therapeutic dosage according to weight".
Outcomes	Seizure recurrence after withdrawal of AED. Correlation of seizure recurrence with CT Scan findings.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation based on lottery system
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of patients excluded or withdrawing from the study not mentioned

Thussu 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not available. Insufficient information to confirm reporting bias.
Other bias	Unclear risk	Seizure recurrence discussed but timing of recurrence, i.e. during or after AED therapy not clear

Verma 2006

Methods	Randomised clinical trial. Single centre in India. Duration of trial 2 to 3.5 years in two groups.
Participants	227 people with NCC, 206 randomised. Inclusion criteria: people with epilepsy with CT Scan criteria of Del Brutto et al. Only people with complete resolution of lesion at 3 to 6 months CT scan or presence of calcified residua included. Exclusion criteria: persistent lesions on repeat CT scan at 3 to 6.months interval. Mean age 21.8 ± 6.1 years in group A, 19.5 ± 8.8 years in group B. Gender distribution in two groups comparable. Seizure type, duration at randomisation and frequency comparable in the two groups. Follow-up for a minimum of 18 months after drug withdrawal.
Interventions	AEDs for 6 months in Group A and 24 months in Group B. 176 people treated with carbamazepine (600 to 1000 mg/day). 51 people treated with phenytoin (300 to 400 mg/day).
Outcomes	Seizure recurrence during and after withdrawal of AED. Severe side effects to AED. Correlation of seizure recurrence with CT scan finding in follow-up scans.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple random sampling by coin toss method
Allocation concealment (selection bias)	Unclear risk	Authors do not detail the conduct of the coin toss and wether result of the coin toss was visible to the researchers or participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not stated

Verma 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of people lost to follow-up in both groups and number of people completing study mentioned in table 1
Selective reporting (reporting bias)	Low risk	Study protocol not available, no differences between planned and reported outcomes evident
Other bias	Low risk	Insufficient evidence to suggest risk of bias

AED: antiepileptic drug
CT: computed tomography
EEG: electroencephalography
NCC: neurocysticercosis

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

Study	Reason for exclusion
Chang 1998	Case series study of 4 adult patients with NCC with epilepsy. Tiagabine HCL was used as an add-on drug in 4 patients (2 on carbamazepine and 2 on phenytoin).
Kaushal 2006	Comparison of clobazam with phenytoin sodium for prevention of seizures in people with single NCC. This is an underpowered study which was prematurely terminated due to relocation of one of the authors. The reason for the difference in numbers between the two comparison groups is not clear. It is not clear whether the two groups were balanced as far as the prognostic variables are concerned. The number of participants randomised to phenytoin and clobazam differ in the text and in the CONSORT flow chart. The study planned to enrol 135 participants in each of the two groups, in order to provide sufficient power to detect 10% difference in the primary outcome measure with 90% confidence. The numbers accrued, however fell short on account of premature termination of the study.
Lanchote 2002	The objective of this study was to determine the interaction between the AEDs and the selective metabolism of albendazole. In this study plasma concentrations of albendazole sulfoxide (ASOX) and albendazole sulphone (ASON) metabolites were measured in 32 adults who received phenytoin, carbamazepine, phenobarbital or no AED. None of the primary or secondary outcome measures in this review were assessed.

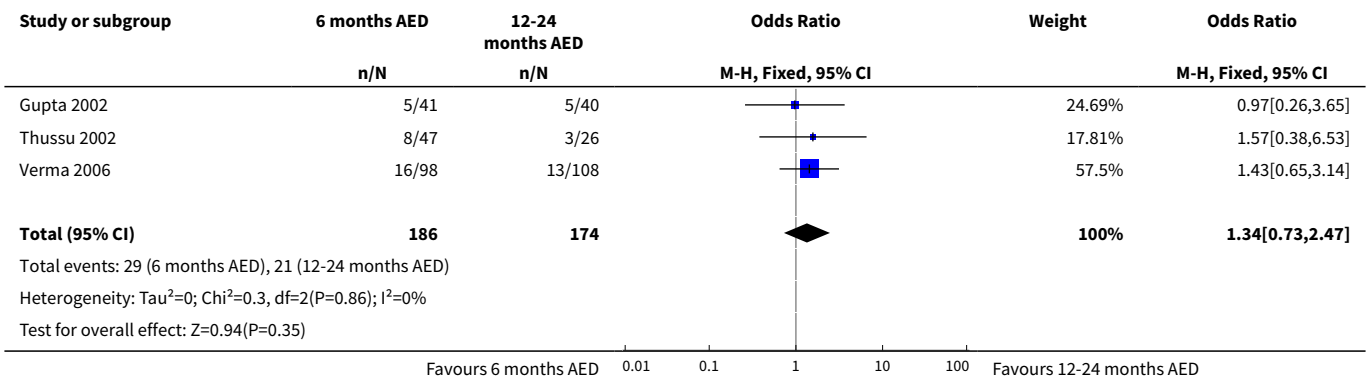
AED: antiepileptic drug
HCL: hydrochloride
NCC: neurocysticercosis

DATA AND ANALYSES

Comparison 1. 6 months AED treatment versus 12 to 24 months AED treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure recurrence	3	360	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.73, 2.47]

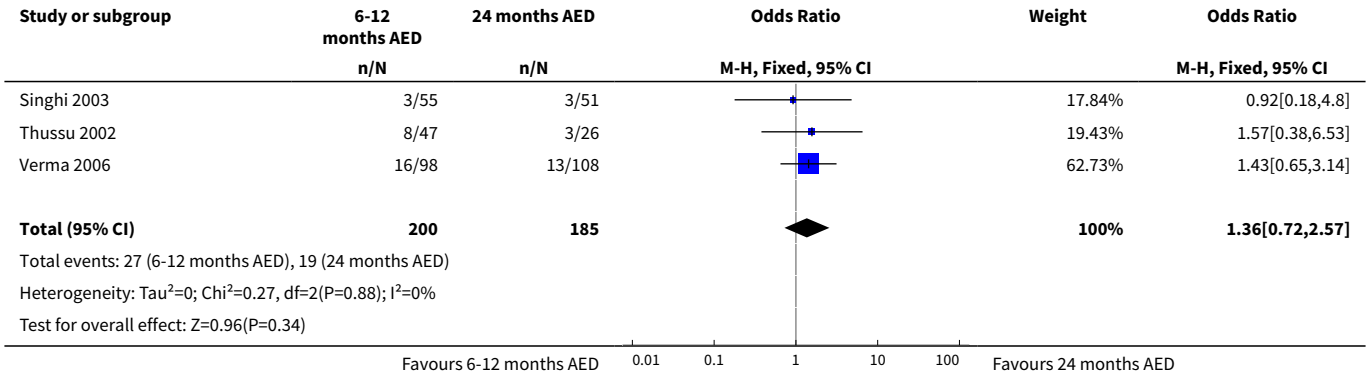
Analysis 1.1. Comparison 1 6 months AED treatment versus 12 to 24 months AED treatment, Outcome 1 Seizure recurrence.



Comparison 2. 6 to 12 months AED treatment versus 24 months AED treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Seizure recurrence	3	385	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.72, 2.57]

Analysis 2.1. Comparison 2 6 to 12 months AED treatment versus 24 months AED treatment, Outcome 1 Seizure recurrence.



APPENDICES

Appendix 1. CRS Web search strategy

1. MeSH DESCRIPTOR Neurocysticercosis Explode All AND CENTRAL:TARGET

2. neurocysticercosis AND CENTRAL:TARGET

3. MeSH DESCRIPTOR Taenia solium Explode All AND CENTRAL:TARGET

4. "Taenia solium" AND CENTRAL:TARGET

5. tapeworm OR "tape worm" AND CENTRAL:TARGET

6. #1 OR #2 OR #3 OR #4 OR #5 AND CENTRAL:TARGET

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

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

9. MeSH DESCRIPTOR Anticonvulsants Explode All AND CENTRAL:TARGET

10. MeSH DESCRIPTOR Midazolam Explode All AND CENTRAL:TARGET

11. MeSH DESCRIPTOR Methazolamide Explode All AND CENTRAL:TARGET

12. MeSH DESCRIPTOR Propofol Explode All AND CENTRAL:TARGET

13. MeSH DESCRIPTOR Temazepam Explode All AND CENTRAL:TARGET

14. MeSH DESCRIPTOR Thiopental Explode All AND CENTRAL:TARGET

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

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

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

18. (Calepsin or Carbagen or Carbamazepen* or Carbamazepin* or Carbatrol or Carbazepin* or Carbelan or Carisbamat* or Castilium or CBZ or Celontin or Cerebyx or Chlonazepam or Chloracon or Chlorepin or Clorepin or Chlormethiazole or Clormethiazole or Clarmyl or Cloazepam or Clobam* or Clobator or Clobazam or Clofritis or Clonazepam* or Clonex or Clonopin or Clopax or Clorazepate or Comfyde or Convulex):AB,KW,MC,MH,TI AND CENTRAL:TARGET

19. (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 Distraneurin or Divalpr* or Dormicum):AB,KW,MC,MH,TI AND CENTRAL:TARGET

20. (Ecovia or Emeside or Epanutin or Epiject or Epilepax or Epilex or Epilim or Episenta or Epitol or Epival or Eptoin or Equanil or Equetro or Ergenyl or Erimin or Erlosamide or Eslicarbazepine or Estazolam or Ethadione or Ethosucci* or Ethosuxi* or Ethotoin or Ethylphenacemide or Etosuxi* or Euhypnos or Exalief or Excegran or Ezogabine):AB,KW,MC,MH,TI AND CENTRAL:TARGET

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

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

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

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

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

26. (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,MC,MH,TI AND CENTRAL:TARGET

27. (Neogab or Neptazane or Nesdonal or Neurontin or Neurotop or Nimetazepam or Nitrados or Nitrazadon or Nitrazepam or Nobrium or Nocturne or Noiafren or Norkotral or Normison or Normitab or Nortem or Novo-Clopate or Nuctalon or Nupentin or Nydrane):AB,KW,MC,MH,TI AND CENTRAL:TARGET

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

29. (Pacisyn or Paraldehyde or Paramethadione or Paxadorm or Paxam or Peganone or Penthiobarbital or Pentothal or Perampanel or Petinutin or Petril or Phemiton or Phenacemide or Pheneturide or Phenobarbit* or Phensuximide or Phenylethylbarbit* or Phenylethylmalonylurea or Phenytek or Phenytoin* or Planum or Posedrine or Potiga or Pregabalin or Primidone or Prodilantin or Progabide or Prominal or Pronervon or Propofol or Prosom or Prysoline):AB,KW,MC,MH,TI AND CENTRAL:TARGET

30. (Ravotril or Remacemide or Remestan or Remnos or Resimatil or Restoril or Retigabine or Riluzole or Rilutek or Rivotril or Rudotel or Rufinamide or Rusedal or "RWJ-333369"):AB,KW,MC,MH,TI AND CENTRAL:TARGET

31. (Sabril or Seclar or Sederlona or Selenica or Seletracetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or Stavzor or Stazepin* or Stedesa or Stiripentol or Sulthiam* or Sultiam*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

32. (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,MC,MH,TI AND CENTRAL:TARGET

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

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

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

36. #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 OR #31 OR #32 OR #33 OR #34 OR #35 AND CENTRAL:TARGET

37. #6 AND #36

Appendix 2. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials published in Lefebvre 2011.

1. exp NEUROCYSTICERCOSIS/

2. neurocysticercosis.tw.

3. Taenia solium.tw.

4. exp Taenia solium/

5. (tape worm or tapeworm).tw.

6. 1 or 2 or 3 or 4 or 5

7. exp *Epilepsy/dt [Drug Therapy]

8. exp Seizures/dt [Drug Therapy]

9. exp Anticonvulsants/

10. exp Midazolam/

11. exp Methazolamide/

12. exp Propofol/

13. exp Temazepam/

14. exp Thiopental/

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

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

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

18. (Calepsin or Carbagen or Carbamazepen$ or Carbamazepin$ 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.

19. (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 Distraneurin or Divalpr$ or Dormicum).tw.

20. (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.

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

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

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

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

25. (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.

26. (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.

27. (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.

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

29. (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.

30. (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.

31. (Sabril or Seclar or Sederlona or Selenica or Seletracetam or Sentil or Sertan or Sibelium or Signopam or Sirtal or Sodipental or Somnite or Stavzor or Stazepin$ or Stedesa or Stiripentol or Sulthiam$ or Sultiam$).tw.

32. (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.

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

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

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

36. or/7-35

37. 6 and 36

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

39. clinical trials as topic.sh.

40. trial.ti.

41. 38 or 39 or 40

42. exp animals/ not humans.sh.

43. 41 not 42

44. 37 and 43

45. remove duplicates from 44

Appendix 3. LILACS search strategy

(anticonvulsant OR mh:("anticonvulsants")) AND (mh:("NEUROCYSTICERCOSIS" OR "TAENIA") OR neurocysticercosis OR taenia OR (tape AND worm) OR tapeworm)

WHAT'S NEW

Date	Event	Description
8 July 2019	New search has been performed	Searches updated 8 July 2019; no new trials identified.
8 July 2019	New citation required but conclusions have not changed	Conclusions are unchanged.

CONTRIBUTIONS OF AUTHORS

MS independently screened all 180 citations and abstracts and evaluated the eligibility of the study for the review. MF and BDM independently screened 48 newly identified citations and abstracts and evaluated the eligibility of the study for the review. MS and AM independently extracted data using a tailored data extraction form. TS supervised data extraction and resolved any discrepancies between MS and AM, if needed. MS prepared the first draft of the review. TS reviewed the final draft.

DECLARATIONS OF INTEREST

MF: none known
MS: none known
TS: none known
AM: none known
BDM has received funding from the NIHR, Wellcome Trust, Academy of Medical Sciences, British Medical Association.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we planned to analyse seizure control with AEDs over a specified period of time. We had also planned to look at studies comparing duration of treatment with respect to seizure control. A subgroup analysis between patients with single versus multiple cerebral lesions and monotherapy versus polytherapy was planned.

In the final review, we were restricted to comparing short-duration versus long-duration therapy according to the studies identified and included in the review. All the included studies were carried out on people with single cerebral lesions and all patients received monotherapy. The intended subgroup analysis was hence not possible.

In the protocol, we had mentioned that we would exclude studies comparing two AEDs. However, we decided to include such studies after this oversight was pointed out in the review process. This was essential to answer our primary question of "which AED is better for seizure control?"

In the protocol, we intended to look at the effect of drugs in seizure control in a population with neurocysticercosis and therefore planned to calculate the risk ratio (RR). As we were able to find studies that compared short duration versus long duration AED treatment, we calculated the odds ratio (OR) to look at the odds of seizure recurrence in long duration of AED treatment against short duration of treatment.

As far as the search methods, data collection and analysis are concerned, we were able to proceed as per the protocol design.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Brain Diseases [*complications] [parasitology]; Carbamazepine [therapeutic use]; Epilepsy [drug therapy]; Neurocysticercosis [*complications]; Phenytoin [therapeutic use]; Randomized Controlled Trials as Topic; Seizures [etiology] [*prevention & control]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Female; Humans; Male; Middle Aged