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Antiepileptic drugs for the primary and secondary prevention of seizures after stroke (Review)

Sykes L, Wood E, Kwan J

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[Intervention Review]

Antiepileptic drugs for the primary and secondary prevention of seizures after stroke

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in 2010, Issue 1. Seizures after stroke are an important clinical problem, and they may be associated with poor outcome. The effects of antiepileptic drugs for the primary and secondary prevention of seizures after stroke remain unclear.

Objectives

We aimed to assess the effects of antiepileptic drugs for the primary and secondary prevention of seizures after stroke.

Search methods

We searched the Specialised Registers of the Cochrane Epilepsy Group (12 August 2013) and the Cochrane Stroke Group (12 August 2013), the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* 2013, Issue 7), and MEDLINE (OVID, 1946 to 12 August 2013). We also checked the reference lists of articles retrieved from these searches.

Selection criteria

Randomised and quasi-randomised controlled trials in which participants were assigned to treatment or control group (placebo or no drug).

Data collection and analysis

Two review authors independently screened all the titles, abstracts, and keywords of publications identified by the searches to assess their eligibility, and both review authors assessed their suitability for inclusion according to prespecified selection criteria. We included only one study for data collection and analysis.

Main results

We found only one trial that fulfilled the study inclusion criteria of comparison of the effects of an antiepileptic drug with placebo (or no drug) for the primary or secondary prevention of seizures after stroke. This was a prospective randomised, double-blind, placebo-controlled trial comparing valproic acid with placebo for primary prevention of seizures in 72 adults (over 18 years of age) with spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage; no statistically significant difference in outcome (seizure occurrence at one year) was demonstrated between groups.

Authors' conclusions

Currently, there is insufficient evidence to support the routine use of antiepileptic drugs for the primary or secondary prevention of seizures after stroke. Further well-conducted research is needed for this important clinical problem.

PLAIN LANGUAGE SUMMARY

Is there evidence to support the use of antiepileptic drugs for the primary and secondary prevention of seizures after stroke?

Background

Seizures (epileptic attacks) after stroke are a major clinical problem. It is unclear whether antiepileptic drugs are effective in preventing seizures after stroke in adults. This review searched in August 2013 for high quality evidence to help clarify this problem. We found only one high quality clinical trial that looked at whether antiepileptic drugs may be more effective than placebo in preventing seizures after stroke.

Study Characteristics

The only study that was included in this review was Gilad 2011. This was a prospective randomised, double-blind, placebo controlled trial studying the efficacy of valproic acid versus placebo in the primary prevention of seizure in 72 adults (over 18 years of age) with spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage. Patients were randomly allocated to either the treatment or the placebo group with active treatment lasting one month; the primary outcome was seizure occurrence at one year. People with very early seizures (within 24 hours of onset of haemorrhage) were excluded from the study. Seizure was diagnosed on the basis of eye-witness evidence from staff, relatives or other eye witnesses.

Quality Of The Evidence

There does not appear to be bias in Gilad 2011, on the basis of the information available within the study.

Key Results

Gilad 2011 did not show a statistically significant benefit when comparing valproic acid with placebo for the primary prevention of seizures after spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage. Currently, therefore, there is not enough evidence to justify the routine use of antiepileptic drugs to prevent seizures after stroke (evidence current to 08/2013). Further research is needed for this important clinical problem.

BACKGROUND

Stroke is a major health problem in both the developed and developing world. In industrialised countries, it is the third most common cause of death after ischaemic heart disease and cancers, and almost half of all stroke survivors are left with a permanent handicap (Bamford 1991). Stroke mainly affects the older generation, although about 25% of all strokes occur in people under the age of 65, and about 1% in people under the age of 30.

Cerebrovascular disease is the most commonly identified cause of acquired epilepsy. Post-stroke seizures account for 11% of all epilepsy, 22% of all cases of status epilepticus, and 55% of newly diagnosed seizures amongst older people (Camilo 2004; DeLorenzo 1996; Herman 2002). The reported incidence of post-stroke seizures varies widely between epidemiological studies, ranging from 2% to 33% for early seizures (within the first 14 days) and 3% to 67% for later seizures (Camilo 2004). This is mainly due to the varying methods of case ascertainment and definitions used in relation to the timing of post-stroke seizures. According to epidemiological guidelines developed by the International League Against Epilepsy (ILAE 1981) seizures occurring within the first week of stroke are defined as 'early seizures', and those occurring after the first week are defined as 'late seizures'. Using this definition, approximately 2% to 6% of people with stroke suffer early seizures (Lamy 2003; So 1996), and 3% to 5% suffer late seizures (Lamy 2003; So 1996). In the longer term, one

community-based study found that the cumulative actuarial risk of having a post-stroke seizure was 4.2% at one year and 11.5% at five years (Burn 1997).

Development of late seizures is more common in people who have experienced early seizures (risk of about 30% (Kilpatrick 1990)). Moreover, development of post-stroke epilepsy (that is, recurrent seizures) is more common in people who have experienced late seizures, with a risk of about 50% (Olsen 2001), than for those with early seizures where the risk is about 30% (Olsen 2001; Sung 1990). Possible risk factors for post-stroke seizures (Burn 1997; Camilo 2004; Kwan 2007; Lamy 2003; Shinton 1988) include the following:

(1) stroke subtype: cerebral haemorrhage (especially subarachnoid haemorrhage);

(2) location of the lesion: cortical involvement, stroke occurring within the carotid artery territory;

(3) stroke severity (but correlation may be weaker after adjusting for stroke subtype and location);

(4) occurrence of post-stroke bacterial infections.

The pathophysiology of early and late post-stroke seizures is believed to be different. In the first few days following an ischaemic brain lesion, cellular biochemical dysfunction can lead to cortical excitability and seizure activity (Kessler 2002). Acute ischaemia leads to a massive release of glutamate, causing excessive activation of glutamate receptors. This process is believed to be responsible for secondary neuronal injury and epileptogenesis in ischaemic stroke (Sun 2001; Sun 2002). Within the ischaemic penumbra, a mixed population of dead, dying, and surviving neurones can become the underlying substrate for ischaemia-induced epileptogenesis (Kessler 2002). In contrast, late seizures may be caused by development of gliosis and meningocerebral cicatrices, with changes in membrane properties, deafferentation, selective neuronal loss, and collateral sprouting (Camilo 2004). This can result in cortical hyperexcitability and neuronal synchrony sufficient to cause seizures (Kessler 2002).

The relationship between post-stroke seizures and outcome remains unclear. Several studies have found that post-stroke seizures may predict worse functional outcome (Menon 2009), but many of these studies have not adjusted for important covariates such as stroke severity (Camilo 2004). One large study (Labovitz 2001) showed that, before adjusting for stroke severity, occurrence of early post-stroke seizures increased the risk of 30-day mortality (odds ratio (OR) 4.3, 95% confidence interval (CI) 1.5 to 12.5). However, after adjusting for stroke severity using the National Institutes of Health Stroke Scale (NIHSS) score, this association was not statistically significant (OR 2.1, 95% CI 0.6 to 7.1). In another large community-based study, early post-stroke seizures actually predicted a better neurological outcome (Reith 1997). There is also some evidence that post-stroke seizures may significantly affect health-related quality of life (Leidy 1999) but a large prospective study did not find any adverse effect on rehabilitation outcome as measured by the Barthel Index or the Rivermead Mobility Index (Paolucci 1997).

Currently, it is unclear whether antiepileptic drugs should be routinely prescribed for the primary and secondary prevention of seizures after stroke.

OBJECTIVES

We aimed to assess the effects of antiepileptic drugs (AEDs) for the primary and secondary prevention of seizures after stroke.

(1) For the question of primary prevention, we aimed to examine whether AEDs reduce the likelihood of seizures in people who have had a stroke but have not had a seizure.

(2) For the question of secondary prevention, we aimed to examine whether AEDs reduce the likelihood of further seizures in people who have had a stroke and at least one post-stroke seizure.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised and quasi-randomised controlled trials in which participants were assigned to 'treatment' or 'control' group (that is, placebo or no drug).

Types of participants

We used the World Health Organization definition of stroke for this review (WHO 1989). We considered all studies that recruited participants with a new neurological deficit consistent with a clinical diagnosis of stroke. We considered studies that included participants with either ischaemic or haemorrhagic stroke, but we excluded studies that only recruited participants with subarachnoid haemorrhage, subdural haemorrhage, extradural haemorrhage, or other non-stroke diagnoses such as tumour- or infection-related infarction or haemorrhage. We also excluded studies that recruited only participants who had undergone any type of neurosurgery. The management of these excluded patient groups is likely to be substantially different from the generality of people with stroke. For studies which have reported the results for a mixture of participant groups, we attempted to separate them and identify those which were relevant to the participant groups of interest. When we found that this was not possible, we excluded the studies. We included participants of all ages suffering any seizure type.

Types of interventions

AEDs were any of those listed on the Cochrane Epilepsy Group information page, including carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, lorazepam, oxcarbazepine, phenytoin, phenobarbitone, primidone, sodium valproate, tiagabine, topiramate, vigabatrin, and zonisamide. We considered all trials in which the intervention was compared with a placebo or with no drug. We excluded studies comparing two AEDs.

Types of outcome measures

Primary outcome measures

Proportion of participants who experienced seizures in the scheduled follow-up period. In cases where seizures have occurred, we noted their nature (generalised or focal) and timings if reported. As described in the Background, seizures occurring within the first week of stroke were defined as 'early seizures' and those occurring after the first week were defined as 'late seizures' (ILAE 1981). Occurrence of recurrent late seizures was defined as 'post-stroke epilepsy'.

Secondary outcome measures

(1) Proportion of participants who achieved remission for a predefined period of time (e.g. 12 or 24 months).

(2) Proportion of participants who withdrew from the allocated treatment within the scheduled follow-up period. This is a composite outcome which takes into account several factors including adverse events, compliance, and effectiveness of treatment. We were particularly interested in the occurrence of side effects for the different AEDs, which might be physical or neurobehavioural (e.g. problems with memory, attention and performance skills).

(3) Proportion of participants who had died or become dependent at the end of the scheduled follow-up period. 'Independent' individuals were defined as those who did not require regular physical assistance from another person for activities of daily living, such as mobility, dressing, transfers, and feeding. 'Dependent' individuals were those who failed to meet one or more of these criteria.

Other outcomes of interest

(1) Quality of life (e.g. using a recognised scoring system such as SF36 and EuroQol).

(2) Duration of stay for the acute phase of stroke recovery.

(3) 'Optimal' duration of treatment (i.e. length of time that the intervention should be continued).

Search methods for identification of studies

This review drew on the search strategies developed for the Cochrane Epilepsy Group and the Cochrane Stroke Group. We identified relevant trials in each Group's Specialised Register on 12 August 2013.

In addition, we searched:

(1) The Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* 2013, Issue 7, using the strategy outlined in Appendix 1.

(2) MEDLINE (Ovid, 1946 to 12 Augst 2013) using the strategy outlined in Appendix 2.

We also checked the reference lists of articles retrieved from the above searches. Where clarification of information was needed, we attempted to contact the investigators of the relevant studies.

Data collection and analysis

Selection of trials

Two review authors (JK and EW) screened all the titles, abstracts, and keywords of publications identified by the searches to assess their eligibility. The review authors were blinded to the names of the study authors, the institution where the work had been carried out, and the journal (by printing out the titles, abstracts and keywords without the author names etc). Publications that clearly did not meet the inclusion criteria were excluded at this stage. We obtained a paper copy of the full publication of every study that was relevant. Both review authors assessed their suitability for inclusion according to prespecified selection criteria, resolving any disagreement by discussion.

Assessment of methodological quality

Two review authors independently assessed the methodological quality of all the studies and recorded the findings. We noted the important aspects of methodology: study design, type of control, method of allocation concealment, completeness of follow-up, and the presence of blinding for assessments of non-fatal outcomes.

Data extraction

We independently extracted data directly from the one study which fulfilled our inclusion criteria.

Data analysis

Only one study was included, hence we performed no data analysis beyond that performed in the study itself for this review.

RESULTS

Description of studies

For the 2010 review, we screened 841 titles, abstracts, and keywords of publications identified by the searches. Of these, we obtained full-text paper copies for six completed studies (Alvarez-Sabin 2002; Daniele 2005; Gilad 2007; Pulsinelli 1999; Rowan 2005; Tietjen 1996) and one ongoing study (NCT00542802).

For the 2013 update of this review, we requested the full text of four further studies (Consoli 2012; Gilad 2011; Messé 2009; Van Tuijl 2011).

We excluded all studies except Gilad 2011 as they did not meet our review inclusion criteria. Please see Characteristics of excluded studies for details of why each study was excluded. In summary, two studies did not assess the use of antiepileptic drugs (AEDs) for the primary or secondary prevention of post-stroke seizures (Pulsinelli 1999; Tietjen 1996); five studies did not have a placebo/control group (Alvarez-Sabin 2002; Gilad 2007; Rowan 2005; SANAD 2007, Messé 2009); three studies were not randomised controlled trials (Alvarez-Sabin 2002; Daniele 2005; Messé 2009); and two studies evaluated not only stroke patients but also other causes of epileptic attacks (Rowan 2005; SANAD 2007). However, in both of these studies, there was no placebo/control group and we could not separate or extract the data for the stroke subgroup. One study failed to recruit enough participants due to problems with the execution of the trial, and we could therefore draw no conclusion about the ability of the trial drug to prevent post-stroke seizures (Van Tuijl 2011).

Consoli 2012 reports on the results of the ongoing study NCT00542802. For the purposes of this review we have added it as an excluded study; however we may report on it narratively in the next update of this review.

The only study that was included in this review was Gilad 2011. This was a prospective randomised, double-blind, placebo controlled trial studying the efficacy of valproic acid versus placebo in the primary prevention of seizure in 72 adults (over 18 years of age) with spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage. The study included patients consecutively admitted to a neurological centre. They were then randomly allocated to either the treatment or the placebo group with active treatment lasting one month; the primary outcome was seizure occurrence at one year. People with very early seizures (within 24 hours of onset of haemorrhage) were excluded from the study. Seizure was diagnosed on the basis of eye-witness evidence from staff, relatives or other eye witnesses.

The methodology of six of the studies excluded from this review deserve more detailed description because of their relevance (please see the findings of these studies in Effects of interventions):

(1) Rowan 2005 was an 18-centre, randomised, double-blind, double-dummy, parallel study of 593 participants over 60 years of age with newly diagnosed seizures ("geriatric epilepsy"). A minimum of one seizure during the three months preceding enrolment was required. Participants were randomised to gabapentin, lamotrigine or carbamazepine. There was no placebo/control group. The primary outcome measure was retention in the trial for 12 months. Secondary endpoints included seizure freedom at 12 months, time to first seizure and drug toxicity. Cerebral infarction was recorded as the most common primary aetiology of the seizures (29.9%) followed by arteriosclerosis (15%). There were no data on cerebral haemorrhage. A large majority of the study participants had evidence of underlying vascular disease with diagnoses of hypertension (391/593; 65.9%), stroke (302/593; 50.9%) and cardiac disease (286/593; 48.2%). Participants had multiple medical conditions and were on an average of seven other medications.

(2) SANAD 2007 was an unblinded randomised controlled trial in hospital-based outpatient clinics in the United Kingdom (UK). Arm A recruited 1721 participants for whom carbamazepine was deemed to be standard treatment, and they were randomly assigned to receive carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate in a 1:1:1:1:1 ratio. Participants over the age of four were recruited, and 108 participants (6.3%) had a history of stroke or cerebrovascular disease (with no data on proportions of cerebral infarct or haemorrhage). There was no placebo/control group. Primary outcomes were the time from randomisation to treatment failure (i.e. stopping the randomised drug due either to inadequate seizure control or to intolerable side-effects, or both, or the addition of other antiepileptic drugs, whichever was the earliest); and the time from randomisation to the achievement of a one-year period of remission of seizures. Quality of life and health economics were also assessed. Assessment was by both intention-to-treat and per protocol.

(3) Gilad 2007 studied the use of lamotrigine monotherapy versus carbamazepine for people with post-stroke seizure. They included 64 participants with ischaemic stroke in their study, and these were randomised in a 1:1 ratio to either lamotrigine or carbamazepine monotherapy. Only those participants with a middle cerebral artery distribution stroke on computed tomography (CT) or magnetic resonance imaging (MRI) were included. They were followed up prospectively for 12 months. Participants with status epilepticus or more than two seizures within the first 24 hours were excluded from the study (two participants). The primary endpoint of the study was a second seizure or reaching the end of the 12-month follow-up without seizures. The tolerability of the study medications was evaluated as a secondary endpoint. Limitations of the study are that there was no placebo/control group, participant numbers were small, the study was not double-blinded and participants with seizures within the first 24 hours were excluded.

(4) Daniele 2005 studied the use of levetiracetam monotherapy for treating early post-stroke seizures. They included 54 participants in their study, with 34 participants (29 with ischaemic and 5 with haemorrhagic stroke) receiving levetiracetam and 20 participants as controls. It is unclear how the participants were selected and what treatments the control group received. Participants were followed up for a period of 12 months. The participants were not randomised, the study was not blinded, and participant numbers were small.

(5) Alvarez-Sabin 2002 studied the long-term efficacy and tolerability of gabapentin in 71 prospective participants (48 with ischaemic and 23 with haemorrhagic stroke) with a first post-stroke seizure. Participants were followed up for at least a year with a mean follow-up time of 30 months. The participants were not randomised, there was no placebo/control group, and participant numbers were small.

6) Messé 2009 studied whether giving people who had sustained intracranial haemorrhage (ICH) a novel neuroprotective medica-

tion (AED) early was associated with poor outcome at day 90 - defined as a modified Rankin Score of five (severely disabled) or six (dead). Data were analysed from the placebo arm only of the Cerebral Hemorrhage and NXY-059 Trial (CHANT). CHANT was an international multicentre randomised trial that enrolled participants over the age of 18 within six hours of the onset of acute ICH. Three hundred and three participants were entered into the placebo arm of this trial: eight were excluded as they were already on AEDs. As only one arm of this trial was studied, participants in this subanalysis were not randomised and there was no control group.

Risk of bias in included studies

The Gilad 2011 included only 72 participants. This small sample size may introduce bias to the results, although this will have been minimised by the randomisation process.

Seizures were diagnosed on the basis of eye-witness evidence. There was no continuous electroencephalographic (EEG) monitoring during this study; EEG was only done if definite seizures were observed, or if the diagnosis of seizure was in doubt (unexplained confusion, depressed mental status). Therefore, some seizure activity may have gone unnoticed.

In addition, the study excluded participants who experienced seizure within 24 hours of onset of intracranial haemorrhage. The group studied may therefore have been those at lower risk of seizures than those excluded, which could potentially have given falsely optimistic results in terms of seizure prevention at one year and in the secondary outcome of improvement in National Institutes of Health Stroke Scale (NIHSS) score at one year.

Participants in the placebo group were treated with an anticonvulsant if they experienced a seizure. No comment is made in the study about whether participants in the treatment group were also given an increased dose or additional anticonvulsant if they experienced seizure. If both groups of participants experiencing seizures did receive anticonvulsants, this is a potential source of bias.

However, best medical practice is to treat seizures if they were recurrent or did not quickly self terminate. There would be ethical implications in not doing this for both groups regardless of their study status.

Based on the analysis included in the risk of bias table (below) there is a low risk of bias in this study on the basis of the information available.

Effects of interventions

Gilad 2011 found that of 84 participants initially included, five suffered immediate seizures and seven were lost to follow-up. Therefore, 72 participants completed the study, 36 in each arm. There was no statistically significant difference between the group receiving valproic acid and that receiving placebo in terms of demographics, co-morbidities or the primary outcome of seizure occurrence at one year. There was a non-statistically significant reduction in early seizures (less than 14 days after onset of haemorrhage) in the treatment group compared to placebo. There was a statistically significant benefit in the secondary outcome of NIHSS score at one year in the valproic acid group compared to the placebo group (treatment group 4.4 ∓ 4.1, placebo group 8.6 ∓ 6.1, P = 0.002).

The results of six of the excluded studies are mentioned because of their relevance to this area (please see the methodologies for these studies in Description of studies):

(1) Rowan 2005 found that of the 590 participants enrolled and not terminated due to administrative reasons, 276 (46.8%) completed one year in the trial. Tolerability of the three drugs was however different. There were more early terminators in the carbamazepine group (64.5%) than in the groups taking lamotrigine (44.3%) or gabapentin 51% (P = 0.0002). In paired-group comparisons carbamazepine had more early terminators than either gabapentin (P = 0.008) or lamotrigine (P < 0.0001). Few participants terminated the study due to uncontrolled seizures and there were no differences between the three groups. The majority of the participants in the carbamazepine group left the study due to adverse reactions. Hypersensitivity (rash of any degree) was more frequent with carbamazepine than with lamotrigine (P = 0.007). Six of the seven participants hospitalised for hypersensitivity reactions were in the carbamazepine group. Hyponatraemia was also more common in the carbamazepine group. Gabapentin participants were significantly more likely to gain weight over the first 12 months than those on carbamazepine (P = 0.002) or lamotrigine (P = 0.001). Water retention was also significantly greater with gabapentin than with carbamazepine (P = 0.004) or lamotrigine (P = 0.02).

There were no significant differences in the seizure-free rate at 3, 6 and 12 months between the three groups. Seizure-free rates were 63.2% at three months (lamotrigine 63.1%, gabapentin 62.2%, carbamazepine 64.8%; P = 0.93), 58.6% at six months (lamotrigine 56.6%, gabapentin 56.6%, carbamazepine 64.8%; P = 0.39) and 53.3% at 12 months (lamotrigine 51.4%, gabapentin 56.6%, carbamazepine 64.3%; P = 0.09). When seizures occurring during the six-week period of drug titration are excluded, 63.4% of participants were seizure-free at 12 months (lamotrigine 61.3%, gabapentin 60%, carbamazepine 71.4%; P = 0.27). There were no significant differences in time to first, second, fifth and tenth seizures between the three groups. When looking at seizure-free retention, participants on lamotrigine did better at three and six months after seizures occurring during the six-week titration period were excluded. However, the differences at 12 months were not significant (overall P value = 0.16).

(2) SANAD 2007: for time to treatment failure, lamotrigine was significantly better than carbamazepine, gabapentin and topiramate, and had a non-significant advantage compared with oxcar-

bazepine. For time to 12-month remission, carbamazepine was significantly better than gabapentin, and a non-significant advantage for carbamazepine against lamotrigine, topiramate and oxcarbazepine was observed. Longer-term per protocol analyses at two and four years demonstrated non-inferiority of lamotrigine compared with carbamazepine in the proportion of people achieving a 12-month remission. Around half of all participants reported adverse events at some point in the study. For the intention-to-treat population, lamotrigine was the drug with the least number of participants reporting adverse events (45% intention-to-treat, 37% per protocol) and topiramate the most (53% intention-to-treat, 49% per protocol). There were no significant differences in the quality of life between the five groups. The authors concluded that lamotrigine is clinically better than carbamazepine for time-to-treatment-failure outcomes and was therefore a cost-effective alternative for people diagnosed with partial onset seizures.
(3) Gilad 2007 found that more participants in the lamotrigine group were seizure-free (72%) versus those in the carbamazepine group (44%; P = 0.06). Significantly fewer participants withdrew from the study due to adverse events in the lamotrigine group (3%) compared with the carbamazepine group (31%; P = 0.02).
(4) Daniele 2005 observed the recurrence of seizures in two (5.8%) of the 34 participants treated with levetiracetam compared with three (15%) of the 20 participants in the control group.
(5) Alvarez-Sabin 2002 showed that 13 (18.3%) of the participants treated with gabapentin experienced one or more seizures during follow-up. Gabapentin treatment was discontinued in two people due to inadequate seizure control. Side effects were recorded in 27 cases (38%). The most common side effects were drowsiness (17%), dizziness (14%), headache and fatigue (7%), and nausea and vomiting (6%). Only two participants withdrew from the study due to drug side effects.
6) Messé 2009 defined poor outcome at day 90 as a modified Rankin Scale score of five or six (severely disabled or dead). Eighty-two participants (28%) had a poor outcome at day 90; early initiation of AEDs was significantly associated with poor outcome after adjustment for other known predictors of outcome after intracranial haemorrhage (age, initial haematoma volume, presence of intraventricular blood, initial Glasgow coma score, and prior warfarin use).

DISCUSSION

This review aimed to assess the effects of antiepileptic drugs (AEDs) for the primary and secondary prevention of seizures after stroke. Using our review criteria, only one of the selected studies could be included for further analysis. This study of 72 participants did not produce a statistically significant result when comparing valproic acid with placebo for the primary prevention of seizures after spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage. However, the treatment group had a lower, non-statistically significant incidence of early seizures (less than 14 days after onset of haemorrhage) compared to the placebo group. The valproic acid treatment group also demonstrated a statistically significant benefit in the secondary outcome of National Institutes of Health Stroke Scale (NIHSS) score at one year compared to the placebo group. This supports the hypothesis of a neuroprotective/neuro-remodelling effect of valproic acid. Whether these results can be translated to apply to other forms of stroke (e.g. ischaemic, subarachnoid haemorrhage) is not certain.

We did, however, find three interesting randomised controlled trials comparing a number of different AEDs. One study was performed in older adults (mean age 72 years) with a mixture of diagnoses including stroke (Rowan 2005); another study was performed in children and younger adults with a mixture of diagnoses including stroke (SANAD 2007); and the last study was performed in people with stroke only (Gilad 2007). The findings from these three studies suggest that lamotrigine may be a clinically more useful AED than carbamazepine, but this finding cannot be generalised to the post-stroke population as a whole. Results from the non-randomised Daniele 2005 also suggest that it may be worth evaluating levetiracetam in future randomised controlled trials of seizures after stroke.

The management of post-stroke seizures therefore remains controversial. One observational study reported that during a four-year follow-up period half of all people who received AEDs after a first post-stroke seizure had at least one seizure relapse (Hauser 1993). European guidelines recommend the use of AEDs to prevent recurrent seizures after stroke but prophylactic administration to people with stroke who have not experienced a seizure is not recommended (EUSI 2003). American guidelines are less precise, simply stating that: "there are no data about the utility of prophylactic administration of AEDs after stroke".

Due to the lack of trial evidence on the efficacy of AEDs in the treatment of post-stroke seizures, clinical guidelines are often based on the established management of seizures that may complicate any acute neurological illness (ASA 2003). Some other experts go further and recommend that early and late post-stroke seizures should receive long-term prophylactic treatment with AEDs (Asconape 1991; Camilo 2004). In some countries such as the United Kingdom, sodium valproate remains a very popular AED for the treatment of post-stroke seizures (Stephen 2003), although there is no conclusive evidence to support this practice (SANAD 2007).

Neurologists and stroke physicians will probably continue to struggle with the question of whether one isolated post-stroke seizure (especially an early seizure) requires immediate treatment with AEDs, and if so, which drug(s) should be initiated, at what dosage, and for how long. Many clinicians would agree that repeated unprovoked post-stroke seizures probably require treatment with AEDs, but again there is no good evidence to inform which drug(s)

should be initiated, at what dosage, and for how long.

Furthermore, there is some evidence that there may be potential risks with using AEDs in the post-stroke recovery period. For example, there are concerns that the use of phenytoin, phenobarbital, and benzodiazepines in the post-stroke period may adversely affect motor recovery (Goldstein 1990).

Summary of main results

This review aimed to assess the effects of antiepileptic drugs (AEDs) for the primary and secondary prevention of seizures after stroke. Using our review criteria, only one study could be included for further analysis. This study of 72 participants did not produce a statistically significant result when comparing valproic acid with placebo for the primary prevention of seizures after spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage. However, the treatment group had a lower, non-statistically significant incidence of early seizures (less than 14 days after onset of haemorrhage) compared to the placebo group. The valproic acid treatment group also demonstrated a statistically significant benefit in the secondary outcome of National Institutes of Health Stroke Scale (NIHSS) score at one year compared to the placebo group. This supports the hypothesis of a neuroprotective/neuroremodelling effect of valproic acid. Whether these results can be translated to apply to other forms of stroke (e.g. ischaemic, subarachnoid haemorrhage) is not certain.

We did, however, find three interesting randomised controlled trials comparing a number of different AEDs. One study was performed in older adults (mean age 72 years) with a mixture of diagnoses including stroke (Rowan 2005); another study was performed in children and younger adults with a mixture of diagnoses including stroke (SANAD 2007); and the last study was performed in people with stroke only (Gilad 2007). The findings from these three studies suggest that lamotrigine may be a clinically more useful AED than carbamazepine, but this finding cannot be generalised to the post-stroke population as a whole. Results from the non-randomised Daniele 2005 also suggest that it may be worth evaluating levetiracetam in future randomised controlled trials of seizures after stroke.

The management of post-stroke seizures therefore remains controversial. One observational study reported that during a four-year follow-up period half of all people who received AEDs after a first post-stroke seizure had at least one seizure relapse (Hauser 1993). European guidelines recommend the use of AEDs to prevent recurrent seizures after stroke but prophylactic administration to people with stroke who have not experienced a seizure is not recommended (EUSI 2003).

Overall completeness and applicability of evidence

Due to the lack of trial evidence on the efficacy of AEDs in the treatment of post-stroke seizures, clinical guidelines are often based on the established management of seizures that may complicate any acute neurological illness (ASA 2003). Some other experts go further and recommend that early and late post-stroke seizures should receive long-term prophylactic treatment with AEDs (Asconape 1991; Camilo 2004). In some countries such as the United Kingdom, sodium valproate remains a very popular AED for the treatment of post-stroke seizures (Stephen 2003), although there is no conclusive evidence to support this practice (SANAD 2007). Neurologists and stroke physicians will probably continue to struggle with the question of whether one isolated post-stroke seizure (especially an early seizure) requires immediate treatment with AEDs, and if so, which drug(s) should be initiated, at what dosage, and for how long. Many clinicians would agree that repeated unprovoked post-stroke seizures probably require treatment with AEDs, but again there is no good evidence to inform which drug(s) should be initiated, at what dosage, and for how long.

Furthermore, there is some evidence that there may be potential risks with using AEDs in the post-stroke recovery period. For example, there are concerns that the use of phenytoin, phenobarbital, and benzodiazepines in the post stroke period may adversely affect motor recovery (Goldstein 1990).

Quality of the evidence

Due to the lack of high quality clinical evidence available we are not able to answer the question 'is there evidence to support the use of antiepileptic drugs for the primary and secondary prevention of seizures after stroke?' However, the one included study which did attempt to address this question, Gilad 2011, was well designed and with a low risk of bias. Unfortunately it did not provide a statistically significant conclusion. Therefore further research into this area is needed.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is insufficient evidence to support the routine use of antiepileptic drugs (AEDs) for the primary or secondary prevention of seizures after stroke.

Implications for research

More research is needed to assess the efficacy and tolerability of antiepileptic drugs for the primary and secondary prevention of seizures after stroke. Future studies should be randomised, double-blind, double-dummy, comparing one or more AEDs with a placebo. Such studies should aim to recruit large numbers of participants and assess clinically meaningful outcome measures, e.g.

seizure-free periods and withdrawal rates from the allocated AED within the scheduled follow-up period. Other important aspects also need to be answered by future studies, including, for example, optimal timing and duration of AED treatment.

ACKNOWLEDGEMENTS

We are grateful for the input from the Cochrane Epilepsy Group and the Cochrane Stroke Group.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Gilad 2011

Methods	Study design: prospective randomised, double-blind, placebo-controlled study Purpose: to assess the occurrence of seizure and neurological outcome in sICH patients who were treated with valproic acid or a placebo for 1 month and follow-up of 1 year Methods: CT brain scan at baseline, seizures diagnosed on the basis of eye-witness evidence from staff or relatives/other eye witnesses. NIHSS at baseline and at 1 year
Participants	Inclusion criteria: consecutive patients with spontaneous non-aneurysmal, non-traumatic intracerebral haemorrhage admitted to a neurological centre. They were then randomly allocated to either the treatment or placebo group Exclusion criteria: patients with early (less than 24 hours after onset) seizures or those lost to follow-up (due to other illness or withdrawal of consent for inclusion)
Interventions	Oral valproic acid 400mg twice daily or placebo at a corresponding dosage for an active therapy period of one month
Outcomes	Primary outcome: seizure occurrence at 1 year of follow-up. Secondary outcome: NIHSS score at 1 year of follow-up.
Notes	No information provided regarding funding or conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list was used, such that each consecutive patient recruited was assigned to treatment according to the list
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No information provided.

Gilad 2011 (*Continued*)

Other bias	Low risk	The study appears to be free of other sources of bias.

CT: computed tomography
NIHSS: National Institutes of Health Stroke Scale
sICH: symptomatic intracranial haemorrhage

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

Study	Reason for exclusion
Alvarez-Sabin 2002	Not a randomised controlled trial; no placebo arm.
Consoli 2012	No placebo arm.
Daniele 2005	Not a randomised controlled trial; "control group" but no mention of placebo arm
Gilad 2007	No placebo arm.
Messé 2009	Not a randomised controlled trial; analysis of data from placebo arm only of a randomised controlled trial of an unproven neuroprotective medication
Pulsinelli 1999	Investigated the efficacy of fosphenytoin in the treatment of acute ischaemic stroke but not to prevent or treat post-stroke seizures
Rowan 2005	Investigated the efficacy of AEDs in "geriatric epilepsy" - data for people with stroke could not be extracted and analysed separately; no placebo arm
SANAD 2007	Investigated the efficacy of AEDs in focal epilepsy - data for people with stroke could not be extracted and analysed separately; no placebo arm
Tietjen 1996	Investigates the safety of phenytoin in the treatment of acute ischaemic stroke but not to prevent or treat post-stroke seizures
Van Tuijl 2011	Not enough participants recruited therefore no relevant conclusion could be drawn

AED: antiepileptic drug

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

NCT00542802

Trial name or title	Levetiracetam versus carbamazepine in post-stroke late onset crisis (EpIc)
Methods	Official title: Multicenter, comparative, randomized, open trial to evaluate efficacy and safety of levetiracetam versus carbamazepine in post stroke late onset crisis Study design: treatment, randomised, open label, active control, parallel assignment, interventional study Methods: EEG at baseline and 1-year follow-up; cognitive function and quality of life evaluation at 1-year follow-up; and compare seizure frequency at 1-year follow-up
Participants	Inclusion criteria: people having a stroke (ischaemic and haemorrhagic) showing (1) subsequent seizure 14 days up to 3 years after stroke. Exclusion criteria: severe stroke patients with Rankin scale > 3; life expectancy of < 12 months; screened more than 15 days after first seizure; with a diagnosed epilepsy; with clear evidence of myoclonic seizures; with contraindication to levetiracetam
Interventions	Levetiracetam versus carbamazepine
Outcomes	Primary outcome: number of participants free from post-stroke recurrent crisis (seizures) Secondary outcome: to compare retention time of levetiracetam vs carbamazepine since first intake throughout treatment period; to compare time to second seizure in both treatments; to evaluate differences in cognitive function and in quality of life in levetiracetam and carbamazepine participants having post-stroke seizures at the end of treatment period; evaluate EEG changes obtained at the end of treatment period compared with baseline; to compare seizure frequency in levetiracetam and carbamazepine groups throughout treatment period; to evaluate the safety of levetiracetam versus carbamazepine throughout the treatment period
Starting date	2007
Contact information	Contact person: Sara Papetti. Email: spapetti@gbpharmaservices.it
Notes	Principle investigator: Domenico Consoli. Email: domco@tiscali.it

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 (epilep*)
#2 MeSH descriptor Epilepsy explode all trees
#3 (seizure*)
#4 MeSH descriptor Seizures explode all trees
#5 convulsion*
#6 anticonvulsant*
#7 MeSH descriptor Anticonvulsants explode all trees
#8 antiepilep*
#9 phenytoin
#10 valpro*
#11 carbamazepine
#12 ethosuximide
#13 phenobarbit*
#14 MeSH descriptor Phenobarbital explode all trees
#15 primidone
#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 MeSH descriptor Cerebrovascular Disorders explode all trees
#18 MeSH descriptor Basal Ganglia Cerebrovascular Disease explode all trees
#19 MeSH descriptor Brain Ischemia explode all trees
#20 MeSH descriptor Carotid Artery Diseases explode all trees
#21 MeSH descriptor Brain Infarction explode all trees
#22 MeSH descriptor Hypoxia-Ischemia, Brain explode all trees
#23 MeSH descriptor Intracranial Arterial Diseases explode all trees
#24 MeSH descriptor Intracranial Arteriovenous Malformations explode all trees
#25 MeSH descriptor Intracranial Embolism explode all trees
#26 MeSH descriptor Intracranial Hemorrhages explode all trees
#27 MeSH descriptor Vasospasm, Intracranial explode all trees
#28 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29 (stroke* or poststroke* or cva)
#30 (cerebrovascular*) or (cerebral vascular)
#31 cerebral or cerebellar or brainstem or vertebrobasilar
#32 (infarct* or ischemi* or ischaemi* or thrombo* or apoplexy or emboli*)
#33 (#31 AND #32)
#34 cerebral or intracerebral or intracranial or parenchymal
#35 brain or intraventricular or brainstem or cerebellar
#36 infratentorial or supratentorial
#37 (#34 OR #35 OR #36)
#38 haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm
#39 (#37 AND #38)
#40 (#39 OR #28 OR #29 OR #30 OR #33)
#41 (#40 AND #16)

Appendix 2. MEDLINE search strategy

We received guidance from the Cochrane Stroke Group for the stroke section of this strategy. The filter to identify randomized controlled trials was taken from Lefebvre 2008.

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 7 or 5 or 2 or 6 or 1 or 4 or 3
9. (animals not (humans and animals)).sh.
10. 8 not 9
11. epilep$.tw.
12. exp Epilepsy/
13. seizure$.tw.
14. exp Seizures/
15. convulsion$.tw.
16. anticonvulsant$.tw.
17. exp Anticonvulsants/
18. antiepilep$.tw.
19. phenytoin.tw.
20. valpro$.tw.
21. carbamazepine.tw.
22. ethosuximide.tw.
23. phenobarbit$.tw.
24. exp Phenobarbital/
25. primidone.tw.
26. or/11-25
27. Cerebrovascular Disorders/
28. exp Basal Ganglia Cerebrovascular Disease/
29. exp Brain Ischemia/
30. exp Carotid Artery Diseases/
31. exp Brain Infarction/
32. exp Hypoxia-Ischemia, Brain/
33. exp Intracranial Arterial Diseases/
34. Intracranial Arteriovenous Malformations/
35. exp Intracranial Embolism/
36. exp Intracranial Hemorrhages/
37. Vasospasm, Intracranial/
38. 34 or 32 or 31 or 27 or 35 or 37 or 33 or 29 or 36 or 28 or 30
39. (stroke$ or poststroke or cva).tw.
40. (cerebrovascular$ or cerebral vascular).tw.
41. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.
42. (infarct$ or isch?emi$ or thrombo$ or apoplexy or emboli$).tw.
43. 41 and 42
44. (cerebral or intracerebral or intracranial or parenchymal).tw.
45. (brain or intraventricular or brainstem or cerebellar).tw.
46. (infratentorial or supratentorial).tw.
47. 45 or 44 or 46
48. (haemorrhage or hemorrhage or haematoma or hematoma or bleeding or aneurysm).tw.
49. 48 and 47

50. 49 or 38 or 39 or 43 or 40
51. 10 and 26 and 50

WHAT'S NEW

Last assessed as up-to-date: 12 August 2013.

Date	Event	Description
12 August 2013	New search has been performed	Searches updated 12 August 2013.
12 August 2013	New citation required but conclusions have not changed	One new study has been added (Gilad 2011). Conclusions remain unchanged.

CONTRIBUTIONS OF AUTHORS

Professor Joseph Kwan and Dr Emma Wood performed the original bibliographic searches, identified the studies, and assessed the methodological quality of the studies. Both review authors contributed to the writing of the manuscript with Professor Joseph Kwan being the main contributing author. This 2013 review update has been performed by Dr Lucy Sykes with Professor Joseph Kwan.

DECLARATIONS OF INTEREST

None known.

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Internal sources

- No sources of support supplied

External sources

- Cochrane Incentive Scheme, UK.

Cochrane Incentive Scheme leading to an award of £5000 upon completion of this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made a slight amendment to the search terms that were set out in the protocol, as 'Cerebrovascular Accident' is no longer used as an index term in MEDLINE. Please see Appendices for details.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Primary Prevention [methods]; Randomized Controlled Trials as Topic; Secondary Prevention; Seizures [etiology; *prevention & control]; Stroke [*complications]

MeSH check words

Aged; Humans