Antiepileptic drugs as prophylaxis for post-craniotomy seizures (Review)

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# Table of Contents

- Header .................................................................................................................. 1
- Abstract ................................................................................................................. 1
- Plain Language Summary ....................................................................................... 2
- Summary of Findings for the Main Comparison ...................................................... 3
- Background .............................................................................................................. 5
- Objectives ............................................................................................................... 5
- Methods ................................................................................................................. 5
- Results ..................................................................................................................... 7
  - Figure 1 ................................................................................................................. 8
  - Figure 2 ................................................................................................................. 10
- Discussion .............................................................................................................. 11
- Authors’ Conclusions ............................................................................................ 12
- Acknowledgements ............................................................................................... 13
- References ............................................................................................................. 13
- Characteristics of Studies ..................................................................................... 14
- Data and Analyses ................................................................................................ 25
- Additional Tables .................................................................................................. 25
- Appendices ............................................................................................................ 28
- What’s New .......................................................................................................... 29
- Contributions of Authors ..................................................................................... 30
- Declarations of Interest ....................................................................................... 30
- Sources of Support ............................................................................................... 30
- Differences Between Protocol and Review ......................................................... 30
- Index Terms .......................................................................................................... 30
Antiepileptic drugs as prophylaxis for post-craniotomy seizures

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Abstract

Background

The incidence of seizures following supratentorial craniotomy for non-traumatic pathology has been estimated to be between 15% to 20%; however, the risk of experiencing a seizure may vary from 3% to 92% over a five-year period. Postoperative seizures can precipitate the development of epilepsy; seizures are most likely to occur within the first month of cranial surgery. The use of antiepileptic drugs (AEDs) administered pre- or postoperatively to prevent seizures following cranial surgery has been investigated in a number of randomised controlled trials (RCTs).

Objectives

To determine the efficacy and safety of AEDs when used prophylactically in people undergoing craniotomy and to examine which AEDs are most effective.

Search methods

Searches were run for the original review in January 2012. We performed subsequent searches in September 2012 and up to 04 August 2014. We searched the Cochrane Epilepsy Group’s Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE. We did not apply any language restrictions.

Selection criteria

We included RCTs of people with no history of epilepsy who were undergoing craniotomy for either therapeutic or diagnostic reasons. Trials with adequate randomisation methods and concealment were included; these could either be blinded or unblinded parallel trials. We did not stipulate a minimum treatment period, and we included trials using active drugs or placebo as a control group.

Data collection and analysis

Two review authors (JP and JG) independently selected trials for inclusion and performed data extraction and risk of bias assessments. We resolved any disagreements through discussion. Outcomes investigated included the number of patients experiencing seizures (early - occurring within first week following craniotomy, and late - occurring after first week following craniotomy), the number of deaths and the number of people experiencing disability and adverse effects. Due to the heterogeneous nature of the trials, we did not combine data from the included trials in a meta-analysis; we presented the findings of the review in narrative format.
Main results

We included eight RCTs (N = 1602), which were published between 1983 and 2013. Three trials compared a single AED (phenytoin) with a placebo or no treatment. One three-arm trial compared two AEDs (carbamazepine, phenytoin) with no treatment. A second three-arm trial compared phenytoin, phenobarbital and no treatment. Three other trials were head-to-head trials of AEDs (phenytoin vs. valproate; zonisamide vs. phenobarbital) and levetiracetam vs. phenytoin. Of the five trials comparing AEDs with controls, only one trial reported a significant difference between AED treatment and controls for early seizure occurrence. All other comparisons were non-significant. Of the head-to-head trials, none reported statistically significant differences between treatments for either early or late seizures. One head-to-head trial showed an increase in the number of deaths following one AED treatment compared to another AED treatment. Incidences of adverse effects of treatment were poorly reported, and the most trials reported no significant differences between treatment groups. However data on adverse events were limited.

Authors’ conclusions

There is little evidence to suggest that AED treatment administered prophylactically is effective or not effective in preventing post-craniotomy seizures. The current evidence base is limited due to the differing methodologies employed in the trials and inconsistencies in reporting of outcomes. Further evidence from good-quality, contemporary trials is required in order to assess the effectiveness of prophylactic AED treatment compared to control groups or other AEDs in preventing post-craniotomy seizures properly.

Plain Language Summary

The use of antiepileptic drugs to prevent seizures following brain surgery

Antiepileptic drugs (AEDs) have been used in trials to prevent seizures occurring after surgery in people with no previous history of epilepsy. A small number of trials have compared different AED treatments against each other, while others have compared AEDs to a placebo or no treatment group.

This Cochrane Review examines the differences between the AED treatments in relation to number of patients experiencing seizures, number of patient deaths and number of adverse effects experienced following craniotomy surgery (a type of brain surgery most commonly used to remove brain tumours).

We carried out a search of databases up to 04 August 2014. Eight trials met our inclusion criteria, and included 1602 people with partial epilepsy.

We did not find any evidence to suggest that preventative AED treatments are effective in reducing the number of seizures which occurred post-surgery, deaths or adverse effects.

Taking all the studies together, we judged the quality of the study methods to be unclear due to the lack of details present in the reports. Further good quality studies are needed to validate the findings mentioned above.
**SUMMARY OF FINDINGS FOR THE MAIN COMPARISON**

Antiepileptic drugs as prophylaxis for post-craniotomy seizures

**Patient or population:** patients with post-craniotomy seizures  
**Settings:** hospital setting  
**Intervention:** antiepileptic drugs

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (trials)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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### Adverse effects

| (number of events) | See comment | See comment | Not estimable | 926 (6 trials) | ⌂ ⌂ ⌂ low¹ | Most trials found low numbers of adverse effects, and no significant differences across comparisons were reported. Two trials found significant differences between comparisons².

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¹The basis for the **assumed risk** (e.g. the median control group risk across trials) is provided in footnotes. 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).

²**GRADE Working Group grades of evidence**

- **High quality**: Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality**: We are very uncertain about the estimate.

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¹Methodological biases identified in trials (no allocation concealment, one study unblinded, unclear methods of dealing with missing data).

²All trials differed in comparisons made.

³**Beenen 1999** found number of seizures was significantly lower in the phenytoin group compared to valproate group.

⁴**Foy 1992** found large differences in the number of deaths between treatment groups. Statistical significance level unreported.

⁵**Fuller 2013** reported significantly higher adverse events in the phenytoin group (rash/itch, lethargy/tiredness/asthenia) and **Wu 2013** reported significantly higher overall adverse events in the phenytoin group compared to no treatment.
BACKGROUND

Description of the condition
The incidence of epilepsy following supratentorial craniotomy for non-traumatic pathology has been estimated to be 15% to 20% (Foy 1981); however, due to the nature of the underlying disease for which surgery is undertaken, the risk of post-craniotomy seizures may vary from 3% to 92% over a five-year period. It is likely that such seizures may cause epilepsy in previously unaffected people. The probability of de novo seizures occurring in people who have no history of epilepsy decreases over time. The highest incidence of postoperative epilepsy (two-thirds of the seizures) occurs within the first month after craniotomy (North 1983), and 75% of those who do develop epilepsy will do so within one year of surgery. Few people (approximately 8%) have their first seizure more than two years after surgery. The risk of seizures for particular groups of people is higher; for example for those with an arteriovenous malformation who have had a spontaneous intracerebral haematoma, the overall risk does not fall below 10% between year two and five after surgery, while people who suffered from an abscess continue to run a risk of developing epilepsy (92%) after five years (Shaw 1991).

Description of the intervention
Due to the risk of postoperative seizures, the prophylactic use of antiepileptic drugs (AEDs) has been advocated for patients undergoing cranial surgery. However, it is also argued that AEDs should not be used prophylactically, but should only be administered following at least one seizure (Temkin 2002). Other investigators maintain that early postoperative seizures do not justify the diagnosis of epilepsy and only late seizures are considered to be true epilepsy (Manaka 2003).

How the intervention might work
Uncontrolled retrospective trials support the use of AED treatment in patients with a predisposition towards developing postoperative seizures (Matthew 1980) and data from pathological trials suggest that certain AEDs could have a neuro-protective action on damaged cerebral cortex (Calabresi 2003).

Why it is important to do this review
To inform decision-making regarding the prophylactic use of AEDs for people undergoing craniotomy, reliable high-quality evidence is required. Benefits and harms and any trade-offs between these need to be examined carefully. Potential benefits include reduced short-term seizure recurrence, reduced long-term epilepsy rates, and better surgical outcome and quality of life. Harms include adverse effects and poorer surgical outcome. This Cochrane Review will provide a summary of the currently available evidence from randomised controlled trials (RCTs) regarding the prophylactic use of AEDs for people undergoing craniotomy by examining the following outcomes: occurrence of early and late seizures, occurrence of death, functional disability and occurrence of adverse events.

OBJECTIVES
To determine the efficacy and safety of AEDs when used prophylactically in people undergoing craniotomy and to examine which AEDs are most effective.

METHODS

Criteria for considering studies for this review

Types of studies
1. RCTs.
2. Double, single or unblinded trials.
3. Placebo (PCB)-controlled, active drug control group or no treatment control group.

Types of participants
People of any age and either gender undergoing a supratentorial or infratentorial craniotomy for either therapeutic or diagnostic reasons for all pathologies, who have had no history of seizures or prior exposure to AEDs. We excluded people with traumatic brain injuries from this review.

Types of interventions
1. The active treatment group receive treatment with any AED administered prior to or immediately post craniotomy.
2. The control group receive matched PCB, different AED or no treatment.

Types of outcome measures

Primary outcomes
1. Early seizures
The proportion of people experiencing seizures occurring within the first week following craniotomy.
2. Late seizures
The proportion of people experiencing seizures after the first week from craniotomy including follow-up period of one, two and five years postoperatively from craniotomy.

Secondary outcomes

1. Death
The proportions of deaths occurring within the treatment period or during follow-up.

2. Functional outcome
The proportion of people experiencing disability (partially or fully dependent on others in normal activities of daily living).

3. Adverse effects
The proportion of people who experience any of the following adverse events:
   - Skin irritation;
   - Dizziness;
   - Fatigue;
   - Nausea;
   - Headache.

In addition, we decided to look at the proportion of people experiencing the five most common adverse effects mentioned in the included trials if these differed from the list above.

Search methods for identification of studies

Electronic searches
Searches were run for the original review in January 2012. Subsequent searches were run in September 2012 and August 2014. For the latest update we searched:
   1. the Cochrane Epilepsy Group Specialized Register (04 August 2014) using the search strategy outlined in Appendix 1.
   2. the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), 04 August 2014, using the search strategy outlined in Appendix 2.
   3. MEDLINE (Ovid, 1946 to 04 August 2014) using the search strategy outlined in Appendix 3.
We did not impose any language restrictions.

Searching other resources
We reviewed the reference lists of retrieved trials to check for additional reports of relevant studies.

Data collection and analysis

Selection of studies
Two review authors (JP and JG) independently assessed articles for inclusion. We resolved any disagreements through discussion, and failing this, we sought the opinion of a third review author (AM). The same review authors independently carried out data extraction and assessed risk of bias. Again, any disagreements were resolved through discussion. Failing this, we sought the opinion of the third review author (AM).

Data extraction and management
We extracted the following information for each trial using a data extraction sheet:

Methodology/trial design
1. Method of randomisation and concealment.
3. Number of people excluded from analyses.
4. Duration of baseline, treatment and follow-up periods.
5. Type of AED and dose tested.
6. Time of treatment commencement.

Participant demographics
1. Total number of people randomised to each group.
2. Age/gender.
3. Pathological group.
4. Type of surgery.
5. Site of lesion.
6. Number of people with previous acute symptomatic seizures.

Results
1. Sample size.
2. Summary data for each intervention.
For all trials we attempted to confirm the above information with trial authors/researchers and sponsors.

Assessment of risk of bias in included studies
Two review authors (JP and JG) independently assessed the risk of bias for each trial using the Cochrane 'Risk of bias' table, as described in Higgins 2002. Any disagreements were discussed and resolved. We rated the included trials as adequate, inadequate or unclear on six domains applicable to RCTs: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias. Also, we created a 'Summary of findings' table.
Measures of treatment effect
We have presented treatment effects as they were given in the original reports.

Assessment of heterogeneity
We assessed clinical heterogeneity by examining the differences in trial characteristics in order to inform decisions regarding the combination of trial data.

Assessment of reporting biases
Reporting biases, such as publication bias, were examined by identifying certain aspects of each trial (e.g. sponsors of the research, research teams involved).

Data synthesis
We synthesised data narratively as we considered meta-analysis inappropriate given the differences across trials in AED treatment, trial intervention characteristics and control groups (see Table 1). Data under each comparison listed below were minimal and we could not combine these data across all outcomes. We have discussed the following comparisons in the narrative:
1. Treatment group vs. control group on early seizures.
2. Treatment group vs. control group on late seizures.
3. Treatment group vs. control group on number of deaths.
4. Treatment group vs. control group on functional outcome.
5. Treatment group vs. control group on adverse effects (for each adverse effect see Types of outcome measures).
We stratified each comparison by type of drug and control group (i.e. PCB, other AED or no treatment).

RESULTS

Description of studies

Results of the search
Our searches identified 101 records from the databases outlined in the Electronic searches section. We identified 10 additional records through the reference lists of the included trials. Sixty-nine records remained after we removed duplicates, and we screened all for inclusion in the review. We excluded 43 records at this point, leaving 26 full-text articles to be assessed for eligibility. Following this, we excluded 15 texts (see Figure 1 and Characteristics of excluded studies for reasons of exclusion). We included eight trials from ten reports in a narrative synthesis and one record is awaiting classification (see Characteristics of studies awaiting classification).
Figure 1. Study flow diagram.

101 records identified through database searching

10 additional records identified through other sources

69 records after duplicates removed

69 records screened

43 records excluded

15 full-text articles excluded:
- not RCTs (N = 7)
- review article (N = 2)
- participants met exclusion criteria (N = 6)

1 study in Studies awaiting classification section (unavailable)

26 full-text articles assessed for eligibility

8 studies included in narrative synthesis (from 10 reports)

0 studies included in quantitative synthesis (meta-analysis)
**Included studies**

We identified eight parallel RCTs (Beenen 1999; Foy 1992; Franceschetti 1990; Fuller 2013; Lee 1989; Nakamura 1999; North 1983; Wu 2013) examining the effectiveness of AEDs on post-craniotomy seizures. The treatment periods varied across trials from three days to 24 months; in one trial the treatment period was unclear (Franceschetti 1990). People were excluded from five of the trials if they were taking AEDs already and if they had a history of epilepsy (Beenen 1999; Foy 1992; Lee 1989; Nakamura 1999; North 1983). One trial (Franceschetti 1990) included both people who had preoperative seizures (Group A) and those who did not (Group B); Group A and Group B were analysed separately compared to controls. We only extracted data pertaining to Group B to be included within this Cochrane Review as Group A did not meet our inclusion criteria.

**Beenen 1999** was a single-centre trial with a treatment period of 12 months. People aged between 18 and 80 years who were undergoing supratentorial craniotomy were eligible to be randomised. The trial authors randomised 100 patients: 50 people to phenytoin 100 mg (PHT) and 50 people to valproate 500 mg (VAL) treatment. Both treatments were administered intravenously immediately post operation in a recovery room. Outcomes reported included early and late seizures, death and adverse effects. No data were reported for functional outcome.

**Foy 1992** was a single-centre, head-to-head (active drug comparison) trial with a treatment phase of either six or 24 months, and follow-up occurred for a minimum of three years to a maximum of eight years. People aged over 16 years undergoing supratentorial craniotomy were eligible to be randomised. The trial authors randomised 276 patients: 50 to carbamazepine (CBZ) for a six-month treatment period, 56 to CBZ for a 24-month treatment period, 55 to PHT for a six-month treatment period, 56 to PHT for a 24-month treatment period and 59 to no treatment. Administration of CBZ (200 mg) was every six hours for the 24 hours immediately pre-operation and every eight hours thereafter; PHT (15 mg/kg) was administered 24 hours pre-operation and increased to 100 mg every eight hourly thereafter. Outcomes reported included number of patients with seizures and death. No differentiation was made between early and late seizures, and no data were reported for functional outcome or adverse effects. All data were reported at six months into the treatment.

**Franceschetti 1990** was a single-centre, head-to-head, three-arm trial that included a ‘no treatment’ group. People undergoing surgery for supratentorial neoplasms were randomised and patients with a history of seizures formed Group A and patients who had no history of seizures formed Group B. Sixty-three Group B patients were randomised: 25 to phenobarbital (PB), 16 to PHT and 22 to no treatment. The PB (4 mg/kg) was intravenously administered daily for five days and then decreased to 2 mg/kg daily via oral administration. PHT (10 mg/kg) was intravenously administered daily for five days and then decreased to 5 mg/kg daily via oral administration. Outcomes reported included early and late seizures, and minimal data on adverse effects were presented.

**Fuller 2013** was a single-centre, head-to-head, two-arm trial with a treatment period of 30 days. Eighty-one people undergoing craniotomy were randomised: 39 to zonisamide (ZNS) and 42 to PHT. LEV (250 to 1000 mg) was administered twice daily either intravenously or orally and PHT (1000 mg) daily in the same form. Outcomes measured included discontinuation of treatment due to side effects and clinically undesirable event and seizure occurrence.

**Lee 1989** was a PCB-controlled trial with a treatment period of three days. People receiving intracranial, supratentorial surgery were eligible to take part in the trial. Four hundred patients were selected for participation and randomised, and 26 early deaths occurred leaving 189 people randomised to PHT and 185 people to PCB. PHT (15 mg/kg) was administered 15 to 20 minutes prior to wound closure followed by intravenous PHT (5 to 6 mg/kg) three times daily for the first three postoperative days. Outcomes measured included number of seizures occurring within the three days of the trial. Data for late seizures, death, functional outcome and adverse effects were not recorded.

**Nakamura 1999** was a multi-centre, head-to-head trial with a treatment phase of one year and a follow-up of two years without medication. People undergoing craniotomy for cerebral tumours, cerebrovascular disease and head trauma were selected for eligibility. Two hundred and seventy-eight patients were randomised: 141 to zonisamide (ZNS, 100 mg twice daily) and 137 to PB (40 mg twice daily). Both drugs were administered orally, at least one week before surgery and then increased (ZNS to 100 mg three or four times daily and PB to 40 mg three or four times daily) for one year followed by a tapering period of six months (three months at 100 mg (ZNS) or 40 mg (PB) twice daily then three months at 100 mg (ZNS) or 40 mg (PB) once daily). Outcomes reported were seizure frequency, death (during follow-up period only) and adverse effects. No data were collected on functional outcome.

**North 1983** was a single-centre, PCB-controlled trial with a treatment period of 12 months. People undergoing supratentorial operation (either burr hole, craniectomy or osteoplastic flap procedures) were eligible for inclusion for the trial. The trial authors randomised 281 patients: 140 to PHT and 141 to PCB. PHT (250 mg twice daily) was administered in a recovery room intravenously, and then continued with oral medication (100 mg three times daily) for one year. Outcomes reported were early and late seizures, death and adverse effects. No data were collected on functional outcomes.

**Wu 2013** was a single-centre, no treatment controlled trial with a...
treatment period of seven days. People with supratentorial tumours were eligible for inclusion in the trial. The trial authors randomised 123 people to either PHT (n = 62) or a no treatment control group (n = 61). PHT (100 mg) every eight hours was administered to the treatment group. Outcomes reported were seizure occurrence and adverse reactions.

Excluded studies
Overall we excluded 15 full-text articles for the following reasons: seven were not RCTs (Baker 1995; Boarini 1985; De Santis 1996; Grobelny 2009; Hayashi 1999; Murri 1992; Notani 1984), two were review articles (Manaka 2003; Shaw 1991), and six studies had participants that did not meet our inclusion criteria (De Santis 2002; Levati 1996; Lim 2009; Temkin 1990; Temkin 1999; Tisolaki 1987).

We categorised one study (Zhang 2000) in the Studies awaiting classification section as it was unavailable.

Risk of bias in included studies

Allocation
For sequence generation, we rated two studies at low risk of bias (Beenen 1999; Foy 1992), six studies at unclear risk of bias (Franceschetti 1990; Fuller 2013; Lee 1989; Nakamura 1999; North 1983; Wu 2013) and no studies were rated at high risk of bias.

For allocation concealment, we rated one study at low risk of bias (Beenen 1999) and seven studies (Foy 1992; Franceschetti 1990; Fuller 2013; Lee 1989; Nakamura 1999; North 1983; Wu 2013) at unclear risk of bias due to the lack of detail of these methods.

Blinding
Four studies were rated at low risk of bias due to the methods of blinding employed (Beenen 1999; Lee 1989; Nakamura 1999; North 1983). We rated two studies at unclear risk of bias (Franceschetti 1990; Fuller 2013) and two studies at high risk of bias as only the outcome assessor appeared to be blinded in one trial and the other was unblinded (Foy 1992; Wu 2013).

Incomplete outcome data
We rated three studies at low risk of bias due to no missing data (Beenen 1999; North 1983; Wu 2013). Five studies were rated at unclear risk of bias due to lack of detail regarding the analysis (Foy 1992; Franceschetti 1990; Fuller 2013; Lee 1989; Nakamura 1999). We did not rate any studies at high risk of bias.

Selective reporting
We rated all of the included studies at unclear risk of bias due to the lack of protocols available for comparison (Beenen 1999; Foy 1992; Franceschetti 1990; Fuller 2013; Lee 1989; Nakamura 1999; North 1983; Wu 2013). All protocols were requested from the study authors if contact details were available, however we did not receive any responses.

Other potential sources of bias
Six studies were rated at low risk of bias as we did not identify any other bias (Beenen 1999; Franceschetti 1990; Fuller 2013; Lee 1989; Nakamura 1999; North 1983). We rated two studies at unclear risk of bias (Foy 1992; Wu 2013). See Characteristics of included studies tables and Figure 2 for risk of bias judgements.

Figure 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included trials.
Effects of interventions

See: Summary of findings for the main comparison

Antiepileptic drugs as prophylaxis for post-craniotomy seizures

Due to the variety of head-to-head drug comparisons within the included trials, we have presented the effects of the interventions by outcome measure as opposed to comparisons under trial. See Table 2 and Table 3 for individual trial results and Table 1 for a comparison of treatment protocols.

Seizures

Beenen 1999 examined seizure outcome between PHT and VAL and reported 4/50 early seizures occurring in the PHT group compared to 2/50 early seizures in the VAL group. Three late seizures occurred in the PHT group compared to five late seizures in the VAL group. Foy 1992 examined three treatment groups: CBZ, PHT and no treatment. They reported 41/106 seizures (early and late) occurring in the CBZ group, 37/111 occurring in the PHT group and 25/59 occurring in the ‘no treatment’ group at six months. Franceschetti 1990 also looked at three groups: PB, PHT and no treatment. They reported 3/41 early seizures occurring in the PB and PHT groups and 4/22 early seizures in the ‘no treatment’ group. Only 39 patients were followed up and they reported 3/25 late seizures in the PB and PHT group and 3/14 late seizures in the ‘no treatment’ group. Fuller 2013 looked at LEV in comparison to PHT. They reported 0/39 early seizures in the LEV group and 6/42 in the PHT group. No late seizure data were reported. Two trials (Lee 1989; North 1983) examined differences between PHT and a PCB-controlled group. Lee 1989 treated patients for three days with no further follow-up, and therefore only reported early seizures within the three days. They found 2/189 seizures occurred in the PHT group compared to 9/185 in the PCB group. North 1983 reported 4/140 early seizures in the PHT group compared to 14/141 in the PCB group. For late seizures, 14/140 occurred in the PHT group compared to 12/141 in the control group. Nakamura 1999 conducted a head-to-head trial of ZNS versus PB. They reported 6/129 early seizures occurring within the ZNS group compared to 3/126 early seizures occurring within the PB group. For late seizures, 7/129 occurred in the ZNS group and 8/126 occurred in the PB group. Overall, only one trial had a significant difference between AED treatment and controls for early seizure occurrence (North 1983). All other comparisons were non-significant. Wu 2013 examined PHT compared to a no treatment group and found 2/62 people experienced early seizures compared to 5/61 in the no treatment group. Thirteen out of 62 people experienced late seizures compared to 6/61 people in the control group.

Deaths

Across all included trials, 13/50 deaths were reported in the PHT group compared to 10/50 in the VAL group (Beenen 1999), 9/50 occurred in the CBZ (six month) group and 10/56 in the CBZ (24 month) group compared to 15/55 in the PHT (six month) group and 27/56 in the CBZ (24 month) group and 13/59 in the no treatment group (Foy 1992), 3/39 occurred in the LEV group compared to 5/42 in the PHT group (Fuller 2013), 8/112 occurred in the ZNS group compared to 13/107 in the PB group (Nakamura 1999), and 20/140 occurred in the PHT group compared to 24/141 in the PCB group (North 1983). Three trials did not collect any data for this outcome (Franceschetti 1990; Lee 1989; Wu 2013).

Adverse effects

Four trials reported information on adverse effects. In the Beenen 1999 trial, 4/50 people experienced a skin reaction, 3/50 people experienced liver dysfunction, 1/50 people experienced thrombopenia and there was one case of nausea within the PHT group (N = 50). In the VAL group there were three cases of liver dysfunction, and one case of a rise in liver enzymes (N = 50). Nakamura 1999 reported two cases of somnolence and six cases of nausea in the ZNS group (N = 129), and seven cases of somnolence and two cases of nausea in the PB group (N = 126). Overall they reported 28/129 adverse effects in the ZNS group and 30/126 in the PB group. The North 1983 trial reported eight cases of rash, one case of involuntary movements, one hirsutism, one headache and one case of discomfort of the face in the PHT group (N = 140) compared to one case of rash, one dizziness and one nausea in the PCB group (N = 141). Franceschetti 1990 reported minimal data on the adverse effects, only that 3/10 people in the PHT group and 1/10 people in the PB group experienced neurological side effects. No data from the remaining trials were provided (Foy 1992; Lee 1989). In the Fuller 2013 trial, a total of 22 people taking LEV experienced adverse events, eight experienced lethargy/tiredness or asthma, four people experienced rash, one person had delirium, one had headache, one had pruritus and seven experienced mood/irritability problems. In the PHT group a total of 18/42 people experienced adverse events, ataxia (n = 1), nausea (n = 1), rash/itch (n = 5), drug intoxication (n = 2), anaphylaxis (n = 2), thrombophlebitis (n = 3), mood/irritability problems (n = 3) and lethargy/tiredness/asthenia (n = 1).

Discussion

See: Summary of findings for the main comparison

Antiepileptic drugs as prophylaxis for post-craniotomy seizures

Due to the variety of head-to-head drug comparisons within the included trials, we have presented the effects of the interventions by outcome measure as opposed to comparisons under trial. See Table 2 and Table 3 for individual trial results and Table 1 for a comparison of treatment protocols.

Seizures

Beenen 1999 examined seizure outcome between PHT and VAL and reported 4/50 early seizures occurring in the PHT group compared to 2/50 early seizures in the VAL group. Three late seizures occurred in the PHT group compared to five late seizures in the VAL group. Foy 1992 examined three treatment groups: CBZ, PHT and no treatment. They reported 41/106 seizures (early and late) occurring in the CBZ group, 37/111 occurring in the PHT group and 25/59 occurring in the ‘no treatment’ group at six months. Franceschetti 1990 also looked at three groups: PB, PHT and no treatment. They reported 3/41 early seizures occurring in the PB and PHT groups and 4/22 early seizures in the ‘no treatment’ group. Only 39 patients were followed up and they reported 3/25 late seizures in the PB and PHT group and 3/14 late seizures in the ‘no treatment’ group. Fuller 2013 looked at LEV in comparison to PHT. They reported 0/39 early seizures in the LEV group and 6/42 in the PHT group. No late seizure data were reported. Two trials (Lee 1989; North 1983) examined differences between PHT and a PCB-controlled group. Lee 1989 treated patients for three days with no further follow-up, and therefore only reported early seizures within the three days. They found 2/189 seizures occurred in the PHT group compared to 9/185 in the PCB group. North 1983 reported 4/140 early seizures in the PHT group compared to 14/141 in the PCB group. For late seizures, 14/140 occurred in the PHT group compared to 12/141 in the control group. Nakamura 1999 conducted a head-to-head trial of ZNS versus PB. They reported 6/129 early seizures occurring within the ZNS group compared to 3/126 early seizures occurring within the PB group. For late seizures, 7/129 occurred in the ZNS group and 8/126 occurred in the PB group. Overall, only one trial had a significant difference between AED treatment and controls for early seizure occurrence (North 1983). All other comparisons were non-significant. Wu 2013 examined PHT compared to a no treatment group and found 2/62 people experienced early seizures compared to 5/61 in the no treatment group. Thirteen out of 62 people experienced late seizures compared to 6/61 people in the control group.

Deaths

Across all included trials, 13/50 deaths were reported in the PHT group compared to 10/50 in the VAL group (Beenen 1999), 9/50 occurred in the CBZ (six month) group and 10/56 in the CBZ (24 month) group compared to 15/55 in the PHT (six month) group and 27/56 in the CBZ (24 month) group and 13/59 in the no treatment group (Foy 1992), 3/39 occurred in the LEV group compared to 5/42 in the PHT group (Fuller 2013), 8/112 occurred in the ZNS group compared to 13/107 in the PB group (Nakamura 1999), and 20/140 occurred in the PHT group compared to 24/141 in the PCB group (North 1983). Three trials did not collect any data for this outcome (Franceschetti 1990; Lee 1989; Wu 2013).

Adverse effects

Four trials reported information on adverse effects. In the Beenen 1999 trial, 4/50 people experienced a skin reaction, 3/50 people experienced liver dysfunction, 1/50 people experienced thrombopenia and there was one case of nausea within the PHT group (N = 50). In the VAL group there were three cases of liver dysfunction, and one case of a rise in liver enzymes (N = 50). Nakamura 1999 reported two cases of somnolence and six cases of nausea in the ZNS group (N = 129), and seven cases of somnolence and two cases of nausea in the PB group (N = 126). Overall they reported 28/129 adverse effects in the ZNS group and 30/126 in the PB group. The North 1983 trial reported eight cases of rash, one case of involuntary movements, one hirsutism, one headache and one case of discomfort of the face in the PHT group (N = 140) compared to one case of rash, one dizziness and one nausea in the PCB group (N = 141). Franceschetti 1990 reported minimal data on the adverse effects, only that 3/10 people in the PHT group and 1/10 people in the PB group experienced neurological side effects. No data from the remaining trials were provided (Foy 1992; Lee 1989). In the Fuller 2013 trial, a total of 22 people taking LEV experienced adverse events, eight experienced lethargy/tiredness or asthma, four people experienced rash, one person had delirium, one had headache, one had pruritus and seven experienced mood/irritability problems. In the PHT group a total of 18/42 people experienced adverse events, ataxia (n = 1), nausea (n = 1), rash/itch (n = 5), drug intoxication (n = 2), anaphylaxis (n = 2), thrombophlebitis (n = 3), mood/irritability problems (n = 3) and lethargy/tiredness/asthenia (n = 1).
Summary of main results

The trials included in this Cochrane Review were all RCTs investigating the effects of a range of AEDs given either immediately before or after a craniotomy procedure to people with no previous history of seizures or exposure to AEDs. The underlying pathologies for craniotomy surgery were mixed within the studies (e.g., tumour, abscess, meningioma), with a small percentage of patients having surgery as a result of head injuries. One study included a substantial proportion (210/374) of head-injury patients (Lee 1989). This is a major limitation of this review as the objective is to examine outcomes for patients undergoing craniotomy presenting with non-trauma pathology. We acknowledge the possibility of differences in the risk of seizure post surgery depending on the underlying pathology of the patient.

For the outcome of incidence of seizures, overall most trials reported no significant difference between treatment with AEDs and no treatment or treatment with AEDs and no treatment. Head-to-head drug comparisons also yielded non-statistically significant results. Only two trials reported any statistically significant findings. In Fuller 2013, significantly more people experienced early seizures in the LEV group compared to the PHT group (P = 0.01). In North 1983, the incidence of early seizures was reduced in the AED group (PHT) compared to PCB (P < 0.05). Overall, the majority of results from the individual trials showed few significant differences between AED treatment participants and control participants for outcomes relevant to the number of death and adverse effects. However, two trials did show significant differences for adverse event outcomes (Fuller 2013; Wu 2013). None of the included trials examined the functional outcome of patients.

Overall completeness and applicability of evidence

We were unable to meta-analyse any of the data and structuring a narrative summary was difficult for a number of reasons: Few trials were available under each comparison examined (see Data synthesis for list of comparisons under investigation) and the interventions varied substantially with regards to duration of treatment period, dose and method of drug administration, country, methodological rigour and underlying pathologies. Trials differed regarding their reporting of outcomes, not all trials differentiated between early and late seizures and information about adverse effects of treatment was very limited. Most trials had similar inclusion and exclusion criteria. Patients undergoing supratentorial craniotomy were randomised in six of the eight included trials, but Fuller 2013 and Nakamura 1999 did not specify the type of surgery.

Quality of the evidence

The outcome of the risk of bias assessments conducted for each trial are noteworthy. We rated most trials as unclear on several of the criteria. Only two of the eight trials were rated at low in bias due to the method used to generate the randomisation sequence (Beenen 1999; Foy 1992) and only one trial used adequate methods for concealing the allocation of intervention (Beenen 1999). Most trials used adequate methods for blinding participants and outcome assessors; however, one trial was unblinded (Foy 1992) and therefore we rated it at high risk of bias for this criteria. There were no protocols available for any of the trials, therefore assessing selective reporting across trials was rated as unclear. We rated several trials as unclear as to how missing data were managed within their analyses. In most cases trials reported attrition and described the reasons for withdrawal.

Potential biases in the review process

We did not identify any biases in the review process.

Agreements and disagreements with other studies or reviews

A systematic review published in 1996 (Kuijlen 1996) assessed the effectiveness of prophylactic AED use in people undergoing supratentorial craniotomies. The review included three studies (Foy 1992; Lee 1989; North 1983) that were considered to be of satisfactory methodological quality. Odds ratios were calculated as a means of assessing the degree of association between treatment and the incidences of convulsions. The results of pooling the data from these three trials demonstrated no statistically significant difference between prophylaxis with AEDs and no treatment. The authors noted that there were only a small number of studies available in this area.

Authors’ Conclusions

Implications for practice

Our results from this review show that there is not enough evidence of sufficient quality available to suggest that AED treatment can or cannot be recommended to reduce post-craniotomy seizures. There is no evidence on which to base clinical practice.

Implications for research

More trials are needed to evaluate the effectiveness of prophylactic treatment with AEDs in preventing seizures following cranial surgery better. These trials must address the methodological weaknesses and protocol inconsistencies we identified within this review including:
1. Timing of AED administration (pre- or post-surgery).
2. Adequate length of treatment and follow-up period.
3. Head-to-head or other control group.
4. Methodological aspects (well controlled trials with adequate methods employed for generating randomisation sequences and concealing allocation).
5. Outcome reporting (differentiating between early and late seizures, adverse effects of treatment, handling of missing data) or other important outcomes (functional outcomes in terms of activities of daily living including working, driving etc.) not currently addressed.

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Programme Grant funding to the Epilepsy Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Beenen 1999 [published data only]

Foy 1992 [published data only]

Franceschetti 1990 [published data only]

Fuller 2013 [published data only]

Lee 1989 [published data only]

Nakamura 1999 [published data only]

References to studies excluded from this review

North 1983 [published data only]

Wu 2013 [published data only]

Baker 1995 [published data only]

Boarini 1985 [published data only]

De Santis 1996 [published data only]

De Santis 2002 [published data only]

Grobelny 2009 [published data only]
Grobelny BT, Ducruet AF, Zacharia BE, Hickman ZL, Andersen KN, Sussman E, et al. Preoperative antiepileptic drug administration and the incidence of postoperative...

Hayashi 1999 [published data only]

Levati 1996 [published data only]

Lim 2009 [published data only]

Manaka 2003 [published data only]

Murri 1992 [published data only]

Notani 1984 [published data only]

Shaw 1991 [published data only]

Temkin 1990 [published data only]

Temkin 1999 [published data only]

Tsolaki 1987 [published data only]

References to studies awaiting assessment

Zhang 2000 [published data only]

Additional references

Calabresi 2003

Foy 1981

Higgins 2002

Kuijlen 1996

Lefebvre 2011

Matthew 1980

Temkin 2002

References to other published versions of this review

Pulman 2013

* Indicates the major publication for the study.
### CHARACTERISTICS OF STUDIES

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

**Beenen 1999**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised double-blind, PCB-controlled, single-centre (Netherlands), parallel trial. 2 treatment arms: phenytoin (PHT) and valproate (VAL). Allocation concealed using sealed envelopes, trial medication identical in pre-coded packaged materials. Treatment period: 12 months</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Adults aged 21 to 78 (mean age in PHT arm = 55 years, mean age in VAL arm = 51 years). Overall 47 males and 53 females, all patients undergoing craniotomy for different pathological conditions. Patients were not taking AEDs prior to randomisation and had no history of seizures. 100 randomised: 50 to PHT and 50 to VAL</td>
</tr>
</tbody>
</table>
| **Interventions** | Group 1: PHT 100 mg intravenous 3 times daily administered immediately post-operation in recovery room  
Group 2: VAL 500 mg intravenous 3 times daily administered immediately post-operation in recovery room  
Patients took medication in oral form as soon as was possible for 12 months |
| **Outcomes** | Primary outcome: drug efficacy (number of seizures).  
Secondary outcomes: tolerability (number of withdrawals, adverse effects), quality of life and cognitive functioning |
| **Notes** | Intention-to-treat (ITT) analysis employed for primary outcome, not for other outcomes (quality of life) |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Study used computer-generated randomisation method.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Sealed envelopes, pre-coded and packaged medication.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Adequate blinding techniques used for personnel and participants</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>Study attrition reported, employed ITT analysis for primary outcome</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No trial protocol available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected.</td>
</tr>
</tbody>
</table>
## Methods
Randomised, controlled, parallel, single-centre (UK) trial. 5 treatment arms: carbamazepine (CBZ) 6 months and 24 months, phenytoin (PHT) 6 months and 24 months, no treatment. Patients randomised in blocks of 5 from prepared lists. Treatment period: 6 or 24 months.

## Participants
Patients aged 16 to 77 years (median 45 years), 134 males and 142 females all undergoing supratentorial craniotomy. Patients had no previous history of seizures. 276 randomised: 50 to CBZ (6 months), 56 to CBZ (24 months), 55 to PHT (6 months), 56 to PHT (24 months), 59 to no treatment.

## Interventions
- **Group 1**: CBZ 200 mg/6 h for 24 h pre-surgery, 200 mg/8 h thereafter for 6 months
- **Group 2**: CBZ 200 mg/6 h for 24 h pre-surgery, 200 mg/8 h thereafter for 24 months
- **Group 3**: PHT 15 mg/kg 24 h pre-surgery, 100 mg/8 h thereafter for 6 months
- **Group 4**: PHT 15 mg/kg 24 h pre-surgery, 100 mg/8 h thereafter for 24 months
- **Group 5**: no treatment.

## Outcomes
- **Primary outcome**: drug efficacy (number of seizures).
- **Secondary outcomes**: seizure freedom, death.

## Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Used blocks of 5 from prepared lists.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Trial was unblinded.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Study attrition reported; however, missing data and ITT analysis is unclear within the text</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No trial protocol available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>The first 102 patients were randomised to treatment with CBZ or PHT for 6 or 24 months. Since analysis showed little difference in the incidence of postoperative seizures in this group relative to a retrospective study of postoperative seizures, the subsequent 176 patients were randomised equally between policies of no treatment, treatment with CBZ and treatment with...</td>
</tr>
</tbody>
</table>
### Franceschetti 1990

<table>
<thead>
<tr>
<th>Methods</th>
<th>Group B participants randomised to 1 of 3 treatment arms: phenobarbital (PB), phenytoin (PHT), no treatment. No details available in text of randomisation or blinding methods employed. Treatment period: unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>128 patients entered trial, 65 had pre-operative seizures and were treated with AEDs (Group A), 63 patients had no seizures prior to operation and were not taking any AEDs (Group B). 3 treatment arms for Group B randomised patients: PB, PHT and no treatment. Mean age 55 years, 34 males and 29 females undergoing supratentorial craniotomy for neoplasms</td>
</tr>
</tbody>
</table>
| Interventions | Group 1: PB (4 mg/kg daily for 5 days), followed by 2 mg/kg daily  
Group 2: PHT (10 mg/kg daily for 5 days), followed by 5 mg/kg daily  
| Outcomes | Primary outcomes: efficacy (number of seizures (early and late seizures), adverse effects |
| Notes | |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
</tr>
</tbody>
</table>
| Blinding of participants and personnel (performance bias)  
All outcomes | Unclear risk | No details in text. |
| Incomplete outcome data (attrition bias)  
All outcomes | Unclear risk | Attrition unreported, 24 patients with missing data for late seizure outcome |
| Selective reporting (reporting bias) | Unclear risk | No trial protocol available. |
| Other bias | Low risk | No other bias detected. |
Methods
Pragmatic, prospective, randomised, single-centre (Australia) study. 2 treatment arms: levetiracetam (LEV) or phenytoin (PHT). Block randomisation. Treatment period: 90 days

Participants
Patients aged 25 to 89 years with neurosurgical indications requiring craniotomy for which perioperative intravenous seizure prophylaxis was routine or otherwise warranted. Participants must have been on no AED or stable dose AED(s) excluding study AEDs for 3 weeks before enrolment, and must not have contraindication to either study medication. 81 randomised: 39 to LEV, 42 to PHT

Interventions
Group 1: LEV 250 to 500 mg bd IV or PO. Group 2: PHT 300 mg (up to three doses in 24 hours) or 1000 mg (single dose) IV loading then 300 mg daily IV or PO
Up to two oral doses of allocated AEDs were allowed between randomisation and intravenous administration. One preoperative intravenous dose was required. Additional PHT titration to therapeutic serum levels was allowed but not mandated. Doses were within standard range. After randomisation, treating teams made all decisions regarding study AED treatment including intravenous and oral durations, serologic monitoring, dose adjustment and cessation

Outcomes
Primary outcomes were discontinuation of study AED because of side effects. Seizure occurrence was a secondary outcome. Outcomes were reported at 3 days and 90 days

Notes
Not ITT analysis. The pragmatic nature of the trial is highlighted. The reviewers also note the length of active treatment in the trial. Four people in the trial had prior seizures

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Methods of sequence generation not described. Block randomisation was reported as used. However, the paper reports that early during data collection the contractor communicated that allocation was as follows: each 10 sequentially recruited patients were not internally randomised but received the same drug, determined by hat-draw at enrolment of the first patient in each block, with eight blocks of 10 patients then two blocks of four to be randomised with equal probability. At study completion, impact of allocation procedure on bias was assessed by statistical comparison of baseline patient characteristics, with similar age and gender distribution and proportion of serious pathologies and death from underlying pathology found between treat-</td>
</tr>
</tbody>
</table>
### Fuller 2013  
*(Continued)*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>The allocation procedure was communicated to quarantined keeper for randomisation data. However, it is unclear what the procedure was. Also, see above note as to failure of block randomisation.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>The investigation team conducting the information and consenting process, data collection, outcome adjudication and analysis was blinded. The quarantined keeper and liaison for randomisation data did not participate in recruitment, patient treatment, data collection, outcome assessment or analysis. Recruiting neurosurgical teams including anaesthetists were blinded to the allocation procedure. Otherwise the study was open-label.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>ITT analysis not used. 81 people randomised, 74 were included in the analyses at 3 days and 61 at 90 days.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No trial protocol available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>UCB Pharma provided funding and levitiracetam.</td>
</tr>
</tbody>
</table>

### Lee 1989

**Methods**
Randomised, double-blind, PCB-controlled trial. 2 treatment arms: phenytoin (PHT) and PCB. Patients randomised using random digits, all patients received identical medication. Treatment period: 3 days. No follow-up of patients.

**Participants**
Adults, mean age 39.9 years (PHT) and 37.5 years (PLC) all undergoing intracranial, supratentorial surgery. Patients have no history of seizures and not taking AEDs prior to surgery. 400 patients randomised: 189 to PHT and 185 to PLC. 26 died prior to treatment.

**Interventions**
Group 1: PHT 15 mg/kg for 15 to 20 minutes prior to wound closure followed by 5 to 6 mg/kg/day 3 times daily in first 3 post-operative days. Group 2: saline solution administered as described above.

**Outcomes**
Primary outcome: efficacy (number of seizures).

**Notes**
26 patients randomised died prior to treatment, excluded from all data exploration and analysis.
Lee 1989  (Continued)

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Used random digits, unclear how generated, whether open list, etc</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>Identical medication used for both groups. Adequate blinding methods for key personnel and participants</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Unclear details on study attrition rate and how data analysed</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol available.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected.</td>
</tr>
</tbody>
</table>

Nakamura 1999

Methods

Randomised, double-blind, controlled, multi-centre (Japan) trial. 2 treatment arms: zonisamide (ZNS), phenobarbital (PB). Identical medication administered (no details of methods of randomisation). Treatment period: 1 year. Follow-up period: 3 years

Participants

278 patients who were scheduled to receive craniotomy for cerebral tumours, cerebrovascular diseases and head trauma, were randomised. 129 in ZNS group analysed, 126 in PB group analysed

Interventions

Group 1: ZNS (100 mg twice daily) until 1 month after craniotomy
Group 2: PB (40 mg twice daily) until 1 month after craniotomy
In both groups dose was adjusted to therapeutic serum concentration and continued up to 1 year

Outcomes

Primary outcome: frequency of epilepsy.
Secondary outcome: drug concentration, adverse effects.

Notes

23 unsuitable cases not included in the analysis. 36 cases not followed up for full 3 years of the study

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
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</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
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</table>
### Nakamura 1999 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
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<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>Identical medication administered to both groups. Drug name blinded from participating institutions, only blood concentration values provided</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>23 cases not included within analysis, all excluded prior to treatment. 36 lost to follow-up were included in analysis</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Trial reports data for overall adverse effects, only reports data for 2 individual adverse effects</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected.</td>
</tr>
</tbody>
</table>

### North 1983

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised, double-blinded, PCB-controlled, parallel, single-centre (Australia) trial. 2 treatment arms: phenytoin (PHT) and PCB. Patients received identical medication (no details available of randomisation methods). Treatment period: 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adults, mean age 46.7 years (PHT) and 50.21 years (PCB), all undergoing supratentorial craniotomy. Patients had no previous exposure to AEDs and no previous history of epilepsy. 281 patients were randomised: 140 to PHT and 141 to PCB</td>
</tr>
</tbody>
</table>
| Interventions | Group 1: PHT 250 mg twice daily administered intravenously first dose administered in the recovery room post craniotomy followed by oral medication 100 mg 3 times daily for 12 months  
Group 2: PCB medication administered as described above. |
| Outcomes | Primary outcome: efficacy (number of seizures).  
Secondary outcomes: survival time (number of days since randomisation to incidence of seizure or to 365 days in seizure-free patients), adverse effects |
| Notes | 63 patients in PHT arm and 59 patients in PCB received intended treatment. All cases randomised were analysed |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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<td>Unclear risk</td>
<td>No details in text.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No details in text.</td>
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### North 1983  
*(Continued)*

<table>
<thead>
<tr>
<th>Bias</th>
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<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Identical medication used for both groups. Only pharmacologist aware of serum drug</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>levels and both PHT and PCB group participants had blood samples taken</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>Attrition reported and ITT analysis employed. Six patients lost to follow-up</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td>Protocol outlined within paper. All outcomes reported.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No other bias detected</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>No other bias detected</td>
</tr>
</tbody>
</table>

### Wu 2013

<table>
<thead>
<tr>
<th>Methods</th>
<th>Prospective RCT. Single centre (USA) study. 2 study arms: Phenytoin (PHT) vs. no treatment. Treatment period: 7 days at full dose followed by tapering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Patients aged 16 to 84, mean age 56 years (PHT) 61 years (no treatment) with intraparenchymal supratentorial brain tumours either proven by biopsy to be a brain metastasis or a glioma, or with compelling CT or MRI evidence of metastasis or glioma. All patients had to be previously untreated with AEDs. 123 randomised: 62 to PHT and 61 to no treatment</td>
</tr>
</tbody>
</table>
| Interventions                             | Group 1: PHT 100 mg every 8 hrs administered IV or oral  
|                                          | Group 2: No treatment                                                                                                         |
| Outcomes                                  | Primary outcomes: the occurrence of a seizure. Secondary outcomes: the occurrence of adverse reactions to phenytoin |
| Notes                                     | Measurements taken every 2 to 3 months up to 12 months. Timepoints reported in study were 7 days and 30 days. Trial was stopped early due to few events |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method not reported.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Only outcome assessment was blinded.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>No missing data.</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Selective reporting (reporting bias) | Unclear risk | Study protocol not available.
--- | --- | ---
Other bias | Unclear risk | Trial stopped early due to futility.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker 1995</td>
<td>Not a RCT; retrospective trial.</td>
</tr>
<tr>
<td>Boarini 1985</td>
<td>Not a RCT; retrospective study.</td>
</tr>
<tr>
<td>De Santis 1996</td>
<td>Not a RCT.</td>
</tr>
<tr>
<td>De Santis 2002</td>
<td>Patients taking AEDs prior to randomisation.</td>
</tr>
<tr>
<td>Grobelny 2009</td>
<td>Not a RCT; retrospective design.</td>
</tr>
<tr>
<td>Hayashi 1999</td>
<td>Not a RCT.</td>
</tr>
<tr>
<td>Levati 1996</td>
<td>Patients taking AEDs prior to randomisation.</td>
</tr>
<tr>
<td>Lim 2009</td>
<td>Patients taking AEDs and experiencing seizures prior to randomisation</td>
</tr>
<tr>
<td>Manaka 2003</td>
<td>Review paper.</td>
</tr>
<tr>
<td>Murri 1992</td>
<td>Not a RCT.</td>
</tr>
<tr>
<td>Notani 1984</td>
<td>Not a RCT.</td>
</tr>
<tr>
<td>Shaw 1991</td>
<td>Review paper.</td>
</tr>
<tr>
<td>Temkin 1990</td>
<td>No craniotomy surgery performed. Brain injury patients.</td>
</tr>
<tr>
<td>Temkin 1999</td>
<td>No craniotomy surgery performed. Brain injury patients.</td>
</tr>
<tr>
<td>Tsolaki 1987</td>
<td>Patients taking AEDs prior to study.</td>
</tr>
</tbody>
</table>
## Characteristics of studies awaiting assessment  

**Zhang 2000**

<table>
<thead>
<tr>
<th></th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>No information available.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>No information available.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>No information available.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>No information available.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>No information available.</td>
</tr>
</tbody>
</table>
**DATA AND ANALYSES**

This review has no analyses.

**ADDITIONAL TABLES**

Table 1. Comparison of treatment protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and daily dose (N)</th>
<th>Comparator (s) and daily dose (N)</th>
<th>Time of administration (reoperation/ post-operation)</th>
<th>Treatment duration</th>
<th>Measurement period reported - early</th>
<th>Measurement period reported - late</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beenen 1999</td>
<td>PHT 300 mg (N = 50)</td>
<td>VAL 1500 mg/day (N = 50)</td>
<td>Post-op</td>
<td>12 months</td>
<td>1 week</td>
<td>2 weeks to 12 months</td>
<td>ITT</td>
</tr>
<tr>
<td>Foy 1992</td>
<td>PHT 300 mg 6 months group (N = 55) 24 months group (N = 56)</td>
<td>CBZ 600 mg 6 months group (N = 50) 24 months group (N = 56)</td>
<td>Pre-op* and post-op (pre- and post-op doses differed)</td>
<td>6 months 24 months</td>
<td>Not reported</td>
<td>4 years (median)</td>
<td>ITT</td>
</tr>
<tr>
<td>Franceschetti 1990</td>
<td>PHT 5 mg/kg (N = 16)</td>
<td>PB 2 mg/kg (N = 25)</td>
<td>No treatment (N = 22)</td>
<td>Pre-op and post-op (pre- and post-op doses differed)</td>
<td>Unclear</td>
<td>1 week</td>
<td>Unclear</td>
</tr>
<tr>
<td>Fuller 2013</td>
<td>LEV 250 to 500 mg bd (N = 39)</td>
<td>PHT 300 mg (N = 42)</td>
<td>Pre-op and post-op</td>
<td>90 days</td>
<td>3 days</td>
<td>90 days</td>
<td>Not ITT Only patients receiving one dose were analysed</td>
</tr>
<tr>
<td>Lee 1989</td>
<td>PHT 5 to 6 mg/kg (N = 189)</td>
<td>PCB (N = 185)</td>
<td>Pre-op* and post-op (pre- and post-op doses differed)</td>
<td>3 days</td>
<td>3 days</td>
<td>Not reported</td>
<td>ITT unclear. Randomised = 400 but 26 deaths prior to treatment</td>
</tr>
<tr>
<td>Nakamura 1999</td>
<td>ZNS 200 mg (N = 129)</td>
<td>PB 80 mg (N = 126)</td>
<td>Pre-op and post-op (doses changed across course)</td>
<td>12 months</td>
<td>Not reported</td>
<td>1 to 12 months</td>
<td>ITT for 255 patients who received treatment 23</td>
</tr>
</tbody>
</table>
Table 1. Comparison of treatment protocols (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>AED group</th>
<th>AED control</th>
<th>No treatment control</th>
<th>Early seizures</th>
<th>Late seizures</th>
<th>randomised patients were excluded prior to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>North 1983</td>
<td>PHT 300 mg (N = 140)</td>
<td>PCB (N = 141)</td>
<td>Post-op</td>
<td>12 months</td>
<td>1 week</td>
<td>12 months</td>
</tr>
<tr>
<td>Wu 2013</td>
<td>PHT 300 mg (N = 62)</td>
<td>No treatment (N = 61)</td>
<td>Pre-op and post-op</td>
<td>7 days</td>
<td>7 days</td>
<td>&gt;30 days</td>
</tr>
</tbody>
</table>

PCB: placebo; CBZ: carbamazepine; ITT: intention-to-treat; PB: phenobarbital; PHT: phenytoin; VAL: valproate; ZNS: zonisamide.

Table 2. Study results for seizure data

<table>
<thead>
<tr>
<th>Trial</th>
<th>All seizures</th>
<th>Early seizures</th>
<th>Late seizures</th>
<th>randomised patients were excluded prior to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AED group</td>
<td>AED control</td>
<td>No treatment control</td>
<td>AED control</td>
</tr>
<tr>
<td>Beenen 1999 1(PHT vs. VAL)</td>
<td>7/50</td>
<td>7/50</td>
<td>-</td>
<td>4/50</td>
</tr>
<tr>
<td>Foy 1992 1(CBZ vs. PHT)</td>
<td>21/50 (6 mo)</td>
<td>21/55 (6 mo)</td>
<td>25/59</td>
<td>-</td>
</tr>
<tr>
<td>Franceschetti 1990 2(PB vs. PHT vs. no treatment)</td>
<td>-</td>
<td>-</td>
<td>7/22</td>
<td>3/41</td>
</tr>
<tr>
<td>Fuller 2013(LEV vs. PHT)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/39</td>
</tr>
<tr>
<td>Lee 1989 1(PHT vs. PCB)</td>
<td>2/189</td>
<td>9/185</td>
<td>-</td>
<td>2/189</td>
</tr>
<tr>
<td>Nakamura 1999 2(ZNS vs. PHT)</td>
<td>13/129</td>
<td>11/126</td>
<td>-</td>
<td>6/129</td>
</tr>
</tbody>
</table>

Antiepileptic drugs as prophylaxis for post-craniotomy seizures (Review)  
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Table 2. Study results for seizure data  (Continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Deaths</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AED group</td>
<td>Control group/other AED</td>
</tr>
<tr>
<td>North 1983</td>
<td>18/140</td>
<td>26/141</td>
</tr>
<tr>
<td>1(PHT vs. PCB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PHT vs. no treatment)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PB: phenobarbital; PHT: phenytoin; VAL: valproate; ZNS: zonisamide.

1 Results from these trials reported the number of patients who had seizures out of the number of patients randomised. However loss to follow-up during the trial was unclear.

2 Results from the trials only reported the number of patients who had seizures out of the number of patients who were followed up. Foy et al followed up 39 patients for late seizures. Franceschetti reported combination of PB and PHT results, cannot differentiate between groups on seizure outcome for all seizures and early seizures.

Table 3. Results for deaths and adverse events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Deaths</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AED group</td>
<td>Control group/other AED</td>
</tr>
<tr>
<td>Beenen 1999</td>
<td>13/50</td>
<td>10/50</td>
</tr>
<tr>
<td>1(PHT vs. VAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foy 1992</td>
<td>9/50 (6 mo)</td>
<td>10/56 (24 mo)</td>
</tr>
<tr>
<td>1(CBZ vs. PHT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Franceschetti</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PB vs. PHT vs. no treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuller 2013</td>
<td>3/39</td>
<td>5/42</td>
</tr>
<tr>
<td>1(LEV vs. PHT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee 1989</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1(PHT vs. PCB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakamura 1999</td>
<td>8/112</td>
<td>13/107</td>
</tr>
<tr>
<td>2(ZNS vs. PB)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Results for deaths and adverse events (Continued)

<table>
<thead>
<tr>
<th></th>
<th>1983 (PHT vs. PCB)</th>
<th>2013 (PHT vs. no treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>20/140</td>
<td>11/62</td>
</tr>
<tr>
<td>Wu</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

AED: antiepileptic drug; PCB: placebo; CBZ: carbamazepine; mo: month; PB: phenobarbital; PHT: phenytoin; VAL: valproate; ZNS: zonisamide.

1 Results from these trials reported the number of patients who died or experienced adverse events out of the number of patients randomised. However, loss to follow-up during the trial was unclear.

2 Results from the trials only reported the number of patients who died or experienced adverse events out of the number of patients who were followed up.

A P P E N D I C E S

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Craniotomy EXPLODE ALL WITH AE CL CT EC ED ES HI IS LJ MT MO NU PX RH ST SN TD UT VE
#2 craniotom* OR postcraniotom*
#3 supratentorial NEXT surgery
#4 infratentorial NEXT surgery
#5 postoperative NEXT epilep*
#6 post-operative NEXT epilep*
#7 postoperative NEXT seizure*
#8 post-operative NEXT seizure*
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 INREGISTER AND >2010:YR
#11 #9 AND #10

Appendix 2. CENTRAL search strategy

The following was used in the latest update to search CENTRAL via the Cochrane Register of Studies Online (CRSO).

#1 MESH DESCRIPTOR Craniotomy EXPLODE ALL TREES
#2 craniotom* OR postcraniotom*
#3 supratentorial NEXT surgery
#4 infratentorial NEXT surgery
#5 #1 OR #2 OR #3 OR #4
#6 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
#7 seizure*
#8 #6 OR #7
#9 #5 AND #8
#10 postoperative NEXT epilep*
#11 post-operative NEXT epilep*
#12 postoperative NEXT seizure*
#13 post-operative NEXT seizure*
#14 #9 OR #10 OR #11 OR #12 OR #13
#15 * NOT INMEDLINE AND 17/10/2012 TO 21/07/2014:DL
#16 #14 AND #15
The following was used previously to search CENTRAL via the Cochrane Library.
#1 MeSH descriptor Craniotomy explode all trees
#2 (craniotom*)
#3 (postcraniotom*)
#4 (supratentorial NEXT surgery)
#5 (infratentorial NEXT surgery)
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Seizures explode all trees
#8 (seizure*)
#9 (#7 OR #8)
#10 (#6 AND #9)
#11 (postoperative NEXT epilep*)
#12 (post-operative NEXT epilep*)
#13 (postoperative NEXT seizure*)
#14 (post-operative NEXT seizure*)
#15 (#10 OR #11 OR #12 OR #13 OR #14)

Appendix 3. MEDLINE search strategy
This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011).
1. exp Craniotomy/
2. (craniotom$ or postcraniotom$ or supratentorial surgery or infratentorial surgery).tw.
3. 1 or 2
4. exp Seizures/
5. seizure*.tw.
6. 4 or 5
7. 3 and 6
8. (postoperative epilep$ or postoperative seizure$).tw.
9. 7 or 8
10. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.
11. clinical trials as topic.sh.
12. trial.ti.
13. 10 or 11 or 12
14. exp animals/ not humans.sh.
15. 13 not 14
16. 9 and 15
17. limit 16 to ed=20120901-20140804
WHAT'S NEW

Last assessed as up-to-date: 4 August 2014.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 August 2014</td>
<td>New citation required but conclusions have not changed</td>
<td>Two new trials have been included (Fuller 2013; Wu 2013); conclusions remain unchanged.</td>
</tr>
<tr>
<td>4 August 2014</td>
<td>New search has been performed</td>
<td>The searches were updated on 04 August 2014.</td>
</tr>
</tbody>
</table>

CONTRIBUTIONS OF AUTHORS

Jennifer Weston and Janette Greenhalgh carried out and completed the original review and review update. Anthony Marson supervised the review. Nikola Vojvodic, Aleksandar Ristic and Dragoslav Sokic developed the protocol for this review.

DECLARATIONS OF INTEREST

We have no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This review was funded as part of a research programme 'Clinical and cost effectiveness of interventions for epilepsy in the National Health Service (NHS) (10/4001/18)' which receives financial support from the National Institute of Health Research (NIHR). This review presents independent research commissioned by the NIHR. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We were unable to make all the intended comparisons specified in the protocol due to lack of data.
INDEX TERMS

Medical Subject Headings (MeSH)
Anticonvulsants [*therapeutic use]; Carbamazepine [therapeutic use]; Craniotomy [*adverse effects]; Isoxazoles [therapeutic use]; Phenobarbital [therapeutic use]; Phenytin [therapeutic use]; Randomized Controlled Trials as Topic; Seizures [etiology; *prevention & control]; Valproic Acid [therapeutic use]

MeSH check words
Humans