
Chang B S, Lowenstein D H

CRD summary
This review assessed the effectiveness of antiepileptic drugs (AEDs) for preventing seizures following severe traumatic brain injury. The authors concluded that prophylaxis with phenytoin reduces risk of early seizures but AED prophylaxis is not effective for late seizures. The authors pooled studies without providing enough information to judge whether this was appropriate. Hence the conclusions should be viewed with caution.

Authors' objectives
To determine the effectiveness of prophylactic antiepileptic drug (AED) use for the prevention of seizures following severe traumatic brain injury (TBI).

Searching
MEDLINE, the Science Citation Index, the Cochrane Controlled Trials Register and Current Contents were searched for studies published in peer-reviewed journals prior to November 2001; the search terms were provided. Reference lists were also checked for additional publications. No language restrictions were imposed. Studies published as abstracts or providing preliminary data only were excluded.

Study selection
Study designs of evaluations included in the review
Randomised and non-randomised controlled trials were eligible for inclusion.

Specific interventions included in the review
Studies evaluating any AED were eligible for inclusion. The AEDs evaluated in the included studies were phenytoin (diphenylhydantoin), carbamazepine, valproate and phenobarbital.

Participants included in the review
Studies of patients with severe TBI, as defined by the individual trialist, were eligible for inclusion. The characteristics of the participants in each of the included studies were not provided.

Outcomes assessed in the review
Studies assessing post-traumatic seizure rates were eligible for inclusion. These were divided into early (occurring within 7 days of TBI) or late (occurring after 7 days of TBI) seizures.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors developed a classification scheme to assess the validity of the included studies, based on their potential risk of bias. Studies graded class I were considered to have a low risk of bias, whereas class IV studies were considered to have a high risk of bias. The criteria used considered study design, blinding of the outcome assessment, use of representative population, clearly defined outcomes and inclusion or exclusion criteria, adequate account of withdrawals, and comparability of the groups at baseline. Further details were provided in the paper. The authors indicate that the grade assigned to each included study was agreed upon by two reviewers.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the occurrence of early and late post-traumatic seizures were extracted from the individual studies and used to calculate a relative risk (RR) and 95% confidence interval (CI), using intention-to-treat where possible. Fisher’s exact test was used to compare the treatment and control groups. Data were also extracted on adverse events, as reported in each included study.

Methods of synthesis
How were the studies combined?
The results from the individual studies were pooled using the inverse variance method of meta-analysis. A pooled RR with 95% CIs was calculated separately for studies that assessed early and late post-traumatic seizures. In studies that assessed early seizures, only those graded class I were pooled; in studies that assessed late seizures, those graded class I and II were pooled.

How were differences between studies investigated?
Differences between the studies were assessed graphically using a forest plot and narratively according to the classification of study validity.

Results of the review
Nine studies (n=1,936) were included in the review. Six were randomised controlled trials (n=1,532), two were quasi-randomised (n=237) and one study did not use randomisation (n=167).

Early post-traumatic seizures.

The risk of early seizure was significantly lower in patients receiving the AED phenytoin compared with controls; the RR was 0.37 (95% CI: 0.18, 0.74) based on 649 patients in two studies.

Few adverse effects were reported. In one study 5.2% of patients receiving phenytoin and 9.2% of patients receiving placebo discontinued use owing to personal request, idiosyncratic and other reactions. In an additional study, one patient receiving phenytoin reported a rash within the first week of treatment.

Late post-traumatic seizures.

There was no statistically-significant difference in the risk of late seizure in patients receiving an AED compared with controls; the RR was 1.05 (95% CI: 0.82, 1.35) based on 1,312 patients in five studies. Adverse effects were frequently reported, but were mild in severity. The development of a rash was the most prevalent adverse effect in patients receiving phenytoin, while fatigue and lethargy were prevalent in patients receiving valproate; these led to a change of medication or the discontinuation of treatment. No studies evaluating carbamazepine reported adverse effects.

Authors' conclusions
Prophylaxis with phenytoin is effective in reducing the risk of early seizures in patients with severe TBI. In contrast, the evidence suggested that AED prophylaxis with phenytoin, carbamazepine or valproate is not effective in the prevention of late seizures in patients with severe TBI.

CRD commentary
The review was based on a clear question and the selection criteria appear to have been appropriate. The methods used to assess relevance and extract the data from the included studies were not transparent, therefore the potential for selection and observer bias cannot be ruled out. The authors attempted to limit language bias; however, the possibility of publication bias cannot be excluded because of the requirement for articles to be published in peer-reviewed journals. Details of the characteristics of the included studies (e.g. definition of severe TBI) and the demographics of the patients were not reported adequately to assess whether the decision to pool the studies was appropriate. Furthermore, the
decision to pool studies considered as class I for early seizures and both class I and II for late seizures may have led to imprecision in the summary estimate. This is due to the apparent variation in precision of the estimate of individual class I studies, compared with class II studies, and the stringent classification scheme used to grade the studies. Consequently, the strength of the authors' conclusions and recommendations for practice should be viewed with caution.

Implications of the review for practice and research
Practice: The authors stated that in adult patients presenting with severe TBI, prophylactic treatment with phenytoin, beginning with an intravenous loading dose, should be initiated within 7 days of injury to reduce the risk of early seizures. The prophylactic use of AEDs in the prevention of late seizures (occurring after 7 days of severe TBI) should not be recommended.

Research: The authors stated that further studies are required to address mild and moderate forms of TBI, and to evaluate newer AEDs and the administration of AEDs to children following TBI. In addition, these studies should assess the utility of electroencephalograms in ascertaining the risk of post-traumatic seizure in different patient subgroups.

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Acute Disease; Adult; Animals; Anticonvulsants /adverse effects /blood /therapeutic use; Brain Injuries /classification /complications /drug therapy; Carbamazepine /adverse effects /blood /therapeutic use; Child; Controlled Clinical Trials as Topic /statistics & numerical data; Dose-Response Relationship, Drug; Electroencephalography; Epilepsy, Post-Traumatic /etiology /prevention & control; Humans; Models, Animal; Phenytoin /adverse effects /blood /therapeutic use; Prospective Studies; Risk; Risk Assessment; Time Factors; Treatment Outcome

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.