Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials

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Authors' objectives
To synthesise evidence concerning the effect of anti-epileptic drugs (AEDs) for seizure prevention, and to contrast their effectiveness for provoked versus unprovoked seizures.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched using the terms 'seizur*', 'epilep*' or 'convul*' combined with 'clinical trial' or 'random*' and 'prevent*' or 'prophyla*'. The Medical Editors' Trial Amnesty (via the Cochrane Library) was also searched. The reference lists of the identified studies were examined for additional relevant studies. For traumatic brain injury, unpublished studies were identified through meetings and through informal communication.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with either true random assignment or some substitute, such as alternate days or alternate patients, that does not depend on the characteristics or preference of the patient, were included.

Specific interventions included in the review
Studies that evaluated treatment with one or more AEDs with a comparator were eligible for inclusion. The actual drugs studied were diazepam, phenobarbital, phenytoin, valproate, lorazepam and carbamazepine. No studies were found that evaluated AEDs approved in the United States after 1980. The usual comparator was placebo, but studies that had an untreated group or one that received a drug thought not to influence the seizure rate were also included.

Participants included in the review
The participants were patients who had not had unprovoked (epileptic) seizures before entering the study. The actual conditions the patients had were febrile seizures, seizures accompanying cerebral malaria, seizures after perinatal asphyxia, alcohol-related seizures, contrast media-associated seizures, brain tumour-related seizures, postcraniotomy seizures and post-traumatic brain injury seizures.

Outcomes assessed in the review
Only studies that reported the number of patients in each group and the number or percentage with (additional) seizures were included in the review.

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

Assessment of study quality
The author does not state that they assessed validity.

Data extraction
The author abstracted data on the number of cases in each treatment group and the number in whom seizures developed during the study. If the number was not given, but the percentage with seizures in each group was available, an approximate number with seizures was calculated. Where data were available, provoked seizures were treated separately from unprovoked seizures. Seizures were considered provoked if they occurred within seven days of the event (e.g.
surgery or trauma) and unprovoked if they occurred more than seven days after it.

**Methods of synthesis**

How were the studies combined?

A summary relative risk (RR) and 95% confidence interval (CI) were calculated for each condition and drug, based on the Mantel-Haenszel analysis controlling for study. A probability value (p value) for the test of no treatment effect was obtained by Fisher’s exact test if there was only one study in the group; otherwise the p value came from the Mantel-Haenszel or random-effects model analysis. All p values were two-sided.

How were differences between studies investigated?

A test for homogeneity of the RRs was performed, and a random-effects model was used if the test indicated that the RRs differed significantly among the studies.

**Results of the review**

Forty-seven studies with a total of 8,218 patients were included in the review.

**Prevention of provoked seizures.**

For each of the drugs and conditions, the estimated effect indicated a lower seizure rate with the AED. The decrease in seizures was significant in 7 of the 19 situations.

For recurrence of febrile seizures, phenobarbital produced the only significant decrease in seizures (RR 0.51, 95% CI: 0.32, 0.82, p<0.01). Intermittent diazepam, valproate, intermittent phenobarbital and phenytoin did not produce significant results.

For seizures accompanying cerebral malaria, phenobarbital was the only AED investigated; it produced a significant decrease in seizures (RR 0.36, 95% CI: 0.23, 0.56, p<0.01).

For seizures after perinatal asphyxia, phenobarbital was the only AED investigated; it did not produce a significant decrease in seizures.

For alcohol-related seizures, lorazepam produced the only significant decrease in seizures (RR 0.12, 95% CI: 0.04, 0.40, p<0.01). Valproate, phenytoin and carbamazepine did not produce significant results.

For contrast media-associated seizures, diazepam was the only AED investigated; it produced a significant decrease in seizures (RR 0.10, 95% CI: 0.01, 0.79, p=0.03).

Only one study investigated brain tumour-related seizures, it found that phenobarbital or phenytoin did not produce a significant decrease in seizures.

For postcraniotomy seizures, phenytoin produced a significant decrease in seizures (RR 0.42, 95% CI: 0.25, 0.71, p<0.01) whereas carbamazepine did not.

Finally, for post-traumatic brain injury seizures, phenytoin (RR 0.33, 95% CI: 0.19, 0.59, p<0.01) and carbamazepine (RR 0.39, 95% CI: 0.17, 0.92, p=0.03) produced a significant decrease in seizures, whereas phenobarbital and phenytoin plus phenobarbital did not.

**Prevention of provoked and unprovoked seizures.**

Only one study investigated postcraniotomy seizures, it found that valproate did not produce a significant decrease in seizures.

For post-traumatic brain injury seizures, phenytoin (RR 0.13, 95% CI: 0.04, 0.59, p<0.01) produced a significant decrease in seizures, whereas phenytoin plus phenobarbital did not.
Suppression or prevention of unprovoked or epileptic seizures.

No condition or drug combination produced significant results. In 4 of the 13 combinations, the estimated RR exceeded 1; in another 4 it exceeded 1 for either all studies or for placebo-controlled studies, favouring the control over the AED. Conclusive evidence against clinically important effectiveness (considered as a greater than 25% decrease in seizures) was available for a number of drugs and conditions. Valproate had little or no effect in preventing unprovoked seizures after traumatic brain injury, and carbamazepine had little or no effect on unprovoked seizures after craniotomy.

Authors’ conclusions
Effective or promising results predominate for provoked (acute, symptomatic) seizures. For unprovoked (epileptic) seizures, no drug has been shown to be effective, and some have had a clinically important effect ruled out.

CRD commentary
The research question and the study selection criteria were clearly stated and the literature search was comprehensive. Attempts were made to identify unpublished studies and there did not appear to be any language restrictions. The author did not report a method for making decisions on the relevance of studies for the review, nor for assessing the validity of those included.

Details of the primary studies were tabulated in adequate detail. The author reported that heterogeneity was assessed, although the specific test used was not stated. The meta-analysis was appropriate, although only one study was identified for some conditions and treatment types.

The results which achieved statistical significance were summarised narratively. The author's conclusions are justified.

Implications of the review for practice and research
Practice: The author states that clinical use of any drug to prevent epileptogenesis should be avoided until clinical trials have proven the drug to be effective for that purpose.

Research: The author states that rigorous clinical trials are needed to evaluate the effects of new drugs on epileptogenesis. She also states that a broader range of conditions might be considered for future trials, such as certain strokes and aneurysms, as well as encephalitis with early seizures, perinatal asphyxia with early seizures and symptomatic status epilepticus, as these conditions may have sufficient risk for developing epilepsy and sufficient prevalence to make evaluation of antiepileptogenesis both justifiable and practical.

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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.