Relapse following discontinuation of antiepileptic drugs: a meta-analysis

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Authors' objectives
The objectives were two-fold:

to determine the risk of relapse at one to two years after discontinuation of antiepileptic medication; and

to assess the relative risk of relapse associated with the age of onset of epilepsy, presence of an underlying neurologic condition, or an abnormal electroencephalogram.

Searching
Index Medicus was searched (search dates were unclear). In addition, the bibliographies of all the retrieved articles and several review papers were examined for references not detected by the computerised search. Articles published in English, French, Italian, German, or Spanish were considered for inclusion.

Study selection
Study designs of evaluations included in the review
All study designs in which the patient groups were assembled primarily for the purpose of examining the outcome of discontinuation of medication were included. Studies in which relapses occurring during discontinuation of medication had been excluded and data were unavailable in the paper, were excluded. All included studies had to be published articles in which the methods and results were adequately described. Studies presented in abstract form only, in a book chapter, or in review papers, were not included unless the manuscript was in press (which included the authors' own study), or the author made the data available for the purpose of the meta-analysis.

Specific interventions included in the review
Antiepileptic drugs (AEDs). No details of the specific drugs were given.

Participants included in the review
Patients (children, adolescents and adults) whose antiepileptic medication had been withdrawn. No further details of the patients were given.

Outcomes assessed in the review
The outcome measures were:

the risk of relapse after initiating (not completing) discontinuation of AED;

the risk of relapse at 1 year and 2 years after initiating AED;

age of onset (childhood versus adolescence; childhood versus adult); and

etiology (idiopathic versus remote symptomatic epilepsy; idiopathic versus epilepsy associated with mental retardation; idiopathic versus epilepsy associated with motor deficits).

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

Assessment of study quality
No formal assessment of validity was undertaken.
Data extraction
One author extracted the data from each study in a standardised way. The estimate of the risk and relative risk (RR) of relapse, and the variance and 95% confidence intervals (CIs), were derived for each study.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest).

How were differences between studies investigated?
Heterogeneity was assessed using the method described by DerSimonian and Laird (see Other Publications of Related Interest). Large variations in the inclusion criteria led to relapse being examined according to prognostic factors within the individual studies.

Results of the review
Twenty-five studies (5,354 participants) were included.

Risk of relapse.
The RR was 0.25 (95% CI: 0.21, 0.30) at one year and 0.29 (95% CI: 0.24, 0.34) at 2 years. Substantial heterogeneity was present among the relapse risks from these studies (p<0.0001).

Age of onset of epilepsy.
For childhood versus adolescence, the RR was 1.79 (95% CI: 1.46, 2.19); there was significant heterogeneity (p=0.002).

For childhood versus adult, the RR was 1.34 (95% CI: 1.00, 1.81); heterogeneity was not quite significant (p=0.063).

Underlying etiology.
For idiopathic seizures versus remote symptomatic, the RR was 1.55 (95% CI: 1.21, 1.98); there was significant heterogeneity (p<0.0001).

For idiopathic seizures associated with mental retardation, the RR was 1.66 (95% CI: 1.30, 2.12); heterogeneity was not significant (p=0.98).

For idiopathic seizures associated with motor deficits, the RR was 1.79 (95% CI: 1.13, 2.83); there was significant heterogeneity (p<0.0001).

Electroencephalogram.
For an abnormal electroencephalogram associated with risk of relapse, the RR was 1.45 (95% CI: 1.18, 1.79); there was significant heterogeneity (p<0.0002).

Authors' conclusions
In relatively unselected groups of seizure-free patients, the risk of relapse after discontinuing AEDs was 25% at one year and 29% at two years. Onset during adolescence appeared to carry the highest risk of relapse, while onset during childhood had the lowest risk.

Not surprisingly, remote symptomatic seizures were associated with an increased risk of relapse.
In most studies there was a relationship between an abnormal electroencephalogram and an increased risk of relapse. These meta-analyses were an attempt to provide a framework to be used in making rational decisions that best meet the specific needs of individual patients. However, they should not be used as the sole basis for decisions on whether to discontinue medication.

**CRD commentary**
This systematic review satisfied several of the criteria for inclusion in the DARE database. The authors’ conclusions appear valid from the data presented in the review, although the results may not be directly generalisable to clinical practice.

The design of the included studies was an important factor in determining the strength of the conclusions. Unfortunately, the study designs were not well described and a variety of study designs may have been included; this partially explains the heterogeneity between the studies. The presence of heterogeneity indicates that it would have been advantageous had other aspects that influence the strength of the evidence been reported; perhaps consideration should have been given to the use of a formal validity assessment.

The search strategy was essentially restricted to Index Medicus, and the dates over which the search was conducted were not given. Despite including studies published in several languages, it is possible that the search missed several studies not represented in this single database.

This was a useful review which, as the authors state, may provide a framework on which to base the treatment decision-making process. However, it should not replace a careful clinical evaluation of each individual patients circumstances.

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**Other publications of related interest**

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Record Status
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.