Phenobarbital for childhood epilepsy: systematic review

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CRD summary
This review found few differences in the efficacy of phenobarbital in preventing seizures in children with epilepsy or febrile convulsions. The results should be interpreted with some caution because of some flaws in the conduct of the review and the very poor quality of the included trials. The reliability of the author's conclusions is unclear.

Authors' objectives
To examine the effectiveness and safety of phenobarbital in the treatment of childhood epilepsy.

Searching
The Cochrane Epilepsy Group Register of Clinical Trials in Epilepsy, The Cochrane Library, MEDLINE, EMBASE, SciSearch and PsycLIT were searched between 1969 and 2005. Search terms were those developed by the Cochrane Epilepsy Group. There were no language restrictions. Citation searches were undertaken. Book chapters, review articles and reference lists of identified articles were checked to identify additional references. The author approached experts in the field for unpublished trials.

Study selection
Randomised controlled trials (RCTs) of the anti-epileptic drug phenobarbital in young people or children with clinically diagnosed generalised tonic-clonic or focal epilepsy or febrile convulsions compared to placebo, no treatment or other active medication were eligible for inclusion.

The comparators included placebo, phenytoin, diazepam, sodium valproate, mephobarbital, carbamazepine and intermittent administration of phenobarbital. Outcomes evaluated were numbers of seizures, cognitive and emotional states and behavioural outcomes. The outcomes were assessed by parental reports and standardised psychological testing.

It was not clear how many reviewers performed the study selection.

Assessment of study quality
Methodological quality was assessed by the author by evaluating treatment assignment, blinding, completeness of follow-up and methods of analysis.

Data extraction
Data were extracted as reported by the author using standard data extraction tables. Data were separated into separate tables for patients who were treated for febrile convulsions and those treated for epilepsy.

Methods of synthesis
The results of the review were summarised in a narrative synthesis.

Results of the review
Eleven studies (2,159 participants) on phenobarbital for febrile convulsions were included in the review. These were simple and stratified trials and two studies described as non-random and "not trial". Five trials used blinded assessments. Concealment of allocation was reported in four trials. Follow-up ranged between 12 to 53 months. Losses to follow-up ranged from zero to 34%. Intention-to-treat analyses were performed in three trials.

There was a lack of evidence of efficacy with phenobarbital in the prevention of febrile convulsions across the 11 trials. Benefits were observed in only five trials compared to placebo (three trials), intermittently administered phenobarbital (one trial) and carbamazepine (one trial). Trials showed a lack of conclusive evidence of more adverse behavioural effects associated with phenobarbital.

Nine trials (956 participants, range eight to 302) that evaluated phenobarbital in children with epilepsy were included in
the review. Follow-up ranged from three months to 44 months. Concealment of allocation and blinded analysis of the results were clearly reported in one trial. Losses to follow-up (where stated) ranged from zero to 34%. Trial quality was judged as being poor.

Phenobarbital was associated with an increase in adverse side effects in three non-blinded studies compared to phenytoin and placebo (one trial) sodium valproate (one trial) and phenytoin and sodium valproate (one trial). There were no differences in side effects observed with phenobarbital and other comparators in six trials, all of which were undertaken in developing countries.

Authors' conclusions
There was no evidence of any differences in efficacy and safety of phenobarbital compared to placebo or other anti-epileptic drugs in the prevention of febrile convulsions or epileptic seizures. There was no evidence of adverse behavioural effects of phenobarbital compared to other anti-epileptic drugs.

CRD commentary
The review addressed a clear question. Criteria for the inclusion of studies were stipulated. There were some discrepancies between the inclusion criteria and study designs that were included in the review. Appropriate electronic databases were searched without language restrictions and attempts were made to identify unpublished studies. No steps to minimise errors or biases by the author were reported at any stage of the review process, but the draft report was checked by a biostatistician. The author's decision to summarise the results in a narrative review appears justified given the clinical heterogeneity across the included trials and the poor quality of the trials. The author correctly acknowledged some of the limitations of the review, particularly those pertaining to the poor quality of the trials.

Some methodological flaws and the very poor quality of the included studies mean that the author's conclusions should be interpreted with some caution and the reliability of the results is unclear.

Implications of the review for practice and research
Practice: The author did not state any implications for practice.

Research: The author stated that further research in the use of phenobarbital should address questions regarding:
potential for cognitive impairment with use of phenobarbital in children with epilepsy; intellectual domains most affected by phenobarbital use; roles of educational interventions to mitigate the effect of phenobarbital on cognition; the degree to which cognitive gains in children severely affected by epilepsy outweigh deficits as a result of treatment; and determination of any dose effect. Molecular diagnostics may also be useful in assessing the prior risk of adverse effects.

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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.