Generic substitution of antiepileptic drugs: a systematic review of prospective and retrospective studies

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CRD summary
The authors concluded that substituting generic for branded anti-epileptic drugs was generally not problematic, but some patients may have been prone to complications. The authors’ conclusions broadly reflected the evidence presented, but their reliability was limited by high risk of bias in the included studies and potential biases in the review process itself.

Authors' objectives
To evaluate the efficacy and safety of generic antiepileptic drug substitution.

Searching
PubMed and CINAHL databases were searched up to October 2010, with an English language restriction; search terms were reported. Reference lists of identified studies were handsearched to locate further studies.

Study selection
Eligible were full text articles that described controlled studies with retrospective or prospective designs and compared branded versus generic antiepileptic drugs. Participants were either seizure/epilepsy patients or healthy participants. Primary outcomes were changes in pharmacokinetic parameters and adverse clinical outcomes (seizure/epilepsy-related events, adverse reactions or medical service utilisation associated with switching to generic antiepileptic drugs). Secondary outcomes related to plasma concentration and switchback rates.

Mean participant age ranged from 33.7 to 45.1 years, where reported. Study populations were either all male (30% of included studies) or males and females (70% of included studies) and contained patients and/or healthy participants. Drugs administered included lamotrigine, topiramate, phenytoin and carbamazepine. Most studies had been funded by pharmaceutical companies; others were funded by local hospitals or USA government.

Assessment of study quality
Methodological quality of studies was not formally assessed but studies were assigned to a class of evidence according to their design and quality-related features (such as description of inclusion/exclusion criteria, drop-out information). Study population, sample size, age, study duration, blinding and financial support were evaluated as bias parameters for individual studies.

The number of reviewers that performed this assessment was not reported.

Data extraction
The authors did not report how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
A narrative synthesis of the results was presented; categorised as retrospective studies, prospective studies with seizure/epilepsy patients or prospective studies with healthy participants. In each category, studies were weighted according to their classification status (Classes I-III) from the AAN system to determine an overall level of evidence for the studies. For retrospective studies, adverse clinical outcome results were prioritised; results for prospective studies focused more on pharmacokinetic parameters.

Results of the review
Twenty studies were included in the review (44,081 participants). Retrospective studies (43,776 patients) had cohort (36,386 patients), case-control (5,628 patients) or case-crossover study designs (1,762 patients); sample sizes ranged from 671 to 33,625 patients.
All prospective studies (305 patients and healthy participants) were randomised crossover trials; sample sizes ranged from 10 to 40 patients for patient populations, and from 16 to 52 participants in healthy populations. Seven prospective studies presented unclear descriptions of their inclusion/exclusion criteria, nine studies did not present a statistical power analysis, and five did not describe participants’ baseline characteristics.

Six of the seven retrospective studies demonstrated statistically significantly greater use of medical care resources for generic substitution versus brand drugs. Most prospective studies demonstrated no statistically significant differences between generic versus brand drugs for adverse clinical outcomes. Across the studies, seizure frequency was not statistically significantly different between generic and brand drugs. Results for pharmacokinetic parameters and secondary outcomes were reported in the paper.

**Authors’ conclusions**

Findings from retrospective and prospective studies of generic antiepileptic drug substitution were inconsistent. The strongest levels of evidence available suggest that generic antiepileptic drug substitution was not problematic, although some patients may have been prone to complications.

**CRD commentary**

The review’s aims were clearly stated and the inclusion/exclusion criteria appeared replicable. Databases searched were relevant and additional literature was identified through handsearching; the restriction to studies in English meant that language bias was possible. Screening was performed by one reviewer and any uncertainty resolved by a second reviewer.

Methodological quality of studies was not assessed using a validated quality assessment tool, but most were retrospective observational studies and hence were likely to be at high risk of bias. Details concerning data extraction and numbers of reviewers involved in data extraction were not reported, so the risk of reviewer error and bias was unclear. The evidence classification system seemed appropriate for the studies included. The narrative synthesis was well-structured and provided good reasoning for the levels of evidence evaluated. The authors’ conclusion and recommendations broadly reflected the findings presented, but their reliability was limited by high risk of bias in the included studies and potential biases in the review process itself.

**Implications of the review for practice and research**

**Practice**: The authors stated that the risk of breakthrough seizures should be minimised through careful monitoring of seizures and adverse events, and maintaining consistency of products provided to the patient.

**Research**: The authors stated that benchmarking of serum concentrations of antiepileptic drugs was required.

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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.