Effectiveness and safety of antiepileptic medications in patients with epilepsy


CRD summary
The authors concluded that some older antiepileptic medications had some efficacy advantages over newer antiepileptic medications and others had similar efficacy. All older medications had more adverse events. Innovator and generic versions of an antiepileptic medication showed similar efficacy and safety. This was a well-conducted review. The authors' conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To compare the effectiveness, safety and tolerability of antiepileptic medications in patients with epilepsy.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews and Web of Science were searched up to March 2011. Search strategies were reported. No language restrictions were applied. Reference lists of trials and reviews were searched manually.

Study selection
Eligible studies were controlled clinical trials and controlled observational studies that compared benefits and harms of older versus newer or innovator versus generic antiepileptic medications in patients with epilepsy. Older drugs included those approved by the US Foods and Drug Administration (FDA) pre-1993 (phenytoin, carbamazepine, carbamazepine sustained release or controlled release, valproic acid, clonazepam, phenobarbital, ethosuximide, primidone). Newer drugs were those approved by the FDA in 1993 or later. Endpoints included health outcomes (mortality, hospitalisations and/or other medical visits, health related quality of life), intermediate outcomes (medication dose needed to control seizures, switchback rates) and adverse events.

Studies not published in English were excluded from the review.

Included studies were conducted between 1974 and 2010. Most studies were conducted in USA or UK; others were multinational or conducted in Asian or European countries. Where reported, the mean age of participants ranged from 8.4 months to 77 years. Some patients had received prior antiepileptic treatment or were receiving concurrent treatment. Epilepsy history and seizure type were sparsely reported.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Study risk of bias was assessed using recommendations specified in the Agency for Healthcare Research and Quality (AHRQ) guide for effectiveness and comparative effectiveness reviews; each study was rated as good, fair or poor. The strength of the evidence for each outcome was rated as insufficient, low, moderate or high based on GRADE criteria for risk of bias, consistency, directness and precision. Applicability of the studies to clinical practice was assessed (as defined in the review).

Two reviewers assessed study quality and level of evidence. Discrepancies were resolved through discussion.

Data extraction
Dichotomous outcome data were extracted to calculate relative risks and continuous data (mean differences and standard deviations) were extracted or estimated to calculate mean differences, along with their 95% confidence intervals. Medical service utilisation data were extracted as incidence rate ratios. Time to first seizure data were extracted to calculate hazard ratios and 95% confidence intervals. Study authors were contacted where necessary.

Two reviewers independently extracted data and resolved discrepancies through discussion.

Methods of synthesis
A DerSimonian and Laird random-effects model was used to pool relative risks (RR) or hazard ratios (HR) and 95% confidence intervals (CIs). Mean differences were combined to calculate standardised mean differences (SMD) or weighted mean differences (WMD), along with their 95% CI. Incidence rate ratios were reported as a narrative synthesis.

Controlled clinical trials were pooled separately to controlled observational studies. Where studies included more than one treatment group these were considered separately and control groups were divided accordingly.

Statistical heterogeneity was assessed using the $I^2$ statistic. Subgroup analyses were performed for older versus newer evaluations, new onset versus chronic (refractory) epilepsy, seizure types, gender and age. Subgroup analyses for innovator versus generic drugs assessed innovator medications versus a known FDA approved A-rated generic medication and innovator medications within a BCS (Biopharmaceutics Classification System) class (I, II or III) versus their corresponding generic medication within the same class.

Publication bias was assessed using Egger's test.

**Results of the review**

Most studies were randomised controlled trials (RCTs) with crossover design. Other studies were RCTs with parallel design, case controls, cohort studies or before-and-after studies. Follow-up ranged from nine days to approximately four years.

**Newer versus older medications:** There were 117 studies (20 to 1,721 participants). Time to first seizure significantly increased for newer medications versus phenytoin (HR 1.59, 95% CI 1.04 to 2.43; two RCTs) but the strength of evidence was low. Seizure remission was less likely with newer medications compared to carbamazepine at six to 12 months (RR 0.81, 95% CI 0.67 to 0.99; two RCTs) and 24 months (RR 0.82, 95% CI 0.72 to 0.94; one RCT). The strength of evidence was moderate or low.

Withdrawals due to lack of efficacy significantly increased with newer medications versus carbamazepine (RR 1.59, 95% CI 1.25 to 2.02; 10 RCTs) but the evidence was low. Other outcomes reported no significant differences between medications or insufficient evidence to evaluate the effect.

**Innovator versus generic medications:** There were 89 studies (five to 18,125 participants). There was a significant increased risk of hospitalisations (four observational studies) and length of hospital stay (four observational studies) with generic medication. The strength of evidence was low. This was reflected in the increased use of medical services when medications were switched between innovator and generic medications (three observational studies).

Other outcomes reported either no significant differences between medications or insufficient evidence.

**Adverse events:** Withdrawals due to adverse events were significantly reduced with newer antiepileptic medications versus carbamazepine (18 RCTs) and carbamazepine sustained release or controlled release (two RCTs) both with medium strength of evidence.

Newer medications significantly reduced risk of fatigue, somnolence, dizziness, nausea and vomiting, skin rash, alopecia and gum hyperplasia compared to some older medications. Risk of attempted suicide was significantly increased with newer medication (gabapentin) versus carbamazepine. There were no significant differences in adverse events between newer and generic medications.

Results for intermediate outcomes and subgroup analyses were reported in the review.

**Authors’ conclusions**

Carbamazepine or controlled/sustained-release carbamazepine have some efficacy advantages over newer antiepileptic medications but have more adverse events and adverse events causing withdrawal. Other older antiepileptic medications agents have similar efficacy versus newer antiepileptic medications and have more adverse events although the adverse events do not lead to a higher rate of withdrawal. Innovator and generic versions of an antiepileptic medication show similar efficacy and safety but switching from one form to the other may be associated with increased risk of
hospitalisation and longer hospital stay.

CRD commentary
The review objectives and inclusion criteria were clearly defined. The literature search was satisfactory but papers in languages other than English were eventually excluded. Each stage of the review process was conducted in duplicate which reduced potential for reviewer error and bias. Study risk of bias and strength of evidence were assessed but overall strength of evidence was not high.

Study details and patient characteristics were reported and a large number of studies were included in the review. The authors acknowledged differences between studies and attempts were made to investigate sources of heterogeneity. The authors acknowledged limitations of the innovator versus generic medications evaluation and lack of power for subgroup analyses. Appropriate methods were used to synthesise data and substantial exploration of the data was undertaken.

This was a well-conducted review and the authors considered the limitations of the evidence in their findings. The authors’ conclusions reflect the evidence presented and are likely to be reliable.

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

Research: The authors stated that with future direct comparative clinical trials the ability to use individual newer versus individual older antiepileptic medication evaluations in agent selection could be enhanced. The authors stated that further randomised double blind trials were needed on benefits and harms associated with older and newer medications in different seizure types and to assess the impact of switching medications in patients.

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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.