CRD summary
This review concluded that polytherapy is clinically preferable to sequential monotherapy, and monotherapy is more likely to be harmful than beneficial, for patients with treatment-resistant epilepsy. The potential for publication and language bias, and error and bias during the review process, should be kept in mind when considering the conclusions.

Authors' objectives
To determine which drug treatment strategy (sequential monotherapy, polytherapy, or optimised current therapy) leads to improved outcomes for patients with treatment-resistant epilepsy, and what are the relative improvements obtained with each strategy. Diagnosis and non-drug treatments are addressed in separate abstracts (see DARE abstract numbers 12005008217 and 12005008219, respectively).

Searching
The authors searched the following: MEDLINE (1975 to 2002), EMBASE (1975 to January 2002), PsycINFO (1975 to January 2002), CIRRIE (November 2001), CINAHL (1988 to January 2002), the Cochrane Database of Systematic Reviews (Issue 4, 2001), the Cochrane CENTRAL Register (Issue 4, 2001), the Cochrane Review Methodology Database (Issue 4, 2001), DARE (Issue 4, 2001), NHS EED (to January 2002), ECRI Health Devices Alerts (1977 to January 2002), ECRI Health Devices International Sourcebase (1977 to January 2002), ECRI Healthcare Standards (1975 to January 2002), ECRI International Health Technology Assessment (1990 to January 2002), ECRI Library Catalogue (to January 2002), ECRI TARGET (to January 2002), ERIC (January 2002), Health and Psychosocial Instruments (to April 2001), LocatorPlus (to January 2002), NDA Pipeline (November 2001), REHABDATA (April 2001), U.S. Centers for Medicare and Medicaid Services (to January 2002) and the National Guideline Clearinghouse (to January 2002); the search strategies were reported. In addition, the reference lists of included studies were checked. Current Contents (Clinical Medicine) was also searched on a weekly basis. Only studies published in English since 1985 were included.

Study selection
Study designs of evaluations included in the review
If 5 or more placebo-controlled trials were available for any drug, other study designs were not considered. Trials had to be phase II or III. If there were fewer than 5 studies, and none were a randomised controlled trial (RCT) with 50 or more patients in the intervention group, no studies were included for that drug. If one of the studies was an RCT with 50 or more patients, the RCT was included even if there were fewer than 5 studies. When there were 5 prospective studies for a given intervention, the retrospective studies were excluded for that intervention. Crossover studies had to report results before crossover, or the frequency of return to baseline at the end of the washout period.

Specific interventions included in the review
Studies of any drug that has been cleared for marketing in the USA by the U.S. Food and Drug Administration (FDA) were eligible for inclusion. Studies including patients treated with non-FDA approved drugs were included if the results for patients receiving the FDA drugs were reported separately. A wide range of drugs and doses were evaluated. Only studies that were evaluated in a minimum of 5 studies of acceptable quality were included in the review.

Participants included in the review
Studies of people with drug-resistant epilepsy, or where results of those with drug-resistant epilepsy were reported separately, were eligible for inclusion. The participants must have received unsuccessful treatment with either carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone or valproate. Only outcomes for compliant patients
were included. The studies had to have a minimum of 10 people to be eligible for inclusion.

Outcomes assessed in the review
Studies had to report quantitative outcome measures. Studies reporting the following were eligible for inclusion: absolute seizure frequency; percentage change in seizure frequency from baseline; proportion of patients seizure-free; proportion of patients with more than a 50% reduction in seizure frequency from baseline; Engel classification; rundown time to seizure-free; seizure-free period; proportion of patients with any reduction in seizures; proportion of patients with any increase in seizures; proportion of patients exiting a trial because of a harmful increase in seizures; quality of life; mood; functional status/ability; cognitive function; ability to stay in or return to work or school; ability to hold a driver's licence; adverse events; mortality.

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

Assessment of study quality
The authors examined studies for sampling bias, sample specification bias, selection bias, regression bias, patient bias, investigator bias, measurement bias, attrition bias, maturation bias and extraneous event bias. Those reporting mortality were evaluated for cause validation bias, mortality ratio bias, sampling bias and sample specification bias. Statistical power was also considered. Studies considered to have design flaws that would bias these results were excluded from the review. The authors did not state how many reviewers performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on seizure frequency, mood, cognitive function, adverse events and mortality were extracted.

Methods of synthesis
How were the studies combined?
All of the studies were combined in a narrative. Some studies were combined in a meta-analysis, using intention-to-treat, and Cohen's h calculated, along with 95% confidence intervals (CIs).

How were differences between studies investigated?
Study characteristics were tabulated and differences between studies were discussed in the text. Forest plots were provided for pooled analyses for visual inspection of heterogeneity.

Results of the review
Fifty studies met the inclusion criteria. There were 13 studies of sequential monotherapy (n=1,542), 30 of polytherapy (n=4,834) and 11 (of which only 7 were included in the analysis) of optimised current therapy (n=311).

Quality.
Of the 50 studies, 0 were clearly subject to sampling bias, 5 were subject to selection bias, 5 to investigator bias, 7 to patient bias, 1 to attrition bias, 47 to measurement bias, 20 to regression bias, 20 to extraneous event bias and 46 to sample specification bias.

Sequential monotherapy (13 studies).
Eleven per cent (95% CI: 5, 18; 4 studies) of patients remained seizure-free when switched to sequential monotherapy in long-term studies; 16% (95% CI: 10, 22; 6 studies) remained seizure-free when short-term studies were included. Sixteen per cent (95% CI: 10, 23; 5 studies) of patients had a doubling of monthly seizure frequency and 14% (95% CI: 8, 21; 5 studies) a doubling of 2-day seizure frequency. Five per cent (95% CI: 1, 12; 13 studies) of patients dropped out of studies of sequential monotherapy because of adverse events.
Polytherapy (30 studies).

Patients receiving additional drugs were less likely to have seizures; Cohen's \( h \) for becoming seizure-free was 0.29 (95% CI: 0.20, 0.37; 16 studies) for high dose and 0.28 (95% CI: 0.20, 0.36; 16 studies) for low dose, favouring treatment over placebo; Cohen's \( h \) for a 50% seizure reduction was 0.52 (95% CI: 0.43, 0.62; 27 studies) for high dose and 0.45 (95% CI: 0.35, 0.55; 27 studies) for low dose, favouring treatment over placebo. However, patients receiving polytherapy were more likely to suffer adverse events compared with placebo, with 8% of patients dropping out of trials in high-dose groups compared with 4% in placebo groups (30 studies). The participants in polytherapy trials tended to have more severe epilepsy than those of the sequential monotherapy trials.

Optimised current therapy (7 studies).

Drug reduction may lead to increases in seizure frequency in some patients and a reduction in seizures in others. There was insufficient evidence to determine changes in quality of life, mood, cognition or adverse events.

Authors' conclusions
Evidence suggests that polytherapy is clinically preferable to sequential monotherapy; monotherapy is more likely to be harmful than beneficial.

CRD commentary
The research question was clear, with well-defined inclusion criteria. An extensive search was undertaken, thus reducing the potential for publication bias. As only English language studies were included, language bias may be present. It was unclear whether the study selection, quality assessment and data extraction processes were conducted in duplicate, therefore these may be subject to error and bias. Study quality was assessed using appropriate criteria but its impact on the results does not seem to have been investigated. When studies were pooled, statistical heterogeneity does not seem to have been assessed; visual inspection of the forest plots seem to show no significant heterogeneity for the pooled primary outcomes. The potential for publication and language bias, along with error and bias during the review process, should be kept in mind when considering the conclusions of this review.

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

Research: The authors suggested direct comparisons of drugs in prospective, randomised, double-blinded controlled trials. Investigation into the incidence of adverse events on switching to a new drug, or the addition of a new drug to the regimen, was also recommended. Large cohort studies are needed to evaluate mortality, particularly in patients with treatment-resistant epilepsy.

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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.