The choice of antiepileptic drugs (AEDs) is rapidly increasing. This review looks at the evidence that guides the decision of which AED to start as monotherapy and aims to aid the choice of treatment if monotherapy fails. Unfortunately, the evidence supporting the prescribing of new drugs is sparse, because most randomised controlled trials answer questions focused on regulatory requirements rather than on clinical use. Ultimately, the choice of one AED will be determined by an individual risk–benefit assessment in which the most effective drug for an individual patient is chosen, and one that would have the lowest risk of significant harm. It is the risk of chronic toxic effects and issues of teratogenicity for women that may affect the choice of drug therapy to the greatest degree. In the future there is a need to improve the quality of clinical data on efficacy and harmful effects of AEDs.

The past 15 years has seen the registration of many new drugs (vigabatrin, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide) for the treatment of epilepsy. This has presented a greatly increased choice for patients and their doctors, which in turn has focused attention on the paucity of information and evidence that can currently support everyday clinical practice. In this article we attempt to review the currently available evidence on drug treatment for epilepsy.

Epilepsy is the most common serious neurological disorder, with a prevalence of 0·5–1% in the general population. On average the incidence of epilepsy is approximately 50 per 100 000 population, but is highest at the extremes of life. A recent prescription cost analysis indicated that the cost of antiepileptic drugs (AEDs) to the UK National Health Service in 2002 (prescribed for all indications) was £142 million of which £99 million was spent on new AEDs.

Epilepsy itself is a varied disorder with many causes ranging from genetic causes through to acquired brain damage and insults. Disease outcomes are also heterogeneous. Most people who develop epilepsy during their life have a relatively short-lasting susceptibility to seizures and enter remission shortly after starting treatment on small doses of AEDs. However, 20–30% of people who develop epilepsy will have a chronic epilepsy that responds incompletely to AED therapy.

One of the key features in the management of epilepsy has been the differentiation between seizures that are focal in onset and those which seem to be generalised from the start. On the basis of clinical experience, there is a strong belief that different AEDs may be effective against different seizure types and to some degree different epilepsy syndromes (figure 1). Thus, drugs that have been shown to be effective against focal seizures may be relatively ineffective against generalised seizures. Despite the clinical

**Figure 1. The spectrum of the effectiveness of AEDs against different seizure types.** Evidence for effectiveness against generalised seizures is largely limited to anecdotal evidence.
beliefs involved, there seems little evidence from clinical trials to support the belief (see below). Increasingly, there is a move to better define the potential interactions between a drug and patient-specific factors, such as the type of epilepsy or seizure, as well as to define the influence of drugs on long-term prognosis. There are several important questions. First, do individual drugs differ in their efficacy in suppressing seizures? Second, do individual drugs exacerbate certain seizure types? And finally, do any of the drugs used to treat epilepsy do more than simply suppress seizures: are they antiepileptogenic and can they modify the natural history of epilepsy?

The ideal drug for someone with epilepsy would not only suppress seizures but also reduce the susceptibility to seizures in the future (both antiseizure and antiepileptogenic). Epileptogenesis is a process in which structural and functional changes occur after a brain insult that can lead to epilepsy, but epileptogenicity may also describe some processes that contribute to the progression that is observed in some types of epilepsy. There are many animal data that support epileptogenesis as a process. This evidence is most clearly seen in the kindling model of epilepsy and in various chronic animal models of epilepsy in which spontaneous seizures may develop after a latent period following an acute brain insult such as induced status epilepticus, neonatal hypoxia, or traumatic brain injury. Despite these models, there is a lack of any firm evidence that the drugs used to treat epilepsy in human beings are antiepileptogenic. Temkin reviewed many clinical trials in which treatment was compared with no treatment in individuals with significant risk for the development of later epilepsy. Whereas the drugs that were tested consistently suppressed seizures in the short term, they did not seem to influence the long-term risk of seizures. These data are supported by a first-seizure study, which showed that treatment reduced seizure recurrence after a first unprovoked seizure but did not effect long-term remission rates. Thus, while a search for genuinely antiepileptogenic drugs continues, current decision making about the choice of drug treatment needs to be based on the relative ability of drugs to suppress seizures in the short term.

We should of course seek to avoid prescription of drugs that might exacerbate seizures in a susceptible patient. This is a difficult area of study in a chronic variable paroxysmal condition like epilepsy, but has been reviewed by Perucca and colleagues. A systematic approach to review did show evidence of some specific drug effects in the exacerbation of seizures. There are many reports of carbamazepine exacerbating typical and atypical absence seizures as well as myoclonic seizures. There is weak evidence that ethosuximide could exacerbate tonic-clonic seizures in children, and somewhat more consistent evidence that vigabatrin can precipitate myoclonus and absence seizures. It is perhaps here that we have the most satisfactory evidence to prefer specific AEDs, such as valproic acid, for the treatment of adults with generalised epilepsies.

Ultimately, the choice of an individual AED will be determined by an individual risk-benefit assessment in which the most effective drug for an individual patient is chosen, and one that would have the lowest risk of significant harm. AEDs are associated with both dose-related and idiosyncratic effects, but it is the risk of chronic toxic effects and issues of teratogenicity for women that may affect the choice of drug therapy to the greatest degree.

**Choice of a first AED**

Reliable evidence about benefit will come from large-scale randomised controlled trials (RCTs) in which drugs have been compared head-to-head, and in which outcomes that have clinical use have been measured. Primary outcomes currently recommended by the International League Against Epilepsy (ILAE) include time to the following events after randomisation: treatment failure, remission from seizures for 12 months, and first seizure. Treatment failure is a composite outcome that indicates both efficacy and tolerability as a drug may fail because of continued seizures, side-effects, or a combination of both.

It is worth considering whether AED monotherapy trials should be designed to detect a difference or equivalence. In 1998, the Commission on Antiepileptic Drugs of the ILAE concluded that such trials should be designed to detect equivalence. In other words, trials should be designed to generate confidence intervals around efficacy estimates that are narrow enough to exclude the existence of important differences. This of course needs an a priori definition of the smallest important clinical difference, but at the time of writing, there is no consensus definition of this smallest clinical difference for the primary outcomes in epilepsy monotherapy trials, and reported trials have used differing definitions. A further challenge for investigators is that most trials designed to detect equivalence will require the recruitment of substantially more patients than those designed to detect a difference. For trials comparing new and standard AEDs, the ILAE Commission suggested that a new drug could be considered for use as a first-line agent if it is shown to have equivalent efficacy to, but is better tolerated than, the standard drug. A new drug showing equivalent efficacy and tolerability to a standard drug would be considered for use as a second-line treatment.

RCTs will also provide information about side-effects, primarily those that are relatively common and occur soon after starting treatment, for example nausea or drowsiness. RCTs are not, however, the most appropriate methodology to assess the risk of other perhaps more important side-effects including teratogenicity, rare but serious reactions (eg, Stevens Johnson syndrome), and late effects (eg, osteoporosis). Evidence about the risk of these side-effects will come from observational studies, primarily case-control and cohort studies. Assessment of the risk to benefit ratio of AEDs therefore requires appraisal of evidence from RCTs and observational studies. Below, we will discuss evidence from RCTs and systematic reviews of RCTs followed by evidence from observational studies. The latter is restricted to data on teratogenicity, the risk of which plays a major part in the choice of drug for women of childbearing age—a third of people with epilepsy.
Focal epilepsies

There have been several RCTs that have compared the effects of standard AEDs such as carbamazepine, phenytoin, valproic acid, and phenobarbital, and their results have been summarised in meta-analyses in a series of Cochrane systematic reviews. Results from reviews providing data on the subgroup of patients with focal-onset seizures are summarised in table 1.

A meta-analysis of trials comparing carbamazepine and valproic acid found no difference for time to treatment failure (hazard ratio [HR] 1.00, 95% CI 0.79–1.26), and a significant advantage for carbamazepine for time to 12 months of remission (HR 1.60, 95% CI 1.21–2.13) and time to first seizure (HR 1.21, 95% CI 1.04–1.41). A meta-analysis that compared carbamazepine with phenobarbital found no significant advantage for either drug. The estimates indicated that phenobarbital was more likely to be withdrawn, presumably due to side-effects, but fared better for time to first seizure. Similarly, a meta-analysis comparing phenytoin found no significant differences, although the estimates suggested that phenytoin was more likely to be withdrawn than carbamazepine, but fared better for time to first seizure. A meta-analysis comparing phenobarbital and phenytoin found that phenobarbital was significantly more likely to be withdrawn, but that there was no significant difference for 12 months of remission or time to first seizure. We therefore have limited data on the comparison between standard AEDs. Where estimates indicate no difference, it is important to understand that the confidence intervals are wide, hence important differences have not been excluded and equivalence cannot be inferred. Meta-analyses that compare carbamazepine with valproic acid do, however, support guidelines that recommend carbamazepine as first-line treatment for patients with focal seizures.

In the past decade, many new AEDs have been developed and marketed, including gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, and zonisamide. All have shown efficacy as add-on treatments for patients with drug-resistant focal seizures when compared with placebo. Fewer head-to-head trials have been undertaken in which standard and newer AEDs have been compared.

Lamotrigine has been compared with carbamazepine in four published trials that recruited patients with focal seizures. In three of these trials, doses were escalated according to clinical need, and all found that carbamazepine was significantly more likely to be withdrawn, mainly because of side-effects. However, none of these trials found a significant difference in terms of seizure control. Two found no difference in the proportion of patients who were seizure free in the final 24 weeks of a 48 week trial, or the final 16 weeks of a 24 week trial; however, these outcomes lacked both statistical power and clinical usefulness. Two trials found no difference in time to first seizures after randomisation. However, estimates were in favour of carbamazepine and confidence intervals were wide, and although lamotrigine seems better tolerated than carbamazepine, we have insufficient evidence about seizure control to inform a choice between these two drugs for patients with focal seizures.

Gabapentin and carbamazepine have been compared in one monotherapy trial recruiting patients with focal seizures. Patients were randomly assigned to receive 600 mg carbamazepine daily, or one of three doses of gabapentin daily (300 mg, 900 mg, or 1800 mg). The primary outcome was time to exit, reasons for which included a single tonic-clonic seizure, three complex partial seizures, and status epilepticus. No significant difference was found between the groups taking carbamazepine and 900 mg or 1800 mg gabapentin daily. Significant differences were found between doses of gabapentin and between the 300 mg doses of gabapentin and carbamazepine. The protocol for this trial deviates substantially from everyday clinical practice, and the results therefore do little to inform clinical practice.

Topiramate has been compared with standard AEDs in one trial in which clinicians chose either carbamazepine or valproic acid as the preferred standard AED. The subgroup for whom carbamazepine was chosen as the standard drug had focal seizures and were randomly assigned to receive 600 mg carbamazepine daily, 100 mg topiramate daily, or 200 mg topiramate daily. For the analyses, data for the 100 mg and 200 mg topiramate groups were pooled. No difference was found between topiramate and carbamazepine for time to treatment withdrawal, time to

<table>
<thead>
<tr>
<th>Drug comparison</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>Drug for which event more likely (hazard ratio &gt; 1)</th>
<th>Outcome: hazard ratio (95% CI)</th>
</tr>
</thead>
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<tr>
<td><strong>Focal seizures</strong></td>
<td></td>
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<tr>
<td>Carbamazepine vs valproic acid</td>
<td>5</td>
<td>813</td>
<td>Valproic acid</td>
<td>1.00 (0.79–1.26)</td>
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<tr>
<td>Carbamazepine vs phenobarbital</td>
<td>4</td>
<td>519</td>
<td>Phenobarbital</td>
<td>1.60 (1.18–2.17)</td>
</tr>
<tr>
<td>Phenytoin vs valproic acid</td>
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<td>186</td>
<td>Phenytoin</td>
<td>1.23 (0.77–1.98)</td>
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<td>Phenytoin vs phenobarbital</td>
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<td>Unknown</td>
<td>Phenobarbital</td>
<td>1.97 (1.09–1.97)</td>
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<tr>
<td><strong>Generalised seizures</strong></td>
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<tr>
<td>Carbamazepine vs valproic acid</td>
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<td>Valproic acid</td>
<td>0.98 (0.61–1.11)</td>
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<td>Carbamazepine vs phenobarbital</td>
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<td>Phenytoin vs valproic acid</td>
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<td>Phenytoin</td>
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<td>Phenytoin vs phenobarbital</td>
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<td>Unknown</td>
<td>Phenobarbital</td>
<td>4.32 (1.77–10.6)</td>
</tr>
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Note that 95% CIs that include 1 indicate no statistically significant difference between the outcome measure of the compared AEDs.
first seizure, or the proportion of patients seizure free for the last 6 months of follow-up. Although this trial found no difference for these outcomes, confidence intervals are wide and the results do not confirm equivalence; hence, this trial falls short of providing data that informs a choice between carbamazepine and topiramate.

Initial monotherapy trials of oxcarbazepine compared it with carbamazepine.27,28 These trials found no difference between these two drugs, but lacked power to show equivalence. In addition, results of the largest trial were confounded by the exclusion of 70 of the 235 randomly assigned patients from the efficacy analyses.27

More recently, oxcarbazepine has been compared with phenytoin in two monotherapy RCTs29,30 and valproic acid in one monotherapy RCT.31 All three trials were of similar design, and lasted 56 weeks. Primary efficacy outcomes were the proportion of patients who were seizure free, and the primary tolerability outcome was time to withdrawal due to side-effects. None of these trials found a difference between oxcarbazepine and its comparators in the proportion of patients who were seizure free. Although no difference was found when compared with valproic acid for time to treatment withdrawal due to side-effects,31 when compared with phenytoin, oxcarbazepine fared significantly better for time to treatment withdrawal due to side-effects in both adults30 and children.31 Although no difference was found for the primary efficacy outcomes, these trials also lacked the power to exclude the possible existence of an important difference, and do not prove equivalence.

In summary, for patients with focal seizures, we have evidence to support a choice of carbamazepine from the standard AEDs. We have no reliable evidence that any of the newer drugs are either superior or inferior to carbamazepine or other standard drugs.

Idiopathic generalised epilepsies

Results from the Cochrane reviews of standard AEDs for patients with generalised seizures are also summarised in table 1. Trials included in these reviews recruited patients with generalised tonic-clonic seizures with or without other types of generalised seizure. Most trials predate the ILAE classification of epileptic syndromes;32 hence, in a large proportion of trials patients were classified according to seizure types but not syndromes. In addition, significant numbers of patients are likely to have been misclassified. For example, on closer inspection of trials comparing carbamazepine and valproic acid, a significant proportion of patients over the age of 25 years who presented with seizures were classified as having generalised seizures, which is extremely unlikely. It is more likely that these patients had focal seizures and had been misclassified. Meta-analysis of trials shows no significant differences between standard drugs for time to treatment withdrawal, time to first seizure, or time to 12 month remission. Existing data from RCTs do not inform a choice among standard AEDs for patients with an idiopathic generalised epilepsy. Guidelines recommend valproic acid as a treatment of first choice for patients with this type of epilepsy, supported by data from observational studies that indicate a good response, particularly for juvenile myoclonic epilepsy,33,34 as well as reports that indicate worsening of myoclonus and absence seizures for patients taking phenytoin or carbamazepine.31

There are few studies of the new AEDs in patients with an idiopathic generalised epilepsy. Lamotrigine is recommended in guidelines as an alternative to valproic acid,35 but there is no RCT evidence to support this use. Similarly, there is no RCT evidence to support the use of levetiracetam and no high quality studies to support the use of zonisamide. Topiramate has been compared with valproic acid in one trial, which has already been described above.30 No difference was found for the primary outcomes, although the results did not confirm equivalence, and fall short of informing a choice between topiramate and valproic acid.

Unclassified epilepsy

There is no evidence from RCTs to inform the management of unclassified epilepsy. Such patients are excluded from many trials. Guidelines recommend the use of broad-spectrum drugs such as valproic acid and lamotrigine (figure 2).

Long-term adverse effects of AEDs

AEDs have been associated with a wide range of chronic adverse effects that are often identified many years after a drug’s introduction into clinical practice. Of the new AEDs,
vigabatrin therapy is associated with irreversible, typically symptomless, bilateral loss of concentric visual fields in 40% of chronically exposed patients.50–52 Twice yearly visual-field assessments are recommended in patients continuing with therapy. With other agents available, vigabatrin should be used as a drug of last resort in adults with partial epilepsy. The efficacy of vigabatrin for infantile spasms,53 particularly when associated with tuberous sclerosis,54 has been shown. The drug still has an important role in paediatric practice, although visual-field loss paradoxically is difficult to reliably assess in children.

Recent concerns have focused on bone density and osteoporosis. Concern began with the discovery of high rates of osteomalacia in institutionalised patients with epilepsy who were taking AEDs long-term.46 There is, however, no evidence of higher fracture rates in patients not in institutions when compared with the general population, once fractures occurring during seizures are accounted for.44 Most,42–44 but not all,45,46 cross-sectional studies have found a reduction in bone-mineral density in patients with epilepsy who are taking AEDs. Because of their design, results of these studies are confounded and it is not possible to reliably untangle any potential effects of AEDs on bone health from other factors associated with epilepsy, such as reduced physical activity, diet, or comorbid illness. Whether there are differences in the effect on bone health of the newer drugs when compared with older agents is unclear. Consensus guidelines argue against screening with bone densitometry in patients whose only risk factor for osteoporotic fracture is epilepsy.47

Teratogenicity
The risk of teratogenic effects has an important influence on the choice of AED for women of childbearing age. Observational studies have consistently shown an increased risk of teratogenic effects associated with the standard drugs. However, studies have tended to be small and have used various designs, both prospective and retrospective, with few being population based. As a result, estimates have varied, although there seems to be a two to threefold increase in the rate of major fetal malformations compared with a background rate of 2–3%.46 Of the standard AEDs, valproic acid is of increasing concern because it is associated with a higher risk of congenital abnormalities, including neural-tube defects.48 There is also growing concern about developmental delay in children exposed to valproic acid in utero.49 In view of these concerns, recent guidelines recommend particular caution when prescribing valproic acid to women of childbearing age.50 Fewer data are available on the teratogenic effects of newer AEDs. To provide information about the teratogenic effects of new and standard AEDs, several pregnancy registers have been established. Lamotrigine is the new AED for which there is the largest amount of data, and interim results of the UK pregnancy register suggest that the risk of a major congenital abnormality associated with lamotrigine is low and similar to that of carbamazepine.51

Although use of valproic acid may be readily avoided in women with focal epilepsies, to do so may be more difficult in those with idiopathic generalised epilepsy. In these patients, lamotrigine may be effective, but some women may require valproic acid for adequate seizure control,52 which is an important consideration in pregnancy. The potential place for use of topiramate and levetiracetam in these patients is uncertain.

Unsuccessful monotherapy
Before considering alternative medication, consideration should be given as to whether the optimum dose has been reached. Seizure response and adverse effects should be used to guide therapy, rather than serum drug concentrations, for all drugs except phenytoin. In the case of phenytoin, the checking of serum concentrations may be helpful, although the therapeutic range is only a rough guide; many patients obtain seizure freedom with concentrations below this range, whereas others tolerate and require concentrations above this range. For patients who continue to have seizures despite an adequate dose of an AED, an explanation of non-compliance should be considered. Thought must be given as to whether the diagnosis of epilepsy is correct, whether the epilepsy syndrome has been correctly classified, and whether the appropriate AED for the epilepsy syndrome has been chosen.

The longer patients continue to have seizures after their initial diagnosis, the lower the probability of subsequent remission.53 Whereas about 70% of patients diagnosed with epilepsy can expect long-term remission,54 only 16% of patients who find the first drug to be ineffective in suppressing seizure activity (as opposed to poor tolerability) can subsequently expect to become free from seizures.55 Therefore, in patients who have seizures despite a good trial of their first AED, a cautious prognosis can be given. Patients who fail a second AED have a small chance of obtaining seizure freedom.56 Guidelines recommend that after efficacy failure of two appropriate AEDs, surgical options should be considered.57

Alternative monotherapy or combination therapy?
After monotherapy failure the physician has a choice: to add on a new therapy or to replace the current drug. The potential advantages of switching include the limiting of toxicity and the separate assessment of drugs. By contrast, polytherapy could offer theoretical advantages of more rapid seizure control and higher seizure-freedom rates through the exploitation of pharmacodynamic interactions. The first trial that specifically tried to compare add-on with alternative therapy has recently been published.58 After monotherapy failure, patients were randomly allocated to adjunctive therapy or alternative monotherapy, although the choice of drug and dosing strategy were chosen by the physician. In the assigned treatment groups no significant difference was found between time to assigned treatment failure or for the cumulative number of patients remaining seizure free for 12 months, with remission rates in both groups at about 15%. Recruitment was difficult and therefore the trial lacked the power to exclude a clinically important difference.

Uncertainty of whether alternative monotherapy or combination therapy is the best therapeutic option therefore continues. If seizure remission is achieved with combination
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therapy, AED withdrawal does carry a risk of return of seizures;54 remaining on combination therapy carries the modest chance that monotherapy with the second agent could give seizure freedom. Patients must be counselled about the potential benefits and risks, and should be allowed to control the decision-making process.

New AEDs as add-on treatments
Table 2 summarises the results of intention-to-treat analyses from systematic reviews in patients with drug-refractory localisation-related seizures. Although all these drugs show efficacy, caution should be used in comparing outcomes as populations differed and doses used varied.

AED combinations after monotherapy failure
There is no evidence in human beings to suggest that a particular combination of AEDs is more efficacious than another. A rational approach is commonly advocated; if two AEDs are used together, their combined effect will be greater if the known mechanisms of action are different. Unfortunately, mechanisms of action for AEDs are only partially known and are not universally agreed; subtle but significant differences may mean that combining drugs with similar mechanisms may be effective. Avoidance of combinations with pharmacokinetic interactions simplifies management. The putative modes of action of AEDs are outlined in table 3. For valproic acid, topiramate, gabapentin, and levetiracetam, a dominant mechanism of action has not been convincingly shown. Although the appropriate drugs for syndromic diagnosis should be used, rational therapy suggests avoiding combination therapy with two AEDs that have the same primary modes of action.

Conclusion
The evidence to support the prescribing of new AEDs is sparse, indicating that most RCTs answer questions focused on regulatory requirements rather than clinical use. A large pragmatic RCT (the Standard and New Antiepileptic Drugs [SANAD] trial), which is comparing new and standard AEDs, will report in the next 2 years and should partially address these concerns. In asbence of good evidence for the difference of efficacy of different AEDs, our practice will be guided by concerns about potential unwanted adverse effects. However, even here, poor methodology of studies hampers decision making. These issues particularly affect women of childbearing age.

In the future there is a need to improve the quality of clinical data on the efficacy and harm of AEDs. There is also a developing agenda in the area of pharmacogenetics which, once methodological issues are addressed, may help clarify choices from the availability of new AEDs.

Authors’ contributions
All authors contributed equally to this review.

Conflict of interest
DMcC, DC, and AM have received hospitality and/or sponsorship to attend conferences from Sanofi-Synthélabo, GlaxoSmithKline, Novartis, Pfizer, Jansen Cilag, and UCB Pharma. DC’s university department has also received research support from these companies.

Role of the funding source
No funding was received for this review.

Search strategy and selection criteria
The Cochrane Library (2004 issue 1) and the Cochrane Epilepsy Group controlled trials register were searched. The latter was compiled from searches of MEDLINE (1966–2004) as well as journal handsearching, which was undertaken by the Cochrane Epilepsy Group, and the Cochrane Collaboration as a whole. When found, results of systematic reviews were selected for inclusion. Where no systematic reviews were found, randomised controlled trials were selected.
References