Choice of anti-
which one to try first an
INTRODUCTION

The prevalence of treated epilepsy in the UK is about 80 per 100 000 people (Wallace et al. 1998). Antiepileptic drugs (AEDs) produce remission of seizures in 60–70% of people with epilepsy (Kwan & Brodie 2000) but many withdraw from AEDs because of lack of efficacy, an adverse effect, or both (Mattson et al. 1985; Marson 1997). The Holy Grail of epilepsy, an AED that is 100% effective but has no adverse effects or drug interactions, remains elusive. So how should we choose which AED to give first and, if that fails, which should be tried next? Choice of the first AED is crucial as many patients remain on that drug for many years (Lhatoo et al. 2001). This article is not intended as some foolproof ‘neurological recipe’, but rather as a guide based on current evidence, however imperfect, and the experience of success and failure over many years in a busy epilepsy clinic.

THE CHOICE

Compared to the physicians in the early twentieth century who had to rely on bromide salts, today we have a plethora of drugs for epilepsy from which to choose (Table 1). But choice, an attractive concept in theory, generates its own problems and choosing an appropriate AED is no exception. Given so many different options, how can the right AED be selected first? Guidelines, such as those produced by the Scottish Intercollegiate Guidelines Network (Fig. 1), provide options for first-line AED therapy based on available evidence. Several factors need to be considered, however, before reaching for the prescription pad.

LIMITATIONS OF CURRENT EVIDENCE

We are encouraged to practice evidence-based medicine but what do we do when the evidence is flawed or inadequate? After all, licensing of AEDs only depends on pharmaceutical compa-

Table 1 The available antiepileptic drugs (in the UK) and the indications for their use

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INDICATIONS FOR USE</th>
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<tbody>
<tr>
<td>Standard AEDs</td>
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<tr>
<td>Carbamazepine</td>
<td>First line for partial and generalized tonic clonic seizures</td>
</tr>
<tr>
<td>Valproate</td>
<td>First line for primary generalized, myoclonic and absence seizures, also used for partial seizures</td>
</tr>
<tr>
<td>Newer AEDs</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Add-on therapy for partial onset seizures</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Primary generalized and partial onset seizures</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Add-on therapy for partial onset seizures, also effective in primary generalized seizures including myoclonic seizures</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Partial and secondary generalized seizures</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Add-on therapy for partial onset seizures</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Generalized tonic-clonic and partial onset seizures</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Restricted to infantile spasms or refractory epilepsy</td>
</tr>
<tr>
<td>Old AEDs</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Generalized tonic-clonic and partial seizures, short-term seizure prevention and treatment</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Generalized tonic-clonic and partial seizures</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>Add on therapy for partial, tonic-clonic and absence seizures</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Add on therapy</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Myoclonic seizures</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Absence seizures</td>
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</table>

Scottish Intercollegiate Guideline Network recommendations for first-line AED treatment

- Carbamazepine, valproate, lamotrigine and oxcarbazepine can all be regarded as first-line treatments for partial and secondary generalised seizures
- Valproate and lamotrigine are drugs of choice for primary generalised seizures and should also be prescribed if there is any doubt about the seizure types and/or syndrome
- The adverse effect profiles should direct the choice of drug for the individual patient

Figure 1 Recommendations for first line Antiepileptic Drug (AED) therapy produced by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2003).
carbamazepine vs. lamotrigine in which patients started on such a steep dose escalation of the carbamazepine that it was not surprising many withdrew because of adverse effects in the early stages of the study (Brodie et al. 1995). In the later part of the trial, patient retention between the two AEDs showed no significant difference. Although many neurologists now use slow-release carbamazepine because it is less likely to produce dose-related adverse effects (Persson et al. 1990), it is not used in comparative trials with new AEDs.

Outcome measures
Comparison and synthesis of AED trials is complicated by the variety of outcome measures used. The most valid outcome would be the proportion of people seizure-free, as this is the outcome that, not surprisingly, correlates best with improved quality of life (Smith et al. 1995). But few trials use seizure freedom because it is such a rare outcome in the population used in trials. Other outcomes such as 50% seizure reduction, time to next seizure, or time to achieve 12 month remission from seizures, are used instead. More recently, data have been presented in the form of survival curves of people remaining on the AED over time on the assumption that people withdraw from AEDs either because they are ineffective or have intolerable adverse effects. This pragmatic outcome may not be perfect but seems as useful as any. Further information about the relative efficacy and tolerability can be obtained using a comparison presented as odds ratios with confidence intervals (Fig. 2). These data reinforce the clinical impression that, of the newer AEDs, those that are most effective as add on therapy seem to have more adverse effects with the possible exception of levetiracetam.

FACTORS TO CONSIDER WHEN DECIDING BEST FIRST LINE TREATMENT

Epilepsy as a symptom not a disease
It is worth remembering that significant numbers of patients have poorly controlled epilepsy because they are taking the wrong AED for their sort of epilepsy. Although it may not always be possible to define the exact epilepsy syndrome (ILAE 1989), an attempt should be made at classifying the patient as having either generalized or partial-onset seizures because this may be
crucial in avoiding AEDs which can exacerbate idiopathic generalized seizures, particularly myoclonic and absence seizures.

A careful history from the patient and a witness of the seizures, knowledge of the age of seizure onset, any characteristic time when seizures occur, provoking factors and an understanding of the pattern of EEG abnormalities that are seen in various syndromes are all essential. View assurances from patients that they have 'petit mal' with profound suspicion; they usually have complex partial seizures, not childhood absence epilepsy. If the patient presents with generalized tonic clonic seizures ask carefully about myoclonic, absence or complex partial seizures which they may fail to mention (King et al. 1998). If the EEG report suggests multifocal spikes or frontal spike and wave don't assume this means the patient has a form of focal epilepsy—these appearances may be seen in idiopathic generalized epilepsies.

Epilepsy syndrome and seizure type
Identification of the precise epilepsy syndrome is helpful because, although there is no good published evidence, most epilepsy specialists believe that some AEDs appear to be particularly effective in certain syndromes. Notable examples are:
• valproate in juvenile myoclonic epilepsy;
• carbamazepine in frontal lobe epilepsy;
• ethosuximide in typical absence seizures.

If the patient has none of these syndromes he or she will probably fall into one of three broad categories: idiopathic generalized epilepsy, localization-related epilepsy, or unclassifiable epilepsy. A number of different AEDs can be used in each of these categories (Table 1). Does the evidence help us to choose between them?

EVIDENCE FOR THE ‘STANDARD’ ANTIEPILEPTIC DRUGS
Ask most neurologists which of carbamazepine or valproate is preferred treatment for the idiopathic generalized epilepsies and which for the partial-onset epilepsies and they are likely to suggest valproate for the former and carbamazepine for the latter. Yet the Cochrane review (Marson et al. 2004) provides little support for this view, being only marginally in favour of valproate for generalized seizures (Fig. 3) in time-to-treatment-withdrawal with the confidence interval including one (indicating no significant difference). Does that mean we should use carbamazepine first in generalized seizures? Probably not. As explained in the review, misclassification of patients in the original trials (by inclusion of those with secondary generalized seizures with the primary generalized seizures) is likely to have confounded the result. Moreover, several of the studies only counted generalized tonic-clonic seizures and neglected to report any effect on myoclonic or absence seizures. In line with clinical experience, the review suggests that carbamazepine may be helpful in treatment of generalized tonic-clonic seizures in idiopathic generalized epilepsy, but valproate remains the preferred choice.

In partial-onset seizures the biggest trial gives some support to the use of carbamazepine ahead of valproate in complex partial seizures (Mattson 1992), though the number of patients seizure free at 1 year was not significantly different and there was no difference in effectiveness between the two drugs in secondary generalized seizures (Marson et al. 2004). In the Cochrane review of five head-to-head studies in partial epilepsy, carbamazepine was just superior to valproate (odds ratio 0.82 95% CI 0.67–1.00) in
THE NEWER ANTIEPILEPTIC DRUGS

A number of the newer AEDs now have a licence for monotherapy. These include lamotrigine and topiramate for partial seizures and generalized tonic-clonic seizures (both primary and secondarily generalized) and oxcarbazepine for partial and secondarily generalized seizures only. Are these better than carbamazepine and valproate as first-line treatment? This question is being addressed by the important UK National Health Service-sponsored study of Standard and New Antiepileptic Drugs (SANAD) (Fig. 4), the largest randomised study in epilepsy.

Pending the outcome of SANAD we are left with several new vs. old AED monotherapy studies, most of which have been sponsored by pharmaceutical companies, and with the limitations that have already been discussed. The UK National Institute for Clinical Excellence (NICE) has recently reviewed the evidence for the newer AEDs (NICE 2004) and has concluded that carbamazepine or valproate should continue to be used as first-line AEDs but that the newer drugs can be prescribed in the following circumstances:

• if there are contraindications to carbamazepine or valproate;
• if carbamazepine or valproate could interact with other drugs the patient is already taking (notably the oral contraceptive);
• if carbamazepine or valproate are already known to be poorly tolerated by the individual;
• if a woman is of childbearing age (see below).

If there is no good evidence on effectiveness upon which we can base our choice of first-line AED, can other information help?

**Does the mechanism of AED action matter?**

Our understanding of the mechanism of action of AEDs is incomplete (Walker et al. 2004). Many have several potential mechanisms including changes in sodium and calcium membrane channels and alterations in inhibitory neurotransmitter systems, in particular those of gamma aminobutyric acid (GABA). Sadly the mode of action seems to be little help in choosing an AED because the pathophysiology of individual epilepsies is so poorly understood.

AEDs can exacerbate seizures. Tiagabine or vigabatrin may trigger absence status epilepticus (Schapel & Chadwick 1996); carbamazepine or phenytoin can worsen myoclonic seizures. The former are powerful GABAergic agents, the latter modify sodium channel conductance, but it is not usually possible to predict adverse outcome on the basis of what is understood about the mechanism of action of an AED.

**Does age matter?**

Epilepsy affects people of all ages. There are two peaks of onset, in childhood/adolescence and in older people. Idiopathic generalized epilepsies tend to present in childhood and adolescence while focal epilepsies present at any age and predominate in later life. But there are exceptions and choice of AED should not be based on age alone.
Older people tend to have more comorbidity, to be on more medications, and to have slower rates of clearance of AEDs. The elderly are therefore at greater risk from drug interactions and the adverse effects of AEDs. In fact, there is little evidence about AEDs in the elderly; one study showed no difference between carbamazepine and lamotrigine in antiseizure effect but suggested that the latter may be better tolerated (Brodie et al. 1999). The result of a large veterin-antrial in the USA comparing carbamazepine, lamotrigine and gabapentin is awaited, though the omission of valproate from this study reduces its value and seems hard to justify (Ramsay et al. 2003). Personal experience suggests that in the frail elderly, carbamazepine is poorly tolerated even in low doses of the sustained release preparation, while the more robust elderly tolerate it reasonably well. Many elderly care physicians continue to favour phenytoin but complex pharmacokinetics make it difficult to use, particularly in those on multiple medications.

**Does gender matter?**
Contraception and childbearing are important factors in choice of AED. Several AEDs, listed in Table 2, induce the metabolism of oestrogen and progesterone and so reduce the efficacy of oral contraceptives and progesterone implants. While this can be countered to some extent by increasing the dose of the contraceptive, this does not restore full efficacy and, as the interaction appears to be unknown to many physicians (Shorvon et al. 2002), guidelines advocate avoiding enzyme-inducing AEDs as first choice therapy in young women (SIGN 2003; NICE 2004).

AEDs may affect reproductive hormones. Carbamazepine and phenytoin are reported to reduce levels of testosterone in men though the significance is unknown (Duncan et al. 1998).

**Table 2** Antiepileptic drugs that do and do not induce hepatic enzyme

<table>
<thead>
<tr>
<th>AEDs that induce hepatic enzymes</th>
<th>Non-enzyme inducing AEDs</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Primidone</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td></td>
<td>Tiagabine</td>
</tr>
<tr>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td>Vigabatrin</td>
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</table>

Valproate has been associated with hyperandrogenism (Vainionpää et al. 1999) and polycystic ovary syndrome (Isojärvi et al. 1996) but cause and effect in the latter has been disputed.

It is likely that all AEDs have teratogenic effects but data, particularly on the newer AEDs, are incomplete. It is lamentable that after so many years of use we still have only a rough estimate of the risk of major malformations with even the older AEDs because there were no rigorous postmarketing surveillance and large population-based prospective studies. Valproate seems to have the highest risk of major malformation of the ‘standard’ AEDs, and polytherapy regimens are associated with significantly higher risk than monotherapy (Kaneko et al. 1999; Samren et al. 1999).

Of the newer AEDs, lamotrigine is the only one that has been used in a sufficient number of pregnancies to establish that it is likely to have a risk of major malformation similar to carbamazepine and lower than valproate (Tennis & Eldridge 2002). Recent data on phenytoin suggest that the rate of major malformation is not as high as was once thought, as it was often prescribed as part of polytherapy and in high doses (Holmes et al. 2001).

If we have insufficient data on major malformation risks, even less is known about the risk of minor malformations, and the effect of AEDs in pregnancy on the intellectual development of the child. Recent studies point to a possible association between valproate in pregnancy and learning difficulties or behavioural disorders in children (Adab et al. 2001; Dean et al. 2002), but these are retrospective, potentially biased data, and the results of prospective studies are awaited. Despite limitations of the available data there is sufficient concern for current guidelines to advise avoiding AED polytherapy and caution with the use of valproate in women planning a pregnancy. Valproate is, however, an extremely effective AED and the choice of AED has to be that of the woman after a thorough discussion of the risks and benefits.

**Co-morbidity**
Most people with epilepsy are healthy but a significant number have additional medical or social problems. People with learning difficulties have a higher risk of epilepsy than those without but few studies have studied this population separately. Moreover, AEDs can be associated with adverse behavioural effects, particularly in people with learning difficulties. Mental health
Disorders such as depression are often associated with epilepsy (O'Donoghe et al. 1999; Harden 2002). Some AEDs, e.g. topiramate seem to have more of a tendency to trigger mood changes and should be used with caution if the patient is known to be at risk (Schmitz 1999). It can be argued that AEDs such as carbamazepine, which is also used for its mood-stabilizing properties, may be particularly beneficial where this is an issue. But often it is a case of trial and error before the best AED is found.

On a more positive note, AEDs can be helpful in the treatment of other conditions, e.g. valproate and topiramate are used in the prophylaxis of migraine so patients with both epilepsy and migraine may benefit from treatment with one of these AEDs ahead of other agents.

Most AEDs are metabolized in the liver but some, notably gabapentin, are excreted exclusively via the kidneys. In patients with impaired renal function it is easier to avoid gabapentin. Liver function has to be severely impaired before there is any effect on the metabolism of AEDs but, because of its association with fulminant hepatic failure, valproate is probably best avoided in those with active liver disease.

Potential adverse effects

All AEDs may have adverse effects (Table 3); knowledge of these can be helpful when selecting an AED but it must be remembered that adverse effects only affect a small proportion of people taking a drug so weighing up the benefit of the drug against its potential harm is important, e.g. a young man with juvenile myoclonic epilepsy is very likely to improve on valproate and the risk of significant weight gain is only about 10% (Biton et al. 2001). Giving him good dietary advice and monitoring his weight is probably a more appropriate course of action than avoiding valproate altogether. Alternatively a young woman who is already overweight and who has menstrual irregularity may choose to try lamotrigine if she is planning to conceive, or topiramate, neither of which is associated with weight gain, as the first-line AED

Drug interactions

These are important to consider when prescribing AEDs. Hepatic enzyme induction (listed in Table 2) reduces plasma levels of oral contraceptives and warfarin (the latter is not affected by oxcarbazepine). Inhibition of metabolism of AEDs by other drugs can lead to toxicity if the interaction is not anticipated, e.g. co-prescription of carbamazepine with erythromycin, diltiazem, verapamil, fluoxetine or valproate.

Using an AED with fewer drug interactions is particularly important in the elderly who are more likely to be taking other medications.

Dosing schedules and preparation of AED

Concordance with medication is more likely if the drug can be given as a once- or twice-daily dose rather than more frequently. Most AEDs can be given in two divided doses, and some once daily. Others, e.g. gabapentin are best given three times daily. Sustained release preparations of AEDs can be useful in reducing the dose frequency and this is particularly so with carbamazepine where there is a lower risk of adverse effects if the sustained release preparation is used (Persson et al. 1990). The value of sustained release valproate is less apparent because the standard preparation can be given twice daily. For patients who have difficulty swallowing large tablets, and those fed via gastrostomy tube, the availability of

Table 3 Important adverse effects and disadvantages of the available antiepileptic drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DISADVANTAGES IN NORMAL DOSE</th>
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<tbody>
<tr>
<td><strong>Standard AEDs</strong></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Rash, hyponatraemia, drowsiness, drug interactions</td>
</tr>
<tr>
<td>Valproate</td>
<td>Weight gain, tremor, teratogenicity</td>
</tr>
<tr>
<td><strong>Newer AEDs</strong></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Few</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Rash</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Occasionally exacerbates seizures</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Rash, hyponatremia, drug interactions</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Agitation, can exacerbate seizures</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Paraesthesiae, weight loss (advantageous for some), cognitive effects</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Irreversible visual field defects</td>
</tr>
<tr>
<td><strong>Old AEDs</strong></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Rash, acne, difficult pharmacokinetics and drug interactions</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Sedation, cognitive impairment in elderly</td>
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</table>
a liquid preparation of an AED will influence the choice.

**Cost**

There is a huge variation in the cost of AEDs (Fig. 5). In many parts of the world, cost limits the choice of AED to phenobarbitone or phenytoin. But even for those of us fortunate enough to have more choice it is important to be aware of the cost of these drugs and to use them as cost-effectively as possible.

**WHICH DRUG FIRST?**

It is clear that choice of the best first AED is not a ‘onesizefitsall’ scenario. Figure 6 outlines a proposed scheme. The first step is to diagnose the epilepsy syndrome. If this is difficult then at least try to ensure the patient does not have juvenile myoclonic epilepsy, which can be exacerbated by carbamazepine and phenytoin, or absence seizures, which are likely to be worsened by carbamazepine, tiagabine, vigabatrin or phenytoin. If it is not possible to classify the epilepsy, the choice of AED is limited to valproate, lamotrigine or topiramate, all of which are effective across a wide range of seizures. Levetiracetam is likely to be added to this list in the future. In the idiopathic generalized epilepsies, valproate

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**Figure 5** Comparative cost of one month treatment in a standard daily dose with different antiepileptic drugs.

**Figure 6** Suggested algorithm for selection of the first antiepileptic drug.
remains the drug of first choice unless there are specific contraindications.

Younger women with unclassified or idiopathic generalized epilepsy are a particularly difficult group. Seizure-freedom is always important, but young people trying to establish themselves in work, wanting to learn to drive, often leaving home for the first time, are very sensitive to the 'social' consequences of seizures. Giving them the most effective AED is therefore particularly important. Valproate is relatively contraindicated in young women because of teratogenicity, association with menstrual irregularity, and 'cosmetic' adverse effects (weight gain for example). I discuss the merits and disadvantages of valproate and lamotrigine with young women, and often start them on lamotrigine but switch to valproate if seizure control is not established quickly. If levetiracetam lives up to its promise in idiopathic generalized seizures and proves safe in pregnancy it could be used as an alternative to valproate but it will be several years before we know.

In localization-related (focal) epilepsy, carbamazepine remains the drug of first choice and the modified release preparation is helpful in reducing dose-related adverse effects. If the patient is a young woman who uses the oral contraceptive it is important to discuss the risks of oral contraceptive failure and alternative contraceptive methods. If she still wishes to take an oral contraceptive, an AED that does not induce hepatic enzymes, usually lamotrigine, can be justified. In the elderly I often avoid carbamazepine as first-line treatment because, although the evidence that it is less-well-tolerated is slim, in my experience this is often the case, particularly in those with cognitive impairment. I usually start older patients on valproate, substituting this with lamotrigine if the seizures prove refractory or adverse effects are troublesome.

**WHAT TO DO WHEN FIRST LINE TREATMENT FAILS**

When the first-line AED fails it is important to review the diagnosis of epilepsy. Most AEDs are effective and no response should lead one to question the diagnosis. Is this really epilepsy? Could the events be acute symptomatic seizures triggered by alcohol, or psychogenic non-epileptic attacks? If they are seizures, has the AED appropriate for that epilepsy syndrome been chosen? Is the patient taking the AED? Or does the patient have a structural lesion such as cortical dysplasia or a tumour that has been missed on the MR scan?

Failure to respond to the first AED has significant implications. Provided the diagnosis is secure and the patient is taking the drug, such failure is an early indication of epilepsy which will be difficult to control (Kwan & Brodie 2000).

**Are two drugs better than one?**

For 25 years AED monotherapy has been accepted as the norm. Proponents of monotherapy argue that a person on a single AED experience fewer adverse effects, but a recent study of alternative monotherapy vs. adjunctive therapy with a second AED, although limited in power, showed no difference between the two options as measured by retention on treatment, seizure freedom or adverse effects (Beghi et al. 2003). Polytherapy increases the risk of drug interactions, e.g. carbamazepine toxicity with the addition of valproate, and the risk of teratogenicity, and for these reasons most epilepsy specialists still prefer monotherapy. Can two AEDs ever work as synergists with supra-additive effects? Results from a substitution study have been interpreted to show a synergistic effect when lamotrigine is added to valproate (Brodie & Yuen 1997). While clinical experience suggests this is a useful combination, it has not been subjected to a rigorous randomised controlled trial. When the first-line AED has failed most epilepsy specialists recommend attempting treatment with at least one other AED as monotherapy before trying combinations of AEDs.

**In what order?**

If a patient fails to show any improvement, or only partially responds to the first AED in maximum tolerated dose, then a second appropriate AED should be chosen. The second AED is introduced alongside the first with a gradual dose escalation until the maximum tolerated dose is reached, or the seizures stop at a lower dose. If the second AED provides a remission in seizures, gradual withdrawal of the first AED may be attempted. If there is no improvement or if there is an exacerbation of the seizures, the second AED is usually tailed off before another is introduced alongside the first. Although there is no good evidence to support this way of adding a new AED before removing the original AED, it does avoid the difficulty of determining which of two drugs is the culprit if seizures escalate as one drug is decreased while the other is introduced. If there is perceived to be a high risk of seizures as one AED is withdrawn (e.g. patients with frequent seizures, if the AED that is being withdrawn has improved but not abolished seizures, if someone is having
sleep-related seizures, and is sleeping alone and thought to be at risk of sudden unexplained death in a seizure), covering the withdrawal and early introduction of the second AED with a short course of clobazam can be an option.

**Standard AED or newer AED?**
Choice of the second monotherapy drug will depend on the criteria outlined above, with the epilepsy syndrome being the main determinant. There are no satisfactory sequential monotherapy studies to help choose between the possible alternatives. In the idiopathic generalized epilepsies options are limited. When lamotrigine is used as the first AED and the syndrome includes absence and myoclonic as well as generalized tonic-clonic seizures, valproate, topiramate and, more recently, levetiracetam are likely to be effective alternatives. Choice between these will be guided by considerations already discussed for first-line therapy. If the patient only has absence seizures ethosuximide can be used. If valproate fails as the first AED an observational study suggested that lamotrigine monotherapy is unlikely to be successful (Nicolson et al. 2004) and topiramate or levetiracetam should probably be prescribed if monotherapy is preferred. With generalized tonic-clonic seizures alone the choice is wider and includes carbamazepine or oxcarbazepine in addition to the above.

In partial-onset seizures the choice of alternative monotherapy is even more difficult. If carbamazepine is effective against seizures but poorly tolerated due to sedation it is probably worth trying oxcarbazepine or lamotrigine next. If carbamazepine fails to control seizures levetiracetam or topiramate are likely to be more powerful than gabapentin or lamotrigine if evidence from add-on studies can be extrapolated to second-choice monotherapy use (Fig. 2), and valproate remains an option.

**When should combination therapy be used?**
It is not possible to achieve a remission with monotherapy in everyone with epilepsy. After trying at least two first-line appropriate AEDs in monotherapy, it is reasonable to consider combination therapy. Choice should again be guided by the type of seizure and informed by response to the AEDs used in monotherapy. Occasionally the use of two AEDs will be used in preference to one, e.g. in juvenile myoclonic epilepsy when tonic-clonic seizures have been controlled with lamotrigine but myoclonic seizures persist, addition of clonazepam before changing to valproate, topiramate or levetiracetam may be preferred, or ethosuximide may be added when absence seizures fail to respond to the first AED.

**Are certain combinations better than others?**
It has been suggested that some combinations of AEDs may be more effective than others and a concept of ‘rational polytherapy’ has evolved, backed, it must be said, by very little hard evidence. Examples of ‘rational’ polytherapy have been suggested as:
- the use of two AEDs with different mechanisms of action, e.g. sodium channel blocker (carbamazepine) with a GABA-ergic agent (valproate);
- the use of two AEDs with pharmacokinetic interactions, e.g. valproate and lamotrigine (enabling lower doses of lamotrigine to be used);
- avoidance of combinations with similar mechanisms of action and/or unhelpful pharmacokinetic interactions, e.g. carbamazepine and phenytoin.

Choosing AED combinations on the basis of their mode of action sounds attractive but, because our understanding of the mechanism of action is incomplete, the first suggestion above is of little practical use in choice of drug combinations. Beneficial pharmacokinetic interactions may save money on drug costs but that does not equate to evidence of improved efficacy. Lamotrigine and valproate do appear to be a ‘good’ combination, particularly in certain idiopathic epilepsies (Deckers et al. 2000) but is that because of their pharmacokinetic interaction or an unknown pharmacodynamic interaction? Conversely, lamotrigine with carbamazepine seems, at least from personal experience, to be a combination associated with a high risk of adverse effects, maybe because both act on sodium channels, and it must be remembered that polytherapy increases the risk of teratogenicity, for example the combination of valproate and lamotrigine seems to be particularly teratogenic (Tennis & Eldridge 2002).

Of the older AEDs, clobazam can be very effective as an ‘add-on’ AED, although tachyphylaxis limits its use (Montenegro et al. 2001) and, before the advent of the newer AEDs, carbamazepine and valproate were often combined in partial onset seizures with considerable success.

Meta-analysis of add-on studies of newer AEDs in partial-onset seizures (short-term, licensing-
led trials) has shown no significant difference in either efficacy or tolerability between them (Marson 1997). The trials do, however, point to an association between effectiveness and higher risk of withdrawal (presumably due to adverse effects). Levetiracetam appears to be both efficacious and well tolerated for the most part and works across a wide range of seizure types. For these reasons it may be used ahead of other ‘new’ AEDs in add-on therapy, leaving those AEDs with apparently lower efficacy and more troublesome adverse effects until later. Seizure exacerbation or behavioural problems noted recently with levetiracetam need to be remembered if this is done.

IF COMBINATION THERAPY FAILS ...

People with epilepsy appear to fall into one of three groups:

- those with seizures easily controlled with one appropriate AED, often in a low or standard doses;
- those in whom changing or combining AEDs eventually achieves a remission;
- those in whom remission is unachievable with current medication - in this group surgery should be considered and, if that is not an option, going back to the AED/s that gave the optimum control of seizures with the minimum of adverse effects is best.

The number of AEDs now available for mono and combination means that it can be years before someone can be said to have tried all available AEDs in monotherapy, and it is not possible to try all the potential combinations. It seems likely that some of the newer AEDs will be sidelined over time (e.g. vigabatrin because of its tendency to cause visual field defects) and only the most effective with the best adverse effect profile will be widely used.

CONCLUSIONS

- The recent rush of ‘new’ AEDs onto the market has increased patient and doctor options in the treatment of epilepsy.
- The automatic choice of valproate for generalized seizures and carbamazepine for partial onset seizures is now being questioned, but we still have surprisingly little good evidence upon which to base decisions about choice of first AED. Such evidence as there is provides no good reason to avoid carbamazepine or valproate in the majority of patients; both are effective drugs that are, in the most part, well tolerated.
- There are groups of patients, for example women planning a pregnancy and older people, in whom there may be reasons for using alternative AEDs because of the risk of adverse effects and drug interactions with the standard AEDs. It is to be hoped that results of studies in progress such as SANAD will provide more information in the near future.
- If the choice of first AED is difficult, then what to choose when the first fails is even more challenging. Current guidelines recommend treatment with a single AED but no studies have addressed which AED is most likely to succeed when the first has not. Meta-analysis of add-on trials of the newer AEDs shows no significant difference between them, and there are no good data comparing standard with new AEDs in this situation. Of the newer AEDs most of those with better antiseizure action appear to have more adverse effects.
- In the end one has to make an assessment of the patient as an individual, weighing up what is known (and what is not) about the risks and benefits of the available AEDs, explaining your choice to the patient and their general practitioner and being prepared to change if the first AED proves ineffective.
- Letters from the epilepsy specialist need to include warnings about common adverse effects and action to take should these occur or if the drug of first choice fails. Good communication between physician and patient and between primary and secondary care is essential for steering the difficult course between the Scylla of uncontrolled seizures and the Charybdis of AED-induced adverse effects.
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REFERENCES