INTRODUCTION
Epilepsy is common, with a lifetime prevalence of 2–5% of the general population (Goodridge & Shorvon 1983a; Goodridge & Shorvon 1983b, Shorvon 1990) and a point prevalence of between 4 and 8 per 1000 (Hauser et al. 1993). Epilepsy represents a significant fraction of the workload for most neurologists, and indeed, never has specialist input been more necessary as the choice of antiepileptic drugs (AEDs) continues to grow: eight new AEDs have been licensed for use in the UK since the late 1980s, with the promise of more to come (Bialer et al. 2001). Despite these recent additions to the ranks of available anticonvulsants, epilepsy remains both stigmatizing and debilitating for many of those with the disorder (Reynolds 1990).

This article deals with a number of issues surrounding the newer drugs. We will look at the certainties surrounding the older drugs, the possibilities surrounding the newer ones, and the work that still has to be done. With decisions about healthcare having increasing focus on cost, it is helpful to ensure that society is getting good value for money from the use of the new AEDs. Our main discussion will address the changes in AED use over the last 15 years: have the newer AEDs made a genuine difference to patient care, or is their increasing use a product of clever pharmaceutical marketing?

THE PAST
History of AED development
In the mid 1970s, AED therapy still relied on the barbiturates, phenytoin, carbamazepine, and...
It was quickly realized within the pharmaceutical industry that any effective AED would have a large potential pool of patients, many of whom would require lifelong therapy. Much of the development of the newer AEDs began in the 1960s in pursuit of the holy grail – an AED that is more efficacious but with fewer systemic, neurological, and psychological adverse effects than those already available. This produced eight new AEDs licensed for use in the last decade of the twentieth century, which were quickly taken up by epilepsy specialists and neurologists. By 1992, the new AEDs represented only 7% of prescriptions for people with epilepsy in the Mersey Region, but accounted for 39% of their total drug costs (Jacoby et al. 1998). The last nine years have seen this faith in the new drugs in large part repaid. Of those that have at some point been licensed,
only vigabatrin (Eke et al. 1997) and felbamate (Pellock & Brodie 1997) have adverse long-term safety records. Neither are now being used routinely in adult practice. But in terms of efficacy, the picture is still unclear.

**AED clinical trial programmes**

The design of clinical trials of new AEDs is dictated by the recognized risks of epilepsy (Cockerell 1994). Ethical constraints ensure that, since monotherapy with an ineffective AED is potentially dangerous, each novel AED is tested as an add-on treatment for refractory seizures. Trials are initiated and run by the pharmaceutical industry to satisfy the demands of various worldwide licensing authorities, the question usually being asked, ‘Is this drug better at inhibiting seizures than placebo?’ Because quicker is usually better (or at least cheaper), ethics and economics combine to ensure that any potential new AED will be called upon to prove its worth in short-term parallel-group studies of refractory patients - often with multiple seizure types - at high dose and with rapid titration rates. Immediately, this makes the vast majority of these studies of questionable relevance to the typical patient with epilepsy (who will require long-term AED monotherapy). Systematic reviews have been used to try and compare the data from individual trials (see below), and while they are a useful tool for summarizing large amounts of reliable information about the effects of medical treatments, undertaking such reviews cannot make up for the absence of studies to better influence clinical practice. But at least the reviews can be used to highlight this problem and to inform the research agenda for both clinicians and industry.

Once the AED has been shown to reduce seizures as an add-on therapy, companies are then in a position to assess its efficacy as monotherapy. The 1988 ILAE Commission on Antiepileptic Drugs concluded that comparative monotherapy trials should be set up to detect equivalence with an existing first-line AED, i.e. be designed to generate confidence intervals around efficacy estimates that are narrow enough to statistically exclude ‘clinically important differences’ (what constitutes an ‘important difference’ is a clinical rather than a statistical matter and is open for debate) (Commission on Antiepileptic Drugs 1998). The Commission suggested that a new drug could be considered a first-line agent if it was shown to have equivalent efficacy but be better tolerated than a standard drug. Second-line status would be accorded to a new drug showing equivalent efficacy and tolerability to a standard drug. But, although this outlook may be acceptable to clinicians, it is of no help in getting a US licence for a potential new product. While European regulatory authorities are willing to accept evidence of equivalence as adequate for licensing an AED monotherapy, the USA’s Food and Drug Administration is not. The arguments for such a
stance are outlined by Leber (Leber 1989), but this leads to a considerable divergence between the needs of the pharmaceutical industry and the needs of the clinician: to gain a license, the industry is required to design and undertake trials that demonstrate the product is better than something – almost anything, in fact.

A variety of monotherapy trial designs have been used for US drug licensing purposes. One approach is to compare high dose monotherapy with low dose monotherapy (sometimes referred to as a pseudo-placebo) in patients with refractory epilepsy (Sachdeo 1997). This is a clinical irrelevance, and there are ethical concerns about giving low dose monotherapy to patients whose seizures were previously uncontrolled by standard AEDs. Even more worrying is the ‘surgical paradigm’ where patients undergoing presurgical evaluation have their AEDs withdrawn before being randomised to receive either placebo or the potential AED under study (Schachter et al. 1999; Bourgeois et al. 1993; Bergey et al. 1997). While patients are protected by continuous monitoring and application of protective trial exit criteria over short periods of time (measured in hours), the data provided by this type of trial are again of no clinical relevance, and the potential risks cannot be ignored. Only once the monotherapy studies are completed is the new AED then tested on specific subgroups of patients with epilepsy: the elderly, children, or patients with learning disabilities, in order to further define its use.

So if premarketing trials don’t help the busy clinician, is the system set up to provide good postmarketing guidance? The ideal way to ascertain any benefits from individual AEDs is to be by head-to-head comparisons, but while the financial imperative requires that a product is licensed, there is little incentive for the companies to obtain comparative data once the compound is let loose in the marketplace – despite the fact that such comparisons are necessary to inform clinical practice. One trial attempting to address this issue by comparing established with new AEDs in a pragmatic way, is the SANAD study (Standard and New Antiepileptic Drugs) funded by the UK National Health Service R & D programme (NHS R & D Health Technology Assessment Programme March 2000). Results are not expected for some years, and until then we have to deduce best practice from studies that are designed, financed, and run, by the pharmaceutical industry.

But can we blame the pharmaceutical industry? It would be surprising for any commercial organization to suddenly adopt an entirely altruistic approach. If society (or we as its neurological representatives) require a league table of AEDs, then perhaps it is our duty to direct the necessary studies and gain funding from health care providers whether or not we have industry support.

The new AEDs: how do they compare with the older AEDs (Table 2)

Monotherapy

The place of the newer AEDs as monotherapy depends on direct comparisons between the subject drug and an older counterpart. Changes in trial design mean that direct comparison of the trial data for old and new AEDs is difficult.
A few trials have compared the effects of standard AEDs in broad populations of patients, for example in patients with partial onset seizures (Mattson et al. 1985; Mattson et al. 1992), patients with generalized onset seizures (Wilder et al. 1983), or patients with generalized or partial onset seizures (Heller et al. 1995; Richens et al. 1994). Such trials have failed to find convincing overall differences between treatments, and also any convincing evidence to support the belief that governs our current practice: namely that carbamazepine has a greater effect for patients with partial onset and valproate for generalized onset seizures (Marson 2000). For the reasons outlined above, randomised and blinded direct monotherapy comparisons between and among AEDs are relatively rare. In this section we will look at each AED in turn, and examine the data supporting any demonstrably better efficacy than their older counterparts.

### Lamotrigine

Lamotrigine has been compared with carbamazepine in three randomised controlled trials (Brodie et al. 1995; Reunanen et al. 1996; Brodie 1998). The largest of these trials recruited 260 patients with partial onset seizures or generalized tonic clonic seizures, and was of 42 weeks duration. While significantly more patients remained on lamotrigine, there was a trend towards lamotrigine being less efficacious for some outcomes. However, the studies lacked the power to exclude the possibility of important efficacy differences.

### Gabapentin

Gabapentin and carbamazepine have been directly compared in one monotherapy trial recruiting patients with partial seizures (Chadwick et al. 1998). This was of 24 weeks duration, with 292 patients randomised to carbamazepine 600 mg/day, gabapentin 300 mg/day, gabapentin 900 mg/day, or gabapentin 1800 mg/day. The primary outcome was ‘time to exit’, and reasons for exit included: a single tonic clonic seizure; three complex partial seizures; or status epilepticus. For this outcome, no statistical difference was found between carbamazepine and 900 or 1800 mg of gabapentin per day. Adverse events were more common in the carbamazepine group. Although this trial met the regulatory needs of the pharmaceutical industry by finding a difference in efficacy between differing doses of gabapentin, the protocol did not at all reflect everyday clinical practice, and the results do little to inform it.

### Vigabatrin

Vigabatrin has been compared with carbamazepine in three monotherapy trials (Kal Vaughan et al. 1995; Chadwick 1999; Tanganelli & Regesta 1996). The largest trial recruited 459 patients randomised to vigabatrin or carbamazepine for 52 weeks. The trial was run
in a double-blind manner, although, in an attempt to mirror clinical practice, the dose was increased according to clinical need. The results showed no significant difference between drugs for the primary outcome (time to treatment failure), or for the time to 6 month remission. Patients taking vigabatrin had significantly earlier first seizures post randomization, and were significantly more likely to have vigabatrin withdrawn due to lack of therapeutic effect, whilst carbamazepine was significantly more likely to be withdrawn because of adverse effects. This trial failed to find evidence to support the use of vigabatrin as monotherapy, and in view of the subsequent description of vigabatrin-associated visual field abnormalities, it is unlikely to be used readily outwith treatment of specific childhood epilepsy syndromes (Appleton 1993; Vigabatrin Paediatric Advisory Group 2000).

**Topiramate**

While topiramate has been tested in a monotherapy trial comparing 100 with 1000 mg per day (Sachdeo 1997) (providing evidence of efficacy as monotherapy), no direct head to head comparisons with any other AEDs have been published, although one trial should report soon.

**Oxcarbazepine**

Oxcarbazepine was licensed in the 1990s for monotherapy in some European countries following monotherapy trials comparing it with carbamazepine (Dam et al. 1989). Close scrutiny of these trials, however, shows they do not provide firm evidence on which to recommend monotherapy with oxcarbazepine: not only did the trials lack the power to exclude the possibility of important differences, but the results of the largest trial were confounded by the exclusion of 70 of the 235 randomised patients from efficacy analyses (Dam et al. 1989).

More recently, three monotherapy trials of oxcarbazepine have been run using either phenytoin (Bill et al. 1997; Guerreiro et al. 1997) or valproate (Christie et al. 1997) as comparators. All three were of similar design, lasting 56 weeks, with none finding a difference between oxcarbazepine and its comparators in the proportion of patients rendered seizure-free. When compared with phenytoin, oxcarbazepine fared significantly better for time-to-treatment withdrawal due to adverse effects in both adults (Bill et al. 1997) and children (Guerreiro et al. 1997), whilst no such difference was found when compared to valproate (Christie et al. 1997). Although no difference was found for the primary efficacy outcomes, these trials lacked the power to exclude important differences, and do not prove equivalence.

**Adverse effect data**

Adverse effect data from the add-on trials are not useful in helping us compare the new with the older drugs; adverse effects from the drug itself are impossible to separate from those generated by interactions (both pharmacokinetic and pharmacodynamic). We would argue then that the monotherapy studies are the best basis for this assessment. The enhanced tolerability in head-to-head comparisons has already been outlined above. Whether this is enough to justify a wholesale change in prescribing policies is a matter of debate. Again, the data from SANAD will be helpful in yielding useful comparisons of the risk of severe and dose-limiting adverse effects.

**Safety in women**

Women with epilepsy have reduced fertility compared to their female siblings without epilepsy. In addition they run an increased risk of abnormal ovarian function, including anovulatory menstrual cycles and polycystic ovaries. Such dysfunction may be more common in women on sodium valproate (Isojarvi 1996). There is widespread and established recognition of the teratogenic effects of AED exposure (Yerby & Collins 1997). Phenytoin, carbamazepine, and the barbiturates have all been associated with some form of congenital abnormality (Yerby & Collins 1997). In addition, there is an increasing feeling that prenatal exposure to valproate may be associated with a reduction in IQ (Adab et al. 2001). While this has so far been shown only with retrospective data, prospective data are needed to assess how much of this is a drug effect, and how much can be attributed to the underlying epilepsy syndrome, maternal seizures, or other as yet unidentified factors.

**Add-on therapy**

The cleanest way to ascertain any benefits from individual AEDs has to be by setting up head-to-head comparisons. Each of the drugs licensed has been successfully put through the
add-on trial phase, but the only conclusion that can be drawn is that all are better than placebo at reducing seizure counts when given alongside other AEDs. As already pointed out, the add-on trials have a number of important limitations when it comes to informing clinical practice. Comparisons are made with placebo rather than with each other or standard treatments, the trials are of short duration (12–20 weeks) and therefore provide no reliable evidence about long-term effects, and the outcomes used (typically a 50% or greater reduction in seizure frequency) are of questionable clinical utility. However, when these drugs are licensed, this is the only available evidence of their effects.

Attempts have been made to draw some conclusions from the large number of trials by carrying out systematic reviews that summarize the evidence (Marson et al. 1997; Castillo et al. 2000; Chadwick & Marson 2000; Chaisewikul 2000; Ramanathan et al. 2000; Jette et al. 2000; Marson et al. 2001).

For many of these drugs, a range of doses was tested and where possible in the systematic reviews, estimates of the proportion of patients responding to individual doses are provided, as well as crude overall estimates that ignore the effect of dose. These systematic reviews provide evidence of effect for all the marketed new AEDs, and can be used to make broad comparisons among drugs. It must however, be borne in mind that the primary comparison made in the original trials was between new drug and placebo, and hence any comparison made between drugs is an indirect rather than a randomised one. Due to wide and overlapping confidence intervals no definite differences between drugs can be found. Substantial differences may still exist, but this requires exploration in future trials.

The outcomes statistic quoted in these reviews is the odds ratio and the relative risk, and such relative estimates (particularly the odds ratio) can be difficult to interpret and put into context. Measures of absolute benefit, for example the ‘number-needed-to-treat’ may appear easier to understand, but have a number of limitations, particularly when used to express the results of a meta-analysis. Others have used data from systematic reviews of new AEDs to generate estimates of number-needed-to-treat and have suggested that differences are found between some of the new AEDs when indirect comparisons are made, but the methods used have been flawed (Elferink & Van Zwieten-Boot 1997) and based on analyses using selected subgroups of patients (Anonymous 2001).

**Ease of use**

The pharmacokinetic profile of the established
AEDs has been well documented (Brodie & Dichter 1996; Dichter & Brodie 1996; Table 3). The barbiturates and phenytoin are potent hepatic enzyme-inducers, which renders them liable to produce many drug–drug interactions. The same can be said of carbamazepine, which, in addition, produces an unpredictable auto-induction of metabolism. Sodium valproate, by contrast, interacts with the hepatic cytochrome P450 system to inhibit the metabolism of some other drugs. Given these activities, it is not difficult to see that the older drugs have many problems. Not only can the efficacy of other drugs (such as the oral contraceptives) be affected by their use, but the extent and nature of their mutual interaction may require careful monitoring (Brodie & Dichter 1996).

On the other hand, the pharmacokinetic profile of the newer AEDs is much more stable. Drug level monitoring is rarely necessary – or helpful. They have much less tendency to interact. Vigabatrin, gabapentin and tiagabine have no recognized important pharmacokinetic interactions with other drugs (Dichter & Brodie 1996). The starting doses and titration rates of topiramate and lamotrigine may differ depending on concomitant treatments (Dichter & Brodie 1996), but these interactions are predictable and easier to plan for, because neither new drug significantly affects the metabolism of any baseline AEDs. As a result, the use of these drugs in combination is easier. Only topiramate and oxcarbazepine among the new AEDs enhance the breakdown of hormones in oral and depot contraceptives (Brodie and French 2000). The addition of topiramate to regimens including digoxin may also require care.

While the older drugs have multiple modes of action, affecting a wide range of neurotransmitters and receptors, the newer AEDs each tend to have a narrower spectrum of action, bringing ‘rational polypharmacy’ closer. However, the prospects for achieving an evidence base for this treatment strategy are at best slim. If head-

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Effect of Add-on drug (top row) on concentration of baseline AED (first column): o, no effect; Dec, decreased concentration; Inc, increased concentration; Un = unpredictable effect; ?, Uncertain effect or no data.

Table 3 Pharmacokinetic interactions between antiepileptic drugs
to-head monotherapy comparisons are difficult enough to obtain, how much more difficult will it be to directly compare AED combinations, which are by definition more numerous?

**THE PRESENT**

**Monotherapy: which drug?**

In the UK, the answer is a simple one – let the SANAD study make up your mind for you! Given the wide inclusion criteria and the pragmatic study design, almost any consenting patient can be randomised. Patients thought to have localization-related epilepsy will usually be randomised to receive carbamazepine vs. one of lamotrigine, topiramate, gabapentin, or now oxcarbazepine. Others, whether undecided or who are thought to have an idiopathic epilepsy, can be randomised to receive lamotrigine, valproate or topiramate. In the event of refusal, or in the unlikely event of any other confounding factor, then a decision has to be made by the clinician, based on individual circumstance.

**Idiopathic generalized epilepsy (IGE)**

The choice of AED in newly presenting IGE probably lies between lamotrigine and valproate. With partial epilepsy, for most clinicians carbamazepine remains the first choice. The choice of AED in newly presenting IGE probably lies between lamotrigine and valproate. With partial epilepsy, for most clinicians carbamazepine remains the first choice.

Partial epilepsy

For most clinicians carbamazepine remains the first choice. Lamotrigine is also licensed for monotherapy. Again, gender and other concomitant treatments (especially the oral contraceptive) may be important factors. While there is evidence of efficacy of monotherapy with topiramate, gabapentin, and oxcarbazepine, most people consider these to be second-line agents, used in the event of either unsatisfactory control or poor tolerability of the first-line agent. Initial use is usually as add-on with the possibility of phased withdrawal of the baseline agent if good control is achieved with the newer drug.

**Add-on treatment**

Failure of initial monotherapy should firstly lead to confirmation of the diagnosis – up to 20% of referrals for refractory epilepsy turn out not to have the disease (Smith 1999). Once the diagnosis is confirmed, initial monotherapy failure usually leads to add-on treatment with another first-line or second-line agent. There are no firm guidelines about how this should be done, but the use of new AEDs will always require careful thought and counselling in females of reproductive age. The following factors may help in making the decision:

- Concomitant medication, especially oral contraceptive when enzyme inducing AEDs are being considered;
• Pharmacokinetic interactions between agents. At the very least, this should lead to caution with starting dose and titration rates in some scenarios (lamotrigine/valproate, topiramate/valproate);
• History of other medical conditions—diabetes (weight gain with valproate), renal stones with topiramate;
• Modo of action. It may make sense to avoid replicating modes of action (e.g. carbamazepine/phenytoin and carbamazepine/lamotrigine are combinations primarily acting on the sodium channel) although we have to take into account that our knowledge of such modes is not as full as it could be.

Additional ‘side benefits’ of new AED use

Anyone considering the benefits of the new AEDs must always consider the ‘side benefits’ they have brought to neurology in general, and to epilepsy care in particular. Human nature makes it inevitable that doctors’ interest in a condition will be enhanced where there is a possibility of effective treatment. It would be nice to think that the input from neurologists has increased since the days when all we had at our disposal were the three mutually interacting modified sedatives and a fatty acid. The introduction of the newer compounds may have changed the culture of learned hopelessness that surrounded the treatment of refractory epilepsy.

In many cases, financial input from the pharmaceutical industry can be linked to an improvement in epilepsy services. Having lagged behind in many areas, the improvement in epilepsy nurses over the last decade has been a direct benefit. Such growth could not have happened without financial input from companies with an interest in epilepsy. At the very least, finance from the pharmaceutical industry has hastened some service changes. At best it may even have brought about improvement.

Another ‘side benefit’ of industry involvement is in financing basic research programmes. The pharmaceutical industry has become the largest provider of medical research funds, filling the void left by the wholesaler reduction in direct government funding. It can be argued that use of the new compounds encourages continued industry interest in important disease areas, indirectly funding the necessary research (Chadwick 1998). Patients, however, would be rightly concerned if we were using drugs solely for these reasons. Such a process would amount to a ‘stealth funding’ of medical research, and if the drugs were not themselves of benefit, would the money not be better spent by administering the money through the accepted research channels?

Drawbacks of new AED use

We should never become too complacent, but the possibility of the new AEDs causing serious harm must be decreasing as years of patient exposure to each of them increases. Lessons were learned from the teething troubles experienced with the introduction of the new drugs and each newer drug has had a successively easier time. In saying this, it took eight years post-launch for the visual field problems associated with vigabatrin to come to light. We must remain vigilant, but the theoretical risk of harm from the new compounds should be weighed against the emergent and real risks of exposing people to the older AEDs – drugs that are not universally efficacious and that carry their own risks.

The issue of cost was alluded to in the introduction. Comparing costs of the new AEDs with the oldest compounds may be misleading. Phenobarbitone, for example, is a remarkably cheap drug, and using that as a comparator will make any other drug appear expensive. For reasons discussed above, in the UK at least, questionable efficacy and multiple adverse effects/interactions ensure that few people use phenobarbitone as a first-line AED, rendering the cost comparison clinically irrelevant. Any comparison should be made against the best established AED (which will vary depending on the epilepsy syndrome) and arguably against the sustained release preparation. One study – which has been open to some justified criticisms (Heaney et al. 1999) – has suggested that a wholesale (and highly unlikely) use of lamotrigine instead of carbamazepine for newly diagnosed epilepsy would add £500 to the annual cost of one patient’s AED therapy. Ascertaining the total economic costs of epilepsy is a complex business but £500 is a fraction of the total cost. Other work has been done, which suggests that taking into account the ancillary costs of poorly controlled epilepsy, the use of new AEDs is cost-effective.

THE FUTURE

There are still a number of drugs undergoing...
clinical development worldwide (Bialer et al. 2001). Some exploit new mechanisms of action, and all exhibit promising properties in preclinical testing. Many will fall at some testing hurdle, but perhaps instead of a headlong rush to release new AEDs on to the market, we might wish to learn how best to use the ones we already have. Economic considerations will always motivate further drug development, but they will prove an obstacle to the large trials that will answer clinically important questions: How do AEDs compare? Which is best for which syndrome? In what order should they be used? What are the optimal combinations of AEDs?

CONCLUSION

The established AEDs are not perfect, their efficacy is not universal, their adverse effects too common, and emergent data on fetal exposure confirm they are not entirely safe in women of childbearing age. There has undoubtedly been room for improvement. The challenge for the newer drugs (and clinicians) is to prove that they embody enough of an improvement to justify their costs. Rendering patients seizure-free is important, but this cannot stand alone as a measure of usefulness. Drugs with fewer interactions, fewer adverse effects (cognitive and otherwise), and a reasonable reduction in seizure rates help to improve patient quality of life. Health economists can analyse many aspects of new treatments, but they require adequate data from well-run unbiased clinical trials. It is arguable whether the current system serves them, the patients, or us well enough.

REFERENCES


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