The promise of new antiepileptic drugs

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Epilepsy is the most common serious disorder of the brain and comprises a wide range of different conditions with varying aetiologies. The long-established antiepileptic drugs (AEDs) control seizures in 50% of patients developing partial seizures, and 60–70% of those developing generalized seizures. Several AEDs were made available in the 1990s. These drugs have efficacy, but have had only a modest impact on those with refractory epilepsies. A 50% seizure reduction, which is commonly used as an endpoint in clinical trials, confers little benefit to a patient. Of the newer AEDs, lamotrigine and oxcarbazepine are now licensed for use as monotherapy and vigabatrin has a monotherapy licence for infantile spasms. Careful and prolonged postmarketing surveillance is essential to detect adverse effects, which may not be evident in premarketing clinical trials. At this time, there are 10 AEDs currently in varying stages of clinical development. Current strategies for selecting an AED for a particular patient are crude. Magnetic resonance spectroscopic measures of cerebral neuro-transmitters and genetic analysis may allow better prediction of which drug is most likely to be efficacious and to have low risk of adverse effects. Present AEDs suppress the occurrence of seizures. Agents that prevent the development of epilepsy and which protect the brain from the consequences of seizures would be of great value, but it will be difficult to prove their effectiveness. At present AEDs are given continually and systemically. Local drug delivery is feasible and could avoid the adverse effects of AEDs. The combination of local drug delivery with prediction of seizure occurrence could revolutionize the treatment of currently refractory epilepsies.

The clinical problem

Epilepsy is the most common serious neurological disorder, with an incidence of 50/100 000/year, a cumulative lifetime incidence of 1 in 20 and a prevalence of 1 in 200 [1]. In the United Kingdom, these figures translate to 30 000 new cases per year and 350 000 individuals with active epilepsy, or requiring regular AEDs to control the occurrence of seizures.

The term epilepsy is a misnomer and conceals the diversity and heterogeneity of conditions and syndromes of which epileptic seizures may be part, that may occur from the neonatal to the geriatric age ranges. It is more appropriate to refer to the epilepsies. Failure to appreciate this may result in oversimplified overviews of responses to antiepileptic drug treatment. The International League against Epilepsy (ILAE) has produced classifications of seizures [2] and epilepsy syndromes [3]. At present, the syndrome classification largely influences strategies of initiation, intensity and withdrawal of treatment, and the classification of seizure types, particularly the dichotomy between partial and generalized seizures, influences which AED is chosen for initial and for add-on therapy. These classifications are reasonably pragmatic, but were heavily based on videotaped seizures in tertiary referral centres. The ILAE has recently proposed a further classification of seizure types and syndromes [4]. It is not yet clear, however, whether this revised classification will aid selection of particular AEDs for individual patients.

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Effectiveness of current AEDs

The long-established AEDs, that are used as first line agents, carbamazepine and valproate, and the older agents phenytoin and phenobarbitone, will result in seizure control in 50% of patients developing partial seizures, and 60–70% of those developing generalized seizures [5–7].

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After a lull of over a decade, many new AEDs were introduced, starting with vigabatrin in 1989, followed by zonisamide, lamotrigine, gabapentin, felbamate, topiramate, tiagabine, oxcarbazepine and most recently, in late 2000, levetiracetam.

The impact of recently licensed AEDs in refractory patients

New AEDs are generally evaluated first in patients with frequent partial seizures who have been refractory to previously available AEDs, with randomized clinical trials in which the new agent or a placebo is added to the baseline therapy. The numbers of seizures are usually counted over a 8–16 weeks baseline period, followed by a titration phase, and then a 12–16 week treatment period. These studies are designed and financed by the pharmaceutical industry, with the specific aim of satisfying the Regulatory authorities that the new compound has efficacy and is safe. It is very rare for a patient with refractory partial seizures to become seizure free with the addition of a new AED [8]. The usual outcome measures are the proportion of patients who have a 50% or more reduction in seizures, and the median seizure frequency. Meta-analyses of placebo-controlled trials of new AEDs has shown efficacy for gabapentin, tiagabine, topiramate, vigabatrin, lamotrigine, levetiracetam, oxcarbazepine and zonisamide (licensed in Countries outside Europe), and no definite differences in efficacy have been found between them [9, 10]. Regression models, examining the effects of varying doses have suggested that there is no flattening off of the response with higher doses of tiagabine and gabapentin, suggesting that less than optimal doses may have been used. In contrast, vigabatrin and topiramate showed flattening off of the therapeutic response at higher doses.

There have been much fewer evaluations of AEDs in generalized epilepsies. Lamotrigine and topiramate have shown efficacy in the refractory generalized Lennox–Gastaut syndrome [11, 12].

Whilst such randomized trials satisfy Drug Regulatory authorities, they do not provide data that are of much clinical relevance. Clinicians and their patients need to know which drug is most likely to be effective for them and what adverse effects may be encountered. It is only adequately powered long-term head to head comparisons between AEDs, in homogenous groups of patients with well described syndromes, that can provide this guidance. Such trials are conspicuous by their absence, principally because of their expense and the lack of incentive for the pharmaceutical industry to undertake such work once their compound is marketed.

Studies of the long-term continuation of AED therapy are attractive in that they reflect clinical practice, as those with adverse effects and a failure to respond will be more likely to stop taking the medication but have the limitations of being uncontrolled, nonrandomized and subject to selection bias. Eighty-six percent of those who commenced lamotrigine and vigabatrin during clinical trials had the new drugs withdrawn in 6–8 years [13]. In an open follow-up of patients attending an epilepsy clinic there was a 57% probability of patients continuing to take lamotrigine and 43% continuing on vigabatrin after 40 months [14]. In an open follow-up study of 174 patients treated with topiramate, 55% remained on the drug at 1 year [15].

Other post-marketing studies of long-term continuation have shown less than 30% of patients continuing on the new agents 3–5 years after commencement [16, 17].

Whilst a 50% reduction of seizures is a pragmatic measure of demonstrating more antiepileptic efficacy than a placebo in add-on trials of new agents in patients with refractory seizures, it is also an admission of defeat. Reducing the number of seizures by half does little for the quality of life of patients. The attacks can still occur at any time, in any place, with the consequent restrictions on activity, embarrassment as well as the risk of physical morbidity and mortality [18, 19]. The measurement of seizure severity is an important facet of AED efficacy that has only been assessed recently [20–22]. This is important, as the occurrence of simple partial seizures is less disruptive to patients than more severe episodes. Clinical trials of AEDs have used a variety of neuropsychological and behavioural measures. This diversity makes it difficult to draw conclusions on the effects of AEDs. A more uniform approach to evaluating these effects would be advantageous [23]. It must also be recognized that the duration of add-on trials of AEDs, which are usually 12–16 weeks, are not sufficiently prolonged for any changes in the perceived quality of life of a person with epilepsy to be develop and to be measurable.

Status epilepticus

Lorazepam is increasingly favoured over diazepam for the first line treatment of status epilepticus. Lorazepam has a lesser volume of distribution, is less lipid soluble, a slower onset but longer duration of action, with efficacy extending for several hours. As distribution is slow, the rate of intravenous injection is not critical. In adults, a bolus dose of 0.07 mg kg^{-1} (to a maximum of 4 mg) is used, which may be repeated once after 20 min if necessary. In children under 10 years, bolus doses of 0.1 mg kg^{-1} are recommended [24].

Fosphenytoin has been introduced as an alternative to phenytoin for intravenous use. Fosphenytoin is converted *in vivo* to phenytoin with a half-life of 8–15 min and has the advantages of solubility in water at neutral pH, and so is not presented in an irritant alkaline solution [25]. It was

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initially thought that the risk of cardiac side-effects and the need to give by slow intravenous infusion was averted, but clinical experience has shown that a maximal advised infusion rate is 50–100 mg of phenytoin equivalents min^{-1}.

The impact of the new AEDs in newly diagnosed patients

New AEDs are usually evaluated for monotherapy use after efficacy and safety data have been acquired with add-on use in refractory patients. The use of adequately powered comparative monotherapy to detect equivalence between AEDs has been recommended [26]. A new drug would be recommended for first-line use if it was as efficacious as a standard agent and better tolerated. A new drug would be regarded as a second line drug if its efficacy and tolerability was not different from the standard. To be adequately powered, such studies would require patients to be regarded in fairly broad categories, with the risk that subgroups with particular responses may not be detected. This study design causes regulatory difficulties as whilst the European Medicine Evaluation Agency is willing to accept equivalence to a standard AED as evidence of efficacy, the US Food & Drug Administration is not and currently requires the use of a placebo arm in monotherapy comparisons. Such a design raises serious ethical and medico-legal issues, which are likely to come to the fore should a patient die as a result of a seizure whilst receiving only a placebo.

Lamotrigine is licensed for use as monotherapy in the UK, having shown similar efficacy and better tolerability than carbamazepine [27, 28]. No significant difference was found between gabapentin and carbamazepine [29]. Vigabatrin has been compared with carbamazepine and withdrawal because of recurrent seizures was more likely in those receiving vigabatrin [30–32]. No significant difference has been found between oxcarbazepine and carbamazepine [33], phenytoin [34, 35] or valproate [36], with the exception that oxcarbazepine appeared better tolerated than phenytoin. These studies, however, were not large enough to rule out potentially relevant differences.

Oxcarbazepine is licensed for the treatment of partial seizures as monotherapy or in combination with other AEDs in adults and children over 6 years [37]. Vigabatrin is licensed for the initial therapy of children with infantile spasms and has considerable efficacy in this syndrome [38, 39].

Adverse effects of the new antiepileptic drugs

The numbers of patients exposed in a clinical development program (usually 1500–2000) is not sufficient to identify occasional adverse effects. These effects will only be detected by post-marketing surveillance. A good example of this is the AED felbamate, which was licensed in 1993 and was found in the subsequent months to result in liver failure or aplastic anaemia in about 1 in 4000 patients exposed to the drug.

Chronic effects may also be identified by post-marketing surveillance, often after a long interval. The first report of visual field constriction in patients taking vigabatrin was in 1997 [40], 8 years after the drug was licensed, and this is now estimated to occur in 40% of patients who take the drug chronically [41]. In consequence, the use of vigabatrin is now restricted to children with infantile spasms and as a remedy of last resort for refractory partial seizures.

Lamotrigine has been associated with a risk of skin rash of up to 9.5%. In 0.4% the rash, due to a hypersensitivity reaction, has required admission to hospital [42]. The risk of a severe skin rash has been higher, approximately 1%, in children [43]. The risk of a skin rash is reduced by using a low starting dose and building up slowly [44].

There are suggestions that the new AEDs may have less adverse cognitive effects than the older agents. Lamotrigine appears favourable in this regard [45, 46]. Vigabatrin has generally not been associated with impairment of cognitive performance, but an increase of depression, irritability, behavioural disturbance and psychosis has been noted [47, 48]. Gabapentin has been found to be well tolerated, in the main [49]. In some patients, topiramate may be associated with marked impairment of verbal fluency, memory and thinking [50, 51]. This has not been a universal finding, however, [52], and it will be important to identify the individual patient factors that underlie susceptibility to the negative effects of this drug. Tiagabine has not been reported to have adverse cognitive effects [53, 54]. Oxcarbazepine has been studied little, but does not appear to have marked effects. Small studies have not reported marked effects with levetiracetam [55].

The potential teratogenic effects of the new AEDs are not established at present. The prospective follow-up of women taking AEDs through pregnancy with careful documentation of foetal outcome is crucial and this is underway in many countries. The establishment of multinational Registries such as the European Antiepileptic Drugs and Pregnancy Registry (EURAP), which has already enrolled over 600 patients prospectively, is a major step forward. This endeavour will produce very important data that will assist treatment decisions and the counseling of women who are contemplating pregnancies, to minimize the risk of teratogenesis.

The clinical evaluation of antiepileptic drugs

There is an acknowledged need for a practical clinical comparison of the long-established and newer AEDs and

this is being addressed in the UK by the NHS funded Standard and New Antiepileptic Drugs (SANAD) trial which will compare carbamazepine, valproate, lamotrigine, gabapentin, topiramate and oxcarbazepine. By their very nature, however, such studies are of populations of patients that include a range of syndromes and aetiologies. Ideally trials would be stratified by syndrome. Even if that were done, however, it is not uncommonly the case that two individual patients with the same clinical features and epilepsy syndrome may respond to different AEDs, and have differing adverse effects.

Future prospects – the need

From the above, it is evident that whilst several new AEDs have become available in the last decade, these have been of limited benefit for those with refractory seizures. To date, AEDs that have been licensed in the last decade have not had a great impact on the treatment of newly diagnosed patients, although lamotrigine and oxcarbazepine are being taken up as drugs of first choice, primarily because of their more favourable adverse effect profile. There is still a clear need for further research to develop new AEDs, and to consider new avenues and strategies to treat the processes of epilepsy and its consequences, rather than just having the rather blinkered objective of suppressing seizures.

Antiepileptic drugs currently in development

At present there are several potential antiepileptic compounds currently undergoing clinical evaluation. The three most advanced agents: pregabalin, retigabine and rufinamide, are currently in phase III development. Pregabalin, a gabapentin derivative is also a structural GABA analogue, which does not seem to affect transmitter response. It does, however, increase GABA content in neuronal tissues and binds to a subunit of Ca^{++} channels and this is likely to be the basis of its antiepileptic action [56]. Retigabine, is structurally unrelated to other marketed AEDs and its potent anticonvulsant activity in animal models is likely to be mediated by increasing K^+ conductance in neuronal cells [57]. The mode of action of rufinamide, a triazole derivative, is likely to be mediated by interaction with the inactivated state of the Na^+, limiting high-frequency firing of action potentials in neurones [58]. Three further agents, losigamone, ganoxolone and remacemide recently had their development terminated. Potential AEDs that are less advanced in their development programme are shown in Table 1.

At present there are several routes of new AED development: high throughput screening of potential agents, modification of existing compounds, enhancing delivery to the brain of current existing drugs, serendipitous discovery and as a result of scientific inquiry into the mechanisms underlying the epilepsies and epileptic seizures. Increasingly, new AEDs are being developed in tandem for other applications, such as pain and migraine.

Table 1 Potential AEDs in development.

Drug	*Class*	*Phase*
AWD131–138	Imidazolin	Phase I
Harkoseride	Aceto-propionamide amino acid	Phase I
NPS 1776	Aliphatic amide	Phase I
NW1015	Methansulphonate	Phase I
SP0294 (DP-VPA)	Valproate in a phospholipid carrier	Phase I
Talamparel	AMPA antagonist	Phase II
Valrocemide	Valproryl derivative of GABA	Phase II
Carabersat	Benzopyran	Phase II

How to predict which drug is best for which patient?

At present, the strategy for choosing a particular AED for a patient is about as sophisticated as choosing an antimicrobial on the basis of the Gram staining of bacteria, and consideration of the likely adverse effects of the drug. Strategies that allow for a better prediction of which AED, or class of AEDs, are most likely to help and with least risk of adverse effects would be useful, and would help to ensure that individual patients were prescribed the optimal therapy sooner rather than later.

There are possibilities. Magnetic resonance spectroscopy (MRS) may be used to measure the concentrations of GABA, glutamate and glutamine in the brain, non-invasively *in vivo*. At present, the neurotransmitter and metabolic pools of these compounds cannot be differentiated and the promise of MRS is predicated on the hypothesis that the overall concentrations of these compounds in a volume of brain is relevant in the pathogenesis of epilepsy and of epileptic seizures, and their prevention by medications. It has been found that low GABA concentrations are associated with an ongoing tendency to seizures, and a range of AEDs result in elevation of cerebral GABA concentrations [59]. It is possible that particular metabolic patterns will predict responsiveness to a particular AED, and that serial studies may assist optimal dosing.

The response to AEDs may be genetically determined. Mice with point mutations in the alpha 1 subunit of the GABA/A receptor have been found to be less sensitive to the sedating effects of diazepam but to show no difference in anticonvulsant sensitivity compared with the wild-type strain [60, 61]. Drug resistance may also be genetically determined [62, 63]. Automated high throughput analysis

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of genotypes of populations is now feasible, using a variety of tools such as characterization of single nucleotide polymorphisms (SNP). This development leads to pharmacogenetic studies of populations of patients with seizures that do, and do not, respond to particular AEDs, or classes of drugs. Large populations need to be ascertained and it is anticipated that these investigations will lead to the identification of SNP patterns in individual subjects that will predict responsiveness to individual AEDs prior to the first prescription being written. Further, these studies are likely to identify targets for potential new antiepileptic therapies. These techniques may also be used to identify patients who are at high risk of adverse effects from a particular AED, for example aplastic anaemia from felbamate, an allergic reaction to carbamazepine [64] or lamotrigine, or a teratogenic consequence from usage during pregnancy [65]. Dosing may also be facilitated by examination of polymorphisms of genes coding for enzymes responsible for the metabolism of AEDs.

Is there a prospect for antiepileptic drugs to do more than suppress seizures?

There has been a long debate about whether seizures beget seizures, and whether the course of epilepsy is progressive by virtue of the occurrence of further seizures, that is beyond the scope of this review [6, 66]. There are two related issues: antiepileptogenesis and neuroprotection.

Antiepileptogenesis

Epileptogenesis refers to the process of changes in the brain that leads to the development of a recurring tendency to have spontaneous seizures. Animal models of this are kindling and perforant path stimulation, whereby repeated electrical stimulation results in the generation of spontaneous seizures. These processes are the subject of intense scrutiny at the receptor, cellular and network levels. Identified changes include loss of specific cell types, gliosis, axonal sprouting, neuronal neogenesis, synaptic reorganization and alterations in neurotransmitter receptors [67–71]. It is unclear which of these processes are detrimental or beneficial, or are merely epiphenomena. Medication that is antiepileptogenic is not necessarily neuroprotectant, and *vice-versa*.

Valproate and phenobarbitone have been found to be antiepileptogenic, but carbamazepine is not [72] and lamotrigine did not retard the development of seizures in the kindling model [73]. Levetiracetam has antiepileptogenic effects [74]. Although AMPA receptors are fundamental to the occurrence of kindled seizures, they appear to be less important to the kindling process, and GluR5 kainate receptors did not contribute to epileptogenesis in the mouse amygdala kindling model [75]. In contrast, NMDA receptor antagonists are effective against kindling, but not against kindled seizures [76]. Free-radical scavengers and antiperoxidants may have useful antiepileptogenic properties [77].

Clearly an AED that was also antiepileptogenic would be a therapeutic advance. Antiepileptogenic activity would be very difficult to evaluate in the clinical setting. Prospective randomized clinical studies would need to be carried out in cohorts of patients who were at risk of developing epilepsy, for example after a stroke or serious head injury. As epilepsy may develop after a considerable latent period the trial would need to be of long duration, such as 5 years. In order to show a worthwhile reduction of risk of developing epilepsy, such as 20%, large groups would be needed. In addition to the cost and logistic issues, such a trial of preventive therapy over 5 years would strain compliance in all but the most motivated patients, particularly if the medication had any adverse effects.

Neuroprotection

It has been known for many years that status epilepticus may result in significant hippocampal and cerebral damage, and this may be demonstrated with serial MRI scans *in vivo* [78]. Seizure induced damage is likely to be due to excitotoxicity and is of two types: necrotic and apoptotic, although the distinction is not always clear [79]. It is less clear whether individual tonic-clonic and complex partial seizures cause secondary brain damage. It is generally held that brief febrile convulsions, simple partial seizures, absences and myoclonic seizures and interictal epileptic activity do not cause cerebral damage, although this has not been proven.

It has been suggested that felbamate [80], lamotrigine [81–83] and topiramate [84] may have neuroprotectant properties. The neuroprotection offered by most antiepileptic drugs in models of ischaemia, however, has yet to find a clinical correlate, and indeed its relevance in ischaemia in humans, let alone epilepsy, is uncertain.

Cross-sectional brain imaging studies cannot determine whether secondary brain damage occurs as a consequence of epilepsy. Longitudinal follow-up studies of patients and control groups are necessary to ascertain whether this does occur, and to identify the risk factors, which are very likely to include individual genetic factors. The most promising methods are quantitative magnetic resonance imaging (MRI) for which patient acceptability and test-retest reliability is excellent [85]. Such studies have been set up and are underway [86, 87]. Other possible methods include MRS measures of the concentration of cerebral metabolites. These may be more sensitive than quantitative MRI but at present the data are also noisier and less reproducible. If the occurrence of secondary cerebral

damage were confirmed, this would have considerable implications for the treatment of epilepsy: there would be more impetus for intensive early medical therapy and the earlier consideration of surgical treatment. In addition, there would be interest in developing and trialling specific neuro-protectant agents to be taken alongside AEDs.

Prospects for local drug delivery

To date, AEDs have been given systemically and prophylactically because of the unpredictability of seizure occurrence and, often, uncertainty as to the sites of seizure generation in the brain. This may result in chronic adverse effects, that could be avoided if the AED was only administered to the critical part of the brain that was involved in seizure generation and, perhaps, only at the critical times.

With current technology it is possible to define the site of seizure onset in some patients with partial seizures and to offer a neurosurgical resection of that part of the brain with a 60–70% chance of rendering the patient seizure free in the long term. The possibility of local delivery of minute doses of AEDs to the critical area is feasible [88] and awaits the technical development of implantable microsystems.

A tenet of epilepsy treatment that may now be challenged is that AEDs need to be taken regularly, as the occurrence of seizures could not be predicted in advance. It has recently been suggested [89] that nonlinear analysis of EEG waveforms recorded from scalp electrodes may be able to predict the occurrence of a partial seizure up to 18 min before the event. This leads to the possibility that a scalp or implanted sensor may be able to predict the occurrence of an impending epileptic seizure and respond by alerting the patient, triggering the systemic or local application of an AED, or neural stimulation that averts the clinical event.

Conclusions

Epilepsy is a common and serious condition. Whilst currently available AEDs suppress seizures in the majority of those who develop epilepsy, there are many who continue to endure recurrent, unpredictable seizures and adverse effects from medication that does not treat the underlying cause. There are promising new AEDs in development, but the development of rationally targeted drugs, antiepileptogenic therapy and the local delivery of effective medication are the real promises for the future treatment of epilepsy.

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