Development of new antiepileptic drugs: challenges, incentives, and recent advances

Emilio Perucca, Jacqueline French, Meir Bialer

Despite the introduction of many second-generation antiepileptic drugs (AEDs) in the past 15 years, a third of patients with epilepsy remain refractory to available treatments, and newer and more effective therapies are needed. Although our understanding of the mechanisms of drug resistance is fragmented, novel AED targets have been identified, and models of refractory epilepsy have been developed that can help to select candidate compounds for development. There are more than 20 compounds with potential antiepileptic activity in various stages of clinical development, and for many of these promising clinical trial results are already available. Several incentives justify further investment into the discovery of newer and more effective AEDs. Moreover, developments in clinical trial methodology enable easier completion of proof-of-concept studies, earlier definition of the therapeutic potential of candidate compounds, and more efficient completion of trials for various epilepsy indications.

Introduction

In the past 15 years, 13 new antiepileptic drugs (AEDs) have been introduced, some of which are advantageous in terms of pharmacokinetics, tolerability, and potential for drug interactions. These AEDs are regarded as second generation compared with older AEDs, such as phenobarbital, phenytoin, carbamazepine, ethosuximide, and valproic acid. However, the second-generation AEDs marketed so far have not been a breakthrough because, altogether, their use leads to freedom from seizures in no more than 15–20% of patients with epilepsy who are refractory to older AEDs. Therefore, despite the current availability of more than 15 drugs, about 30% of people with epilepsy have uncontrolled disease, and novel and more effective third-generation AEDs are needed. In this Review we discuss the hurdles and incentives involved in the development of new AEDs. We also review those compounds that are in the pipeline, and provide suggestions on how future clinical development can be improved.

Challenges to AED development

The development of new drugs is costly and risky. Even when a new drug candidate is at the first-in-man stage (phase Ia) and an investigational new drug (IND) application has been filed, the chance that it will successfully complete development and be approved by the regulatory authorities is only about 10%. Perceived hurdles to investment in new epilepsy treatments include the rapidly increasing costs of drug development, a market crowded with already licensed compounds, and disillusion about the feasibility of easily identifying a product that is an improvement over existing compounds. The biggest hurdle, however, is our incomplete knowledge of the mechanisms of AED resistance, which prevents mechanism-driven drug development. The evidence that epileptic disorders have heterogeneous pathophysiological mechanisms, coupled with the almost certain multifactorial nature of resistance, makes it improbable that a single drug could eradicate refractory epilepsy.

Since the discovery of phenytoin in 1938, the development of new AEDs has relied on testing in animals. Animal models with a similarly high predictive value do not exist for other CNS disorders, such as migraine or bipolar disorder, and, in particular, models based on electrically or chemically induced seizures in rodents have been crucial for discovering all the new AEDs since phenytoin. The effectiveness of a drug in the maximal electroshock model is thought to predict efficacy of a compound against generalised tonic-clonic seizures, whereas protection against pentylentetrazole-induced seizures and against spontaneous seizures in genetic epilepsy models, such as the Strasbourg rat and lethargic mouse, are indicative of efficacy in the treatment of absence and myoclonic seizures. The rationale behind this inference is that successful AEDs either raise seizure threshold or prevent seizure spread. Levetiracetam, although inactive in the standard maximal electroshock and pentylentetrazole models, was effective in the kindled-rat model, which led to increased interest in the assessment of potential new AEDs in more chronic models (eg, kindling) and in the reintroduced 6 Hz psychomotor activity model.

The use of current animal models in the discovery of new AEDs has advantages and disadvantages. The advantages include the use of intact rodents as easy models that detect anticonvulsant effects regardless of the mechanisms of action. Maximal electroshock and pentylentetrazole testing can be used in high-throughput screening, as shown by the National Institutes of Health Anticonvulsant Screening Program, which has screened 27 000 potential compounds since 1974. Furthermore, these models can provide insight into pharmacokinetic–pharmacodynamic relations, which are of value for human studies. The disadvantages relate to the idea that conventional models are likely to identify more of the same new AEDs—eg, drugs that share characteristics with existing drugs, and are unlikely to have an effect on refractory epilepsies. Furthermore, given the heterogeneity of seizure...
disorders, it is unlikely that a few animal models will predict the full therapeutic potential of a drug candidate. Finally, animals have modest value for predicting human tolerability. This is an important consideration because, in the clinical setting, a high degree of efficacy might be masked by dose-limiting adverse effects. An innovative approach to overcome at least the first of these limitations is to use animals with a phenotype that is consistent with pharmacoresistance, such as the phenytoin-resistant kindled rat, the lamotrigine-resistant kindled rat, and the 6 Hz psychomotor seizure model.

If the development of effective AEDs for patients with refractory disorder is a major hurdle, there are greater challenges when developing drugs that, potentially, might modify epileptogenesis (i.e., the process that leads to the seizure disorder becoming chronic) and prevent the occurrence of epilepsy in patients that are at high risk.

**Incentives for AED development**

A new AED is successful if it has at least one of the following properties: greater efficacy than other drugs in the treatment of refractory epilepsies; the ability to prevent or delay the onset of epilepsy (epileptogenesis), or at least modify its progression; broad usefulness in non-epileptic CNS disorders; fewer adverse effects than available drugs; and ease of use, such as rapid titration, linear pharmacokinetics, lack of drug interactions, or a longer half-life that enables once or twice daily doses or extended protection if a dose is missed. Many of the compounds listed in the table have the potential to meet at least some of these criteria, and there is a greater economic incentive to develop a drug if it is also broadly applicable to non-epileptic CNS disorders, as shown by the commercial success of those AEDs approved for other indications, such as migraine prophylaxis (valproic acid, topiramate), neuropathic pain (gabapentin, pregabalin), or bipolar disorder (valproic acid, lamotrigine). The US market value for the use of AEDs in additional indications is triple that for their use in the treatment of epilepsy alone ($3 billion).

Financial returns can benefit from the peculiar resilience of the AED drug market, even when no important additional indications exist for a specific

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**Key structural or pharmacological features**

<table>
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<tr>
<th>Compound</th>
<th>Description</th>
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<td>Brivaracetam</td>
<td>A levetiracetam analogue and 5V2A ligand with additional sodium channel-blocking properties, in phase III development in refractory epilepsy</td>
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<td>Carisbamate</td>
<td>A carbamate derivative completing phase III development for refractory partial epilepsy</td>
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<tr>
<td>E-2007</td>
<td>An AMPA receptor antagonist in phase II development for refractory partial epilepsy</td>
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<td>Eslicarbazepine acetate</td>
<td>An oxcarbazepine derivative completing phase III development for refractory partial epilepsy</td>
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<td>Fluorofelbamate</td>
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<td>Ganaxolone</td>
<td>A neurosteroid that acts as modulator of GABA, mediated transmission, in phase II development for refractory epilepsy</td>
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<td>Hyperaze A</td>
<td>An alkanoid approved in China for Alzheimer’s disease, undergoing initial assessment in epilepsy</td>
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<td>JZP-4</td>
<td>A structural analogue of lamotrigine in phase I assessment</td>
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<td>Lacosamide</td>
<td>A methytopropionamide derivative completing phase III development for refractory partial epilepsy and neuropathic pain</td>
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<td>Licarbazepine</td>
<td>The monohydroxy derivative of oxcarbazepine being developed as a racemate for bipolar disorder</td>
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<td>Losigamone</td>
<td>A β methoxy-butenolide with phase III clinical trial data for refractory partial epilepsy</td>
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<td>NS 1209</td>
<td>A competitive AMPA antagonist in phase II assessment for refractory status epilepticus</td>
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<td>Retigabine</td>
<td>A selective opener of KCNQ2/3 and KCNQ3/5 channels in phase III development for refractory partial epilepsy</td>
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<td>Rufinamide</td>
<td>A sodium channel-blocker approved as adjunctive treatment for Lennox-Gastaut syndrome by EMEA, under assessment by the FDA as adjunctive treatment for the syndrome and for refractory partial seizures</td>
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<td>Selegicatam</td>
<td>A levetiracetam analogue with increased potency, currently in phase II</td>
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<td>Safinamide</td>
<td>A sodium channel-blocker and MAO-B inhibitor, currently in phase III development, which is focused mainly on Parkinson’s disease</td>
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<td>Stimpentol</td>
<td>A metabolic inhibitor that has received conditional approval by EMEA as adjunctive therapy to clonazepam and valproic acid in severe myoclonic epilepsy in infancy</td>
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<td>T2000</td>
<td>A non-sedating barbiturate with antiepileptic activity currently in phase II assessment for essential tremor</td>
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<td>Talampanel</td>
<td>A non-competitive AMPA receptor antagonist that completed phase II studies for refractory partial seizures</td>
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<td>Tonabersat</td>
<td>A canabersat analogue, currently undergoing phase IIa assessment for migraine prophylaxis</td>
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<tr>
<td>Valnoctamide</td>
<td>A metabolically stable constitutional isomer of valproamide (the primary amide of valproic acid) with broad-spectrum anticonvulsant activity in animal models, currently undergoing phase II assessment in bipolar disorder as a racemate</td>
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<tr>
<td>Valproclamide (SPD-493)</td>
<td>A derivative of valproic acid in phase II development in refractory epilepsy with potential additional CNS indications</td>
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<td>XP-13512</td>
<td>A gabapentin produg, with better oral bioavailability than gabapentin, currently undergoing clinical trials for restless-legs syndrome</td>
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<td>YKP3089</td>
<td>A compound with activity in animal models of epilepsy, anxiety, and neuropathic pain, in phase I development</td>
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AED=anti-epileptic drug; AMPA=α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolidinepropionic acid; EMEA=European Medicines Agency; FDA=US Food and Drug Administration; MAO-B=monoamine oxidase B; MHD=monohydroxy derivative; SV2A=synaptic vesicle 2A protein.

**Table: Potential antiepileptic compounds in various stages of clinical development**
Using a pharmacokinetic analogy, the time of peak sales ($t_{max}$) for a new AED is commonly reached slowly, and its peak value ($C_{max}$) might be lower than in high-profile therapeutic areas; however, its half-life ($t_{1/2}$) is usually long, and overall exposure ($AUC_{0-\infty}$) can be large in epilepsy alone, as exemplified by phenytoin. A contributing factor in this pattern is that neurologists are reluctant to switch their patients to generic AEDs because they fear seizure recurrence. Thus, sizeable revenues can be expected after expiration of the patent; indeed, in 2004–2005, the global annual sales of phenytoin and carbamazepine were stable at $325$ and $550$ million, respectively, of which about $250$ million each came from North America. In the case of gabapentin, for which $90\%$ of use was for neuropathic pain, US sales fell from $2.8$ billion in 2004 to $1.4$ billion after its patent expired in 2005.

There are incentives to develop AEDs, even for epilepsy syndromes that are uncommon but for which there are medical needs, including paediatric disorders such as West syndrome, Lennox–Gastaut syndrome, and progressive myoclonic epilepsies. These disorders meet the requirements of orphan indications, and financial incentives have been established for drug development in Europe and the USA. For example, in the USA the Orphan Drug Act guarantees market exclusivity to the sponsor for 7 years and also financial and regulatory benefits during development, including tax credits related to clinical trial expenses, and the elimination of fees for users. Another incentive is provided by the continuing National Institutes of Health Anticonvulsant Screening Program, which provides free screening of antiepileptic compounds to commercial and academic institutions and sophisticated preclinical characterisation of molecules that show promise.

**Molecules in clinical development**

More than 20 compounds are at various stages of clinical development (table). These include drugs with chemical structures that do not resemble existing AEDs, and derivatives of existing drugs that are developed as follow-up compounds with potentially improved properties (figures 1 and 2). Some of these compounds are being investigated by medium to large pharmaceutical companies that already have leading

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**Figure 1:** Derivatives of antiepileptic drugs (AEDs) introduced before 1970

Asterisks denote chiral centres.
products for epilepsy on the market but want to ensure the continuity of their presence through the introduction of innovative products with the attraction of patent protection. However, the peculiarities of a market with niche opportunities also provide incentives for newcomers, including small companies.

For some of the compounds listed in the table, such as rufinamide, stiripentol, eslicarbazepine acetate, and lacosamide, development has advanced substantially and extensive published information is available. For others, data are limited, and for some compounds the results of clinical trials are not yet in the public domain, including compounds that have undergone only preliminary clinical assessment and those that have been in development for many years but are in a dormant state. This category also includes compounds in development for other indications, either because the results of early studies were not encouraging or because strategic considerations unrelated to the scientific data led the sponsor to make alternative investment decisions.

In the following sections, we will briefly discuss some of the compounds currently under investigation; for more detailed information, the reader is referred to recent reviews.

**Figure 2: Derivatives of antiepileptic drugs (AEDs) introduced after 1990**

Asterisks denote chiral centres.
been no recent follow-up reports. Clinical development for valrocemide continues, and animal models show that it has broad-spectrum anticonvulsant activity and that it is not embryotoxic. In human beings, a small fraction (~5%) of valrocemide is converted to valproic acid, and the implications of this are not established.

UCB Pharma is currently developing two levetiracetam analogues: brivaracetam (ucb 34714) and seletracetam (ucb 44212). Compared with levetiracetam, both compounds have higher affinity for the SV2A-binding site, which mediates the antiepileptic activity of levetiracetam, and show much greater potency in animal models of seizures and epilepsy. Brivaracetam, which also has sodium-channel-blocking activity and has been granted orphan drug designation by the US Food and Drug Administration (FDA) for the treatment of symptomatic myoclonus and by the European Medicine Agency (EMEA) for the treatment of myoclonic epilepsies, has shown promising results in randomised placebo-controlled studies. These include a proof-of-concept study in 19 patients with photosensitive epilepsy and a dose-finding adjunctive-therapy trial in 208 patients with refractory partial epilepsy. In the latter trial, 52% of patients in the highest dose group (50 mg/day) had a greater than 50% reduction in seizures, compared with 17% in the placebo group. Overall, the drug was well tolerated. Seletracetam, which is more potent in animals than brivaracetam, is at an earlier stage of development. In a preliminary study in 28 patients with photosensitive epilepsy, seletracetam (0.5–40.0 mg as a single oral dose) was effective in suppressing light-induced electroencephalographic discharges.

Attempts to modify the structure of lamotrigine aim, at least in part, to retain its efficacy while improving its pharmacokinetics and safety. The goal is to identify a derivative whose elimination would neither be vulnerable to enzyme induction and inhibition (pharmacokinetic interactions involving inhibition or induction of lamotrigine metabolism complicate the clinical management of patients treated with this AED) nor lead to the formation of reactive metabolites, such as those that cause idiosyncratic reactions. One compound that might satisfy these requirements is JZP-4 (3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine), a lamotrigine analogue (figure 2) that blocks voltage-activated sodium channels and also causes blockade of voltage-dependent calcium (types N, L and P/Q) channels.

The strategy of improving safety through analogues that are not converted to reactive metabolites is also being applied in the development of fluoroelbamate. This fluorinated felbamate derivative (figure 2) is not converted to the toxic metabolite 2-phenylpropenal, which probably plays an important part in felbamate-induced aplastic anaemia and toxic effects on the liver. Licarbazepine and eslicarbazepine acetate (BIA 2-093) are third-generation derivatives of carbamazepine, and second-generation derivatives of oxcarbazepine (figure 1). Licarbazepine is a racemic mixture of the R and S enantiomers of the monohydroxy derivative of oxcarbazepine; this derivative is the metabolite that is primarily responsible for the activity of oxcarbazepine and is in development for the treatment of bipolar disorder as racemic licarbazepine. Conversely, eslicarbazepine acetate is a prodrug for eslicarbazepine, the S enantiomer of licarbazepine, although smaller amounts of the R enantiomer are formed during the biotransformation of the prodrug to drug. Of the two, only eslicarbazepine acetate has undergone extensive investigations in patients with epilepsy. In an add-on trial in 143 patients with refractory partial seizures, the proportion of patients with more than 50% reduction in seizures was significantly greater in those on a maintenance dose of eslicarbazepine acetate (1200 mg once daily) than in those on placebo (54% vs 28% respectively), whereas improvement in seizure control did not differ significantly from placebo when a dose of 600 mg twice daily was tested.

Compounds with new targets

Studies on the mechanisms of seizure generation and propagation have identified new targets for potential AEDs. The strategy of targeting mechanisms that are not affected by existing drugs is attractive because, in theory, a novel mode of action might prove effective for epilepsy that is refractory to available treatments.

AMPA receptors have an important role in the spread of seizures and seizure-induced damage, and several AMPA receptor antagonists are active in animal models of seizures and epilepsy. Although topiramate has some blocking activity at AMPA receptor sites, no selective AMPA antagonist has, as yet, received regulatory approval. Among the compounds being investigated, talampanel (GYKI-53773, LY300164), a non-competitive AMPA receptor blocker, has undergone initial assessment in patients with epilepsy. In an early adjunctive-therapy crossover trial in 49 patients with refractory partial seizures, median seizure frequency was 21% lower on talampanel than on the placebo, a statistically significant effect (p=0·001). Other AMPA receptor antagonists that are in early clinical development include E-2007 and NS-1209. Although little information is available on the former, NS-1209 is a water-soluble, competitive AMPA antagonist that is being assessed clinically as a potential intravenous treatment for refractory status epilepticus.

Many currently available AEDs inhibit excessive neuronal firing by blocking voltage-gated sodium channels. Although a decrease in neuronal excitability might also be produced by enhancing conductance of potassium channels, no existing AED exerts a primary action at this site. One drug in development that acts...
primarily as a selective opener of neuronal M-current KCNQ2/3 and KCNQ3/5 potassium channels is retigabine. In a randomised, adjunctive-therapy trial of retigabine in 397 patients with refractory partial seizures, a greater than 50% reduction in seizures was observed in 23% of patients at 600 mg/day, 32% at 900 mg/day, and 33% at 1200 mg/day, compared with 16% on placebo. The adverse events most commonly reported with retigabine include somnolence, dizziness, confusion, and difficulty in concentrating; at the highest dose, 29% of patients withdrew prematurely from treatment.

Another class of compounds with an innovative mechanism of action is the neurosteroids, which exert anticonvulsant effects through positive allosteric modulation of GABA, receptor sites. Ganaxolone, the 3β-methylated analogue of allopregnanolone, was assessed in an 8 day placebo-controlled presurgical monotherapy trial in 52 adults with refractory partial seizures, in which there was a non-significant trend for seizures to be delayed in the ganaxolone group. Four small open-label, adjunctive-therapy studies, mostly in children with a history of infantile spasms, also had promising results that require confirmation in controlled studies. Somnolence was the main dose-limiting adverse effect.

Compounds identified through screening procedures in animals
Compounds that are structurally unrelated to existing AEDs have been discovered either serendipitously in pharmacological tests or by screening derivatives of compounds known to have anticonvulsant activity in animals. The distinction between the drugs discovered through screening procedures and those with new identified mechanisms is somewhat artificial because some of the former drugs might ultimately have novel mechanisms of action. Among the compounds indentified through screening, rufinamide, stiripentol, losigamone, and carisbamate have undergone extensive clinical assessment.

Rufinamide is a triazole derivative with a mode of action related, at least in part, to the blockade of voltage-dependent sodium channels. Rufinamide has been the subject of a large clinical development programme that includes randomised trials in patients with refractory partial seizures, primarily generalised tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Rufinamide has been shown to be an effective adjunctive therapy in patients with refractory partial seizures and Lennox-Gastaut syndrome. In a study of 313 patients with partial seizures, rufinamide at a dose of 3200 mg/day, which is close to the upper limit of the tested range, was associated with a median 20% reduction in seizures, compared with a 2% median increase for placebo. In a trial in 138 children and adults with Lennox-Gastaut syndrome, the median reduction in total seizure frequency was 32% on rufinamide (45 mg/kg/day) and 12% on placebo, whereas the reduction in the frequency of tonic-atonic seizures was 42.5% on rufinamide versus –1.4% on placebo. Rufinamide was generally well tolerated; the most common adverse effects included somnolence, headaches, dizziness, fatigue, diplopia, and gastrointestinal disturbances. Rufinamide received orphan-drug approval by the EMEA in January 2007 as an adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, and approval as an adjunctive treatment for partial seizures and for seizures associated with Lennox-Gastaut syndrome is under consideration by the FDA.

Another compound recently approved by the EMEA for an orphan indication (adjunctive therapy to clobazam and valproic acid in severe myoclonic epilepsy in infancy) is stiripentol. This drug, which has a mechanism of action that involves the potentiation of GABAergic transmission and inhibition of the metabolism of concomitant AEDs, has been in clinical development for about three decades. The slow development of stiripentol is probably due to the failure to take into account the confounding effect of drug interactions when designing clinical trials and the delay in assessing its potential value in less common epilepsy syndromes. The most convincing evidence for stiripentol efficacy comes from a placebo-controlled trial in 41 children with severe myoclonic epilepsy in infancy, all of whom were concomitantly receiving valproic acid and clobazam. Almost half of the children on stiripentol were free from convulsive seizures during the second month of the 2 month trial but longer-term
follow-up data were not presented. Serum N-desmethylclobazam concentrations increased markedly in the stiripentol group, and a contribution to the reduction in seizure frequency of this interaction cannot be excluded.

Losigamone, a β-methoxy-butenolide anticonvulsant with an unknown mechanism of action, was effective as an adjunctive therapy in patients with refractory partial seizures. In the largest published trial to date, involving 264 patients, at least 50% seizure reduction was reported in 29% of the patients randomly assigned to receive losigamone 1500 mg/day, 17% of those in the 1200 mg/day group, and 12% of those in the placebo group. The difference between the group receiving the larger dose and the placebo group was statistically significant (p<0.004).

Carisbamate (RWJ-333369) is a monocarbamate derivative that is active in rodent models of partial and generalised seizures but has an unknown mechanism of action. Carisbamate reduced photoparoxysmal EEG responses in a proof-of-principle study in patients with photosensitive epilepsy. The results of a multiple-dose, randomised, double-blind trial in 537 patients with partial seizures provided evidence of efficacy at doses between 300 mg and 1600 mg, with tolerability equivalent to placebo in the lower portion of the efficacious dose range.4

Improving development: lessons from the past

Epilepsy, by its nature, poses challenges to clinical development. Initial studies must be done in patients with treatment-resistant seizures because a sufficient number of seizures need to be present at baseline to detect a statistically significant effect over a short time frame. Because of the seriousness of the disorder, it is ethically justified to use an untested drug in this population. However, this sets a difficult hurdle to achieve efficacy for any new treatment, and trials in this population require add-on designs to prevent deterioration in the control of seizures that would occur if pre-existing treatment was substituted with a placebo. Moreover, drug interactions can complicate trial designs. The next section is a brief discussion of lessons learned after two decades, focusing on phase I and phase II.

Phase I

Determining the best tolerated dose

Many drugs have either languished or failed because phase I trials did not expose patients to a high enough dose. Sometimes this problem arises because toxicological studies in animals have not used doses high enough to provide a cushion for studies in human beings. For example, if the animals used in toxicology studies clear the drug more rapidly than human beings, which is usually the case, sufficiently high serum concentrations might not be reached. Importantly, there should be sufficient toxicology data to attain serum concentrations in human beings that are equal to or, preferably, greater than those necessary to suppress seizures in animals.

If a drug is well tolerated in phase I, it is advisable to investigate higher doses than originally anticipated, not only because the determination of the maximum tolerated dose is one of the main objectives of the phase I programme but also because this will help to achieve doses in the highest range in patients at a later stage, adding the potential for efficacy. Conversely, if dose-related toxic effects are limiting, higher doses should be achieved through gradual titration. For example, to achieve doses of felbamate in the upper limit of the tested range, titration was required. Even then, during postmarketing many patients achieved doses higher than the 3600 mg/day maximum used during development, and benefited from greater efficacy.

Phase IIa: proof-of-principle studies

Once phase I is complete, phase IIa studies should provide some estimate of appropriate doses in terms of tolerability and, possibly, efficacy. Although there is no single trial that will provide all the information necessary to ensure successful development, there are several possibilities.

Photosensitivity tests

Photosensitivity tests are done in the subset of patients with epilepsy who develop paroxysmal epileptiform EEG discharges when exposed to a specific frequency of flashing lights. The ability to prevent the photoparoxysmal response is predictive of antiepileptic activity. Because a range of single doses of the test compound (and placebo) are assessed, these assessments can be done before toxicology studies in animals have been completed. By doing light stimulations at regular intervals after dosing, and measuring serum drug concentrations, a pharmacodynamic half-life can be estimated, which is commonly longer than the pharmacokinetic half-life. This protocol might enable the reasonable prediction of the therapeutic dose range. Photosensitivity is thought by many to be predictive of broad-spectrum activity, and particularly of activity in idiopathic generalised syndromes, although this has not been proven. In fact, one narrow-spectrum AED—vigabatrin—was effective in the photosensitivity model. Moreover, whether the photoparoxysmal model shows adequate sensitivity to detect the antiepileptic activity of all AEDs, irrespective of their modes of action, is unclear.

Small crossover studies

The crossover design can show statistically significant effects on seizures in a small group of patients, and was used in a proof-of-principle study for talampanel.
Unfortunately, a crossover study requires a long duration because of the presence of two treatment periods and a washout period; therefore, recruitment can be difficult. Also, the potential for carryover effects and premature withdrawals can make analysis problematic. Crossover studies are particularly valuable for the assessment of the cognitive effects of AEDs because each patient receives active treatment and placebo; therefore, individuals act as their own controls.

Uncontrolled studies
Open-label, uncontrolled studies are of little value when assessing efficacy because they do not enable the determination of whether an improvement in seizure control is due to a pharmacological effect rather than a placebo effect or regression to the mean. This problem is best shown by the example of cinromide, a compound that was not brought to market. Despite being associated with remarkably good responses in an uncontrolled trial in patients with Lennox-Gastaut syndrome, cinromide was no better than placebo when tested under rigorous conditions. Uncontrolled studies can be useful to investigate drug–drug interactions and to detect signals of potential efficacy in subpopulations; however, any results need to be confirmed in controlled settings.

Presurgical trials
In this trial design, patients who are hospitalised and withdrawn from all drugs for assessment of their seizures in preparation for epilepsy surgery are randomly assigned to receive either the test compound or placebo. The trial proceeds for 8–10 days and has pre-established exit criteria to prevent exposure of the patients to an excessive number or severity of seizures. Outcome is measured as the percentage of patients who complete the trial without reporting a prespecified number of seizures. The advantage of this design is that treatment is short and few patients are required. The disadvantages are that the test compound must be initiated quickly without titration and there are ethical issues because of the risk of worsening in patients randomly assigned to placebo. Recruitment has also proven difficult.

Drug interactions
Drug interactions that cause metabolic inhibition can lead to increased serum concentrations of the compound being investigated or concomitant AEDs. Besides causing unexpected toxic effects, these interactions can confound the interpretation of efficacy data; for example, if the metabolism of concomitant AEDs is inhibited by the test compound, it might be difficult to exclude the possibility that any reduction in seizure frequency was due to increased serum concentrations of other drugs. To circumvent this problem, either patients receiving particular AEDs should be excluded from the study or a blinded investigator should adjust the dose of background AEDs. Either solution can be problematic.

Induction of the metabolism of the test compound by concomitant AEDs, or vice versa, might also complicate the interpretation of trial results. In this situation, the concentrations in the blood of either the test compound or associated AEDs might be reduced, resulting in a reduction in, or loss of, efficacy. For these reasons, drug-interaction studies must be completed early in development. Clinically important metabolic drug interactions can be anticipated with appropriate in-vitro experiments.

Phase IIb
Activity in different syndromes
Trials are usually done first in patients with partial epilepsy and then in patients with other epilepsy syndromes. There has been great interest in exploring other syndromes earlier in development, and this approach can have advantages for some drugs. For example, the marketplace is extremely crowded with drugs for partial seizures, and a new drug would have to show a substantial advantage to be successful. By contrast, there are many unmet needs in other syndromes, particularly devastating paediatric syndromes, such as Lennox-Gastaut syndrome, West syndrome, severe myoclonic epilepsy in infancy, and progressive myoclonic epilepsies. Showing effectiveness in these syndromes can also have a carryover effect because it would provide evidence that a drug has broad-spectrum activity, which is a valued characteristic for a new AED. If trials in these syndromes are done in...
isolation, orphan-drug status can be sought, and, in the near future, modern-era drugs might be approved for a special syndrome (eg, Lennox-Gastaut syndrome) before they obtain approval for partial epilepsy. Also of note is the successful trial of levetiracetam in juvenile myoclonic epilepsy, which led to its approval for use in this syndrome from both EMEA and the FDA. Levetiracetam was the first of the recently developed drugs to obtain such approval, indicating that, although these trials are difficult, they are by no means impossible.

**Endpoints**

A 50% reduction in seizures is a clinically useful measure of improvement. Of course, the ultimate goal is freedom from seizures but this is rarely achievable in previously refractory patients. There has been enthusiasm, particularly from the FDA, for moving away from a 50% seizure reduction and for a continuous distribution plot showing the proportion of patients with any given percentage change in seizure frequency versus placebo (figure 3).

**Phase III: monotherapy**

The FDA and EMEA have substantially different requirements for approval of monotherapy. In fact, the FDA has approved only two second-generation AEDs, oxcarbazepine and topiramate, for initial monotherapy. The problem relates to the conflict between a robust, interpretable trial design and the ethics of doing such a trial. In particular, the FDA does not deem that showing equivalence or non-inferiority are acceptable reasons to grant approval for monotherapy in epilepsy, and has made it a requirement that a new drug shows superiority over a comparator. This restriction has been problematic because of the risk of serious harm if patients with epilepsy are randomly assigned to receive the placebo as a comparator. New trial designs address these concerns. One design randomises refractory patients to two arms: one of which receives, as an add-on therapy, a high dose of the test drug, and the other a low dose (pseudoplacebo) of the test drug or of another AED. Concomitant medication is then withdrawn to test the effects of the two treatments as monotherapies; the outcome measure is the time to meet the exit criteria (eg, a worsening in seizure control). The ethics of this design came under scrutiny but not before nine such trials had been completed. These studies have led to the creation of a control data set that predicts the behaviour of a pseudoplacebo in this particular trial setting. The FDA has now accepted the use of these historical controls under specific circumstances, and several trials using this approach are in preparation.

Superiority designs typically need to investigate doses at the upper limit of the tolerated range to maximise the probability of identifying a difference compared with the comparator, including historical controls. Consequently, these trials typically result in the approval of dose ranges that might be far in excess of those found to be optimal in newly diagnosed patients during postmarketing. To avoid this shortcoming (and the difficulty in extrapolating long-term outcome data from short-term superiority trials), the EMEA guidelines state that a long-term active control trial versus a gold standard at optimised doses needs to be completed to obtain approval for monotherapy in newly diagnosed epilepsy. For this design, the EMEA accepts proof of efficacy on the basis of non-inferiority or therapeutic equivalence, although additional supportive evidence of efficacy (typically from a short-term superiority trial) is also required.

**How can we predict a blockbuster?**

It would be advantageous, both to those with an interest specifically in epilepsy and to the enterprises involved in drug development, if highly promising drugs are identified early in the development process. This would aid the allocation of resources, increase the potential for venture funding, and encourage the overall enthusiasm of investors. Although some predictions can be made, unfortunately, it is easier to identify red flags than signals of great potential (chequered flags).

**Red flags**

Early indications of a low potential for success are mainly influenced by maximum serum drug concentrations, drug interactions, and tolerability. A reasonable estimate of the serum concentrations required to be effective in human beings can be made from maximal electroshock studies in rodents. When serum concentrations effective in the maximal electroshock test cannot be achieved in human beings, for whatever reason (or cannot be sustained because of a short half-life, in the absence of evidence for a longer pharmacodynamic effect), there should be concern for the ultimate success of development. Drugs that are substrates of polymorphic enzymes, such as CYP2D6, CYP2C19, and CYP2C9, might also be problematic because of the high pharmacokinetic variability expected in relation to genetic polymorphisms.

Drugs that are enzyme inducers are increasingly less popular because of their potential to cause drug interactions, bone loss, and disruption of the internal hormonal environment. Although enzyme induction is harder to predict preclinically than enzyme inhibition, some methods are available. By contrast, enzyme inhibition is easily tested on microsomes or enzyme systems in vitro, and the finding of inhibition of CYP3A4, by which several drugs are metabolised, would be a substantial blow to a development programme. Finally, adverse effects such as marked fatigue or cognitive slowness would be unwelcome nowadays. Unfortunately, rare serious idiosyncratic adverse effects are unlikely to be identified in premarketing studies.
Review

Search strategy and selection criteria
Data for this review were identified by a search of PubMed with the terms "pharmacology", "drug development", and "clinical trial" combined with the terms "antiepileptic drugs", "anticonvulsants" and the names of individual compounds. Searches of the authors' files were also done. Searches covered the period up to March 31, 2007. Abstracts were only included when a complete published article was not available. Only studies published in English were reviewed. The purpose of the article was not to provide a comprehensive review of all studies but to highlight those that, on the basis of the authors' judgment, are particularly relevant.

Chequered flags
Whether a drug will be a blockbuster is difficult to predict during the early stages of development. Theoretically, predictors of success should include mechanisms of action and efficacy in early trials. In practice, however, mechanisms of action have not been useful as predictors. In fact, some drugs with novel mechanisms, such as tiagabine, have not fared well, whereas others where the mechanism of action is strongly tied to existing drugs, such as oxcarbazepine, have done much better. Efficacy signals in early trials without the support of evidence from double-blind, placebo-controlled trials can be misleading. However, a high seizure-free rate in a refractory population in a placebo-controlled trial would be a positive sign. Indeed, seizure-free rates greater than 10% have not been achieved in placebo-controlled trials in patients with frequent seizures. Other promising information includes the ability to initiate an effective dose without titration, the absence of drug interactions, and excellent tolerability. Finally, data suggesting a niche in which a particular compound would surpass other available therapies would be extremely useful. This can include trials in subpopulations or the demonstration of benefit in a novel outcome measure.

Future directions
The aims for the future are to validate novel trial designs and to continue to learn from trials in progress. Recruitment for phase III add-on trials is increasingly difficult as more effective therapies enter the market. In particular, patients with refractory epilepsy are unlikely to agree to participate in a trial that might include as much as 6 months of no change in therapy (2 months of prospective baseline and 4 months on treatment). An alternative would be to use novel add-on time-to-therapy seizure designs (ie, studies where patients exit after having a predefined number of seizures) that would enable patients to exit the trial if they are doing poorly. Monotherapy trials with historical controls are being initiated; their success will mean a clear path to FDA approval.

Another area of intense activity over the next few years will be to optimise the methods for assessing therapies aimed at suppressing acute seizures or seizure clusters. The existence of an available therapy (rectal diazepam) and the reluctance of the FDA to accept non-inferiority trials will complicate the study design. Trial designs for special populations, such as those with infantile spasms, epileptic encephalopathies, and idiopathic generalised epilepsy syndromes, also need to advance so that better drugs can be developed for these populations.

Contributors
All authors contributed equally to the preparation of the manuscript.

Conflicts of interest
EP has received speaker fees, consultancy fees, or research grants from Cyberonics, Eisai, GSK, Johnson & Johnson, Ibsa, Novartis, NPS, Pfizer, Neuronox, Ovation, Sanofi-Aventis, Schwarz Pharma, UCB Pharma, and Valeant. JF has received less than $10 000 in speaking fees or consultancy fees from Eisai, Valeant/Schwarz, Spheres, Johnson & Johnson, and AstraZeneca. She has also provided consulting services to UCB, Marinus, Johnson & Johnson, Teva, Schwarz, Valeant, Shire, Intrasal, Jazz, and Eisa. She serves as chair of the data safety monitoring board for a study sponsored by Johnson & Johnson. Throughout the past year, she has provided these services as an agent of the non-profit organisation the Epilepsy Therapy Development Project, which contributes a fixed amount to her salary for this and other services, including chairing their scientific advisory board and grant review. The amount of contribution is not linked to the amount of consulting activity. 20% of her salary is derived from work on behalf of FACES (Finding A Cure for Epilepsy and Seizures), a non-profit organisation. She has been site principal investigator on studies of brivaracetam (UCB), RW-333639 (Johnson & Johnson), seletracetam (UCB), talampanel (Ixas), lacomeside (Schwarz Pharma), retigabine (Valeant), rufinamide (Eisai), and the thalamic stimulator (Medtronics). She is national principal investigator for an ongoing study of rufinamide, retigabine, and the vagus nerve stimulator (Cyberonics). MB has received speakers or consultancy fees from the American Epilepsy Society (AES), BIAL, Destin, Gerson Lehrman Group Councils, Janssen-Cliag, Jazz Pharmaceuticals, Johnson & Johnson, Ovation, NeuroAdjuvants, Neurocrine Biosciences, Shire, Teva, and Valeant. In the past 3 years, MB has received research grants from Jazz Pharmaceuticals, Johnson & Johnson, Teva, and the Epilepsy Therapy Development Project.

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