Antiepileptic drug trials: the view from the clinic*

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ABSTRACT – A golden age of antiepileptic drug development has yielded over a dozen useful new compounds, but the nature of clinical trials has made translation to practical use in the clinic difficult. Most clinical trials are designed for regulatory purposes and fail to answer critical clinical questions. These questions include: which drug is best as initial therapy, which drugs work as monotherapy, what are good drug combinations, what is the best starting dose and titration schedule, what is a reasonable target dose, what is the shape of the dose-response curve and does it vary significantly between patients, what is the true incidence of side effects, and what is the long-term efficacy of the drug? Most of these questions could be answered by changing trial designs, but many changes would entail additional time and money. There are encouraging signs that trials with procedures more directly applicable to the clinic are becoming common. These include direct comparative trials, longer trials with emphasis on seizure freedom, and trials with more flexible dosing schedules. In the past, funding of longer and more naturalistic trials has fallen to government agencies, but commercial funding has been obtained for several recent studies. Better quality control, innovative endpoints, structured searching for side effects, and standardisation of data collection are also promising topics for development.

Key words: epilepsy, clinical trial, antiepileptic drug, trial design

The past quarter-century has been a productive era for the development of antiepileptic therapies. Randomised controlled clinical trials have yielded over a dozen new drugs, many with attractive characteristics. There are new comparative data, and innovative collaborations for answering key clinical questions are developing. Nevertheless, there is a growing sense of lost momentum as the years pass without a true breakthrough drug for refractory epilepsy. Benefits of adjunctive new drugs over adjunctive placebo are, for the most part, modest (Beyenburg *et al.*, 2010).

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There is also a feeling that somehow our past clinical trial designs have failed us and our patients. We still have many unanswered questions about current drugs. This paper will not include discussions of the historical evolution of trial design, of why the new drugs have not proven more efficacious than the old drugs, or what should be done differently during preclinical development; these issues are discussed extensively elsewhere in this edition (by Emilio Perucca) and in a recent review (Löscher and Schmidt, 2011). I shall focus on the difficulties of translating clinical trial data into everyday practice, by posing common clinical questions and asking to what extent they have been addressed by clinical trials, followed by suggestions for improvement.

Major issues in clinical trials of antiepileptic drugs

Early clinical trials of a new drug are designed to answer questions necessary for regulatory approval. Internal validity is of paramount importance; there is a tacit consensus that at this juncture questions of comparisons to other drugs, dosing, patient selection, and long-term efficacy can be deferred. However, clinicians face such questions every day. This is the gap which must be bridged.

The major problems with translating trial data to clinical practice have been aptly summarised (Marson and Williamson, 2009):

– Research populations are not representative of patients encountered in clinical practice (*i.e.* external validity is questionable);

– Efficacy outcomes used in trials are not relevant to patient goals (*i.e.* minor reductions in seizure frequency may be statistically but not clinically significant);

– Dosing in clinical trials is inflexible; with typically rapid titrations to fixed doses;

– Trials are too short to predict long-term drug efficacy;

– Trial data do not help when choices between drugs must be made, because most studies compare the experimental drug to placebo, not to another drug;

– A sixth issue may be added: tolerability surveillance. Clinical trial methodology has not been optimal for early detection of side effects.

Research populations *vs* clinical populations

To what extent are the subjects in a clinical trial similar to the universe of patients with epilepsy seen in a clinical practice? They are not very similar because most trials enrol adults with very refractory and very frequent partial-onset seizures, sometimes the same individuals trial after trial. This improves the internal validity of the study at the expense of external validity. As a corollary, trial results are not necessarily predictive of efficacy, and especially of tolerability, in patients with less severe or less frequent seizures.

On the other hand, study patients are dissimilar to one another because they are entered on a whole array of baseline medications, and with a wide variety of aetiologies, probably extending down to the molecular level. This makes it difficult to identify subgroups of patients who may respond much better or much worse to a particular drug. This roadblock may have to await advances in pharmacogenetics.

Children

Paediatric neurologists have clamoured for years for earlier data. The main data needed to treat children are pharmacokinetic, toxicological, and dosing information, not efficacy. Alexis Arzimanoglou, in this workshop, suggests obtaining this information from pilot studies in children with severe childhood epilepsies, such as the epileptic encephalopathies. However, as he suggested, there is an easier way to address this problem.

The lower age limit for inclusion in clinical trials of new AEDs for partial-onset seizure, which translates directly to labelling recommendations, is biologically arbitrary and in any case is difficult to remember since it varies for each new drug.

There is no good scientific reason to exclude children above some pharmacokinetically appropriate age, which might be 2-6 years of age for most drugs rather than 12 or 18. Above this age, the aetiologies and clinical manifestations of partial-onset seizures do not differ much from those for adults. The hurdles are more related to caution on the part of sponsors and regulatory agencies, who are concerned about protecting children. However, there are now guidelines from the Pediatric Research Equity Act to aid the extension of drug development to paediatric populations (Garofalo, 2006). On the other hand, clinicians need *fewer* clinical trial data on efficacy in children: it is a waste of resources to do efficacy trials in older children with partial-onset seizures since results can be extrapolated from those in adults. This statement does not apply to syndromes which are seen only in children, for which clinical trial data are needed.

Older adults

We need more data on older adults, especially tolerability and dosing information. The Veterans' Administration Cooperative Study of seizures in the

elderly (Rowan *et al.*, 2005) provided class I data that lamotrigine and gabapentin are better tolerated than carbamazepine in older adults, but neither have become standard for this purpose. A comparable study of some of the newer drugs is needed, which should include levetiracetam and others.

Persons with infrequent seizures

Not all persons with refractory epilepsy have frequent seizures. Patients with established epilepsy but with seizure frequency too low to qualify for short-term trials constitute a neglected population, but are quite common. A "time to the nth seizure" design is more appropriate for this group (Ben-Menachem *et al.*, 2010). This could be a difficult and lengthy undertaking, but part of the statistical difficulty can be overcome by utilising analysis of each individual's degree of seizure clustering (Hopkins *et al.*, 1985) (*i.e.* not assuming a Poisson distribution of seizures over time) and by taking into account individual baseline seizure frequencies (Cowling *et al.*, 2007). The particular method for doing this can vary, but should be based on the individual patient's baseline seizure pattern. Mattson (1997) and others have suggested using time to the "n^{th}" seizure as an endpoint, where "n" is the patient's average monthly seizure frequency during a baseline (French, 2001). One month may be a usable epoch for patients with frequent seizures but would preclude inclusion of those with rarer events.

Here is a radical, though not novel (Gilliam, 2003), idea: negotiate an individual study endpoint with each patient. Some patients may be willing to declare a study a failure if they have a third complex partial seizure, some may insist on stopping the study if they have a single convulsion. After all, this is what we do as clinicians; we decide, in consultation with the patient, when a treatment is a success or a failure. The endpoint would need to be determined in advance, not retrospectively. In any event, some kind of "patient-centred outcome criteria" might allow inclusion of patients with a broader range of temporal seizure patterns. This, of course, would create difficulties for statisticians.

Inclusion of clinicians in trial design

Clinical investigators, most of whom are practicing clinicians, are now virtually excluded from the early design phase. Investigators' meetings were once opportunities for thoughtful discussion of trial design with an expectation that suggestions would be considered and trials modified by mutual agreement with the sponsor. These meetings now entail little more than recitation of a predetermined and pre-packaged trial plan; investigators can either take it or leave it.

Clinicians provide valuable perspective which should not be ignored. Investigators also complain of the interposition of clinical research organisations which have little knowledge of epilepsy.

Reliability

Are the trial data trustworthy? Physicians still, for the most part, believe that they are. However, some disquiet is discernable among clinical investigators. The answer hinges on the reputation of the sponsor and the investigators. Clinical trials were once the exclusive domain of a few academic investigators in developed countries, but the trend has been toward enlisting large numbers of investigators all over the world. With more drugs available in developed countries, it has become harder and harder for experienced investigators to enroll patients. This has the desirable effects of increasing the diversity of the study populations and providing earlier access to new drugs in underserved areas. However, it brings with it questions regarding data compatibility, as stratifications of results from different geographical areas make clear. It is also disturbing that placebo response rates have risen gradually in recent years: it is unlikely that we are producing more convincing placebos. The effect of these problems has not been to produce false positives; that is, to bring forth drugs which are not really effective. Rather, it is probably producing false negatives: effective drugs may be discarded because the noise in the clinical trials precludes demonstrating statistical efficacy.

It has been suggested that one factor in this phenomenon is the greater expectation or greater impact of the doctor/patient relationship among patients whose medical care was inadequate before the clinical trial. However, this should have increased the response to active drug as well as placebo, which has not occurred. Furthermore, there is a poor correlation between development of a country and the quality of trial data: excellent data may come from poor countries and *vice versa*. As Krause discusses in this volume, in order of importance, the factors predicting trial quality are: proper subject selection, investigator characteristics, country, and geographical area. It is critical for sponsors to select investigators carefully and for monitors who are knowledgeable to examine procedures closely during the trial.

Endpoints: measurable *vs* meaningful

Standard endpoints for placebo-controlled trials of adjunctive therapy are *median percent seizure reduction* from baseline or *responder rate*; patients with seizure frequency halved from baseline. Neither are

of much importance to patients or to their quality of life (Ben-Menachem *et al*., 2010). Overwhelmingly, patients want to be *seizure-free*. This is not a practical endpoint for early trials in refractory patients, but it must be borne in mind as experience with a drug accumulates. Although few refractory patients will become seizure-free in these trials, the trial report should include the percentage of seizure-free patients and the period of time of seizure freedom. *Time to remission*, for a meaningful period such as a year, should also be reported for patients continuing on therapy.

In the absence of seizure-freedom, how much reduction in seizure frequency is meaningful? There are three points of view*: patient, commercial,* and *regulatory.* From the *patient's* perspective, this is an individual subjective question conditioned by the expectations and previous experiences with drugs. At the study population level, it tends to be a *commercial* question: how does the drug stack up compared to other available agents, considering also its side effect profile? ILAE guidelines (Glauser *et al*., 2006) establish a 20% reduction in median seizure frequency above placebo as the minimum to be considered clinically significant. Perhaps not coincidentally, this is the approximate threshold at which developers have historically (since about 1993) made a go/no-go decision on commercialisation for new adjunctive agents for refractory partial-onset seizure. However, it seems unlikely that this degree of improvement is experienced as a better quality of life for many patients. Finally, and this may be surprising to clinicians, the lowest bar of all, at least theoretically, is *regulatory*; there actually is no lower limit of efficacy below which a drug is ineligible for approval, so long as it shows statistical efficacy in the clinical trials.

For monotherapy of new-onset seizures, the typical endpoint of *time to the first seizure* has more clinical relevance, but again should be followed up by tracking of continued seizure freedom for a clinically-meaningful time; three years is not too long (Perucca and Tomson, 1999).

Thoughts on the monotherapy conundrum

Do clinicians care about monotherapy efficacy? We should. Although all drugs so far demonstrated to have adjunctive efficacy probably have some efficacy by themselves, this is neither logically nor biologically necessary. More to the point, studies have disclosed differences in efficacy for new-onset epilepsy (Kwan, 2003). This is of direct clinical applicability and more of these head-to-head comparisons are highly desirable, as a recent ILAE recommendation notes (Glauser

et al., 2006). There is an ongoing trial comparing zonisamide with timed-release carbamazepine for initial monotherapy and other trials of this design are planned; this is an encouraging development. Naturalistic comparative trials should be extended to adjunctive therapy as well, an example being the recent demonstration that pregabalin was inferior to lamotrigine as an adjunct. (Baulac *et al*., 2010).

Conversely, some drugs are best as monotherapy. Felbamate is virtually worthless as an adjunct, at least to enzyme-inducing agents, but is an excellent monotherapy drug for patients whose risk-benefit assessment is favourable (Pellock *et al*., 2006). We may be ignoring other good monotherapy drugs because of the difficulty of performing monotherapy trials.

Monotherapy trials obviously present more difficulties, both in execution and interpretation (Perucca, 2008). It should be recognised that total reliance on a drug new to a patient, which is what monotherapy means, entails unavoidable risk. It is simply naïve to think otherwise. For this reason, monotherapy trials are easiest to perform and thought to be safer in patients with new-onset seizures.

For patients with established epilepsy, withdrawal to monotherapy trials have used various "*failure criteria*" as the primary endpoints, typically the same for all patients, such as doubling of two-day or thirty-day seizure frequency from the pre-randomisation baseline. Trials employing doses lower than the minimum effective dose (derived from adjunctive trials) as the control can legitimately be termed "pseudoplacebo" trials. Trials using lower and higher, but established as effective, doses of the experimental drug as a control and trials using the standard starting dose of an established drug as a control have been rather pejoratively characterised as pseudoplacebo trials. However, at least the initial stages of these trials can be considered to be active-control designs; for example the 15 mg/kg valproate control was not known *a priori* to be less effective than any dose of an unproven drug. We know this only in retrospect. At the time, it appeared to be a reasonable approximation of equipoise, especially when one considers the very strong belief that monotherapy was the highly desirable goal even for refractory patients. Furthermore, the safety of these trials depended heavily upon very close patient monitoring by very experienced investigators, a condition perhaps no longer to be taken for granted. One suggested way around the difficulty of monotherapy trial design is the historical control design of withdrawal to monotherapy (French, 2001). The scientific basis for this design, however, relies upon the data derived from the previous, randomised, blinded, parallel-controlled monotherapy trials, and the historical control design still involves the risk of reliance on an untried therapy for a serious condition.

Besides choice of control, an equally important factor in patient safety for monotherapy trials is the *choice of stopping criteria*. One can criticise the one-size-fits-all approach; it does not parallel clinical practice wherein the patient and physician jointly decide when a therapy has failed and needs to be altered. Perhaps the stopping criteria should be negotiated with each individual patient in such trials. Furthermore, the investigator may be allowed to titrate both the control and experimental drugs optimally as he or she would in clinical practice, a design which has been advocated for all monotherapy trials (Weijenberg *et al.*, 2010). This idea has been put into practice in some recent open-label initial monotherapy trials.

A trial design employing more naturalistic "failure criteria" might in fact be more ethical for both monotherapy *and* adjunctive therapy trials than the current classic adjunctive therapy design, which does require patients to persevere for the several weeks of the trial. They can quit, of course, but most feel an obligation to finish the study. Randomisation to placebo, even in adjunctive therapy trials, carries risk; the rate of sudden death is higher than in patients randomised to active drug (Ryvlin, 2011).

Using specific drugs

What do clinicians treating patients with epilepsy want to know about a particular drug from clinical trials? To what extent have current trial designs answered these questions? What trials are still needed to answer outstanding clinical questions? What improvements in future trials can be made to ensure that all possible clinical questions are answered as early as possible in drug development? These are very broad issues; let us begin by narrowing the discussion to a few key questions in the minds of every clinician, and then examine the extent to which clinical trial data have answered these questions. In doing this, we will not review exhaustively the data already in hand, but will point to areas of ignorance which may be remediable:
– Dosing considerations
  1. What is the best starting dose?
  2. What is the best initial target dose?
  3. Can the drug be started quickly or "loaded"?
– Choice of drug
  1. What is the best initial drug for each seizure type?
  2. What are the best combinations of drugs for each seizure type?
  3. What is the best drug for defined subpopulations?
– What is the drug's long-term efficacy (effectiveness and tolerability)?
– Is the drug well-tolerated and safe?

Dosing strategy: a critical difference between trials and practice

What is the best starting dose and titration schedule?

No area better illustrates the gap between clinical trial designers and clinicians than dosing. The very first consideration is *initial dose*; with few exceptions, labelled recommendations for initial dose are too high for most drugs for most patients. Why is this? The reason is time, which translates to money; extending clinical trials to include a slow-titration arm is expensive. Furthermore, regulators will only allow labelling to include tested dosages. Subject impatience to move on to a therapeutic dose may be cited, but is a spurious excuse, since trials already take many weeks. This disparity has been well-demonstrated for topiramate, which is clearly better tolerated at lower than higher early doses. Many clinicians routinely start drugs at half or less of the labelled starting dose, such as 500 mg/day for levetiracetam and 300 mg/day for oxcarbazepine.

The other side of the coin is that we need more data on tolerability of larger initial doses, loading doses, of other new drugs. Drugs which can be started quickly have gained an advantage, especially in hospital. It is probable that we could load some other new drugs safely and with reasonable tolerability, based upon their pharmacokinetic profiles (Ramsay *et al.*, 2010). Intravenous formulations are also being developed using technologies for solubilising drugs, which would expand the range of rapidly-effective agents.

What is the target dose?

Here is a critical question which clinicians face on a daily basis. It is often skipped or elided in labelling recommendations. Guidance for clinicians can be improved. The heart of the problem has been described; it is not practical to titrate every patient to the maximum tolerated dose of every drug tried, and the incremental benefit of increasing a drug beyond a relatively low dose is often marginal; most patients who achieve complete control do so at rather average doses (Löscher and Schmidt, 2011).

One would think, then, that product labelling would recommend a target or average dose. In fact this recommendation is often absent even when the data are available from the clinical trials. There is the implication that the old practice of titrating to effect is still the way to go. Here is the dosing recommendation for Keppra XR: "Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every two weeks to a maximum recommended daily dose of
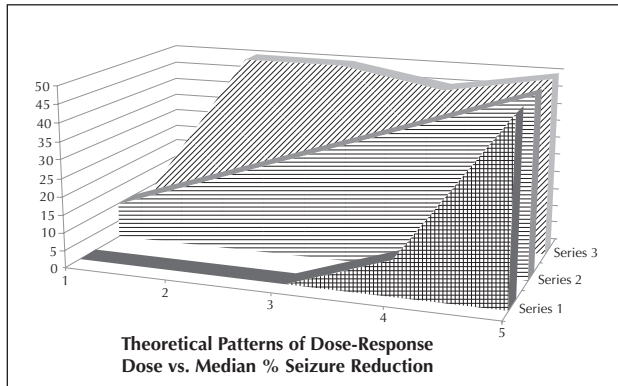
Figure 1. Three dose-response patterns which may apply to the study population or to individual subjects.

Table 1. WHO defined daily doses of antiepileptic drugs (revised 21 Dec 2010).

Drug	Dose (mg/day)
Carbamazepine	1,000
Clonazepam	8
Eslizcarbazine	800
Ethosuximide	1,250
Felbamate	2,400
Gabapentin	1,800
Lacosamide	300
Lamotrigine	300
Levetiracetam	1,500
Oxcarbazepine	1,000
Phenytoin	300
Phenobarbital	100
Pregabalin	300
Primidone	1,250
Rufinamide	1,400
Tiagabine	30
Topiramate	300
Valproate	1,500
Vigabatrin	2,000

3,000 mg" (Physician's Desk Reference, 2011a). A more informative label is found for Lamictal: "Usual maintenance dose (for patients not on enzyme-inducers nor valproate) is 225 to 375 mg/day" (Physician's Desk Reference, 2011b). The latter statement is much more helpful to clinicians. Another way to look at the target dose is as the "decision point dose", that is, the dose at which, if *no* clinical benefit of the drug has been observed, the odds favour switching drugs rather than pushing to the maximal tolerated. The value of this dose, however, depends upon the topography of the dose-response curve; if it is linear then a steady reduction in seizure frequency would be expected with increasing dose. This is the desired result in dose-ranging clinical trials, but in fact other patterns are possible. For some drugs, a plateau is reached at relatively low doses and there is little incremental benefit of higher doses. For example, doses of topiramate above 400 mg/day or doses of vigabatrin above 3 g/day benefit few patients. There is a third possibility, which is that little benefit is seen until some sort of threshold dose is reached, at which point there is a large jump in efficacy *(figure 1)*. Dose-ranging trials with sufficient range will display these patterns for the population studied, but the problem is that they may not predict an individual patient's pattern. If a subset of patients displayed the third type of response, this would not be detected by the typical clinical trial because each patient is not tested for a sufficient length of time on each dose, only their target dose. This problem could be addressed by holding each patient at a lower dose long enough to measure a meaningful effect. No trial has done this because of time and cost; only one trial, with zonisamide, has partially incorporated this feature (Faught *et al*., 2001).

To be fair, we must acknowledge that selecting a target or decisional dose is not straightforward. One approach is to use the World Health Organization Defined Daily Dose (DDD). WHO committees define

this dose mainly to allow usage comparisons between drugs, not really as equal-efficacious or "best" doses. This results in some paradoxes for antiepileptic drugs; some DDDs seem to be average or most-commonly used doses (phenytoin), some are the average doses used in clinical trials (lamotrigine), and some are the maximum tolerated doses (ethosuximide, primidone) *(table 1)*. The decisions of the WHO committee are based mainly on the drug labelling; which as we have seen, does not always provide adequate guidance. It is worrisome that the DDD could be used by insurance companies or governmental agencies to impede physician choice in dosing, especially for the use of doses higher than the DDD.

Is there a better way to guide clinicians toward the most reasonable target dose, the one with the best balance of tolerability and chance of meaningful seizure control? There is always expert opinion, which is often close to the DDD. A more precise alternative method would be to define operationally, in advance, what is meant by "best target dose". For example, this dose could be one which is >10% better than the next lower tested dose for 50% seizure reduction, but with fewer than 25% dropouts during randomised blinded clinical trials (all cause, not just "due to adverse events"). We could then select the target dose as the highest dose which met these criteria. This calculation produces some variations from the DDD. For example,

oxcarbazepine at 1,200 mg/day meets these criteria: the responder rate was 41% (*vs* 27% for the next lower tested dose, 600 mg/day); the dropout rate was 21% (Barcs *et al*., 2000). Oxcarbazepine at 2,400 mg/day does not qualify because although the responder rate was 51%, the dropout rate was 67%.

Empowering patients by clear reporting of trial results

Better still, in clinical practice, why not allow patients to assist with choice of drug and target dose? To facilitate this, published results of clinical trials should include tables with the following headings: "dose per day", "efficacy" (primary endpoint), "seizure-free rate", and "dropouts".

For reasonably safe drugs, some patients may in fact opt for a higher target dose because they are willing to accept a higher chance of typical side effects for a greater chance of seizure control. This may be especially true of patients with new-onset seizures: we often choose lower target doses for these patients (I see many patients targeted to levetiracetam at 1,000 mg/day) in the belief that they may not need higher doses, but in fact the looming possibility of a recurrent seizure is very stressful. Some patients may desire a better margin of safety despite a greater chance of side effects, most of which, after all, are dose-related and reducible.

To reiterate a point, this comment bears on a critical difference between the primary goal of clinical trials, to demonstrate efficacy for some arbitrary criteria such as time to first seizure and *the primary goal of the patient, seizure freedom*.

Long-term efficacy

It is essential to know whether drugs proven tolerable and effective in short-term trials hold up over the long run. Careful follow-up of patients transitioned from double-blind trials to open-label treatment with an experimental drug can provide some insight, but this is an enriched population which has been stripped of drug failures. Trials with new-onset patients in which the end-point is retention provide useful information (Marson *et al*., 2007a; Marson *et al*., 2007b). It is more difficult to obtain this information on adjunctive therapies in refractory patients, since Kaplan-Meier survival curves for continued drug use are dismal, as patients and their physicians continue to search for freedom from seizures. More effort is needed in follow-up of patients taking their second or third drug, not their first or tenth. There is now an opportunity to track the clinical course of such patients using large national databases, for example those populated by Medicare

or commercial insurance clients. Some efforts along these lines have been made, but have not been sustainable because of lack of funding and problems with patient privacy regulations.

Choice of drug

A simple question: what is the drug of choice for initial therapy of partial-onset seizures? That this is still a legitimate question in 2012 (Chadwick *et al*., 2009) is frustrating to clinicians. It is beyond the scope of this review to describe the clinical trial data comparing drugs to one another. For a comprehensive reference, the recent report of the Agency for Healthcare Research and Quality of the US Department of Health and Human Services (Talati *et al*., 2011) may be consulted, though I would advise against taking seriously the rather simplistic conclusions on drug choice incorporated into this report. There are other metanalyses (Rheims *et al*., 2011) but they do not really take the place of direct comparative trials. We are making some progress in formulating an answer. In an example from the SANAD trial, (Marson *et al*., 2007a, 2007b), the authors concluded that lamotrigine is the best drug for this purpose, based mainly on its tolerability. Although this study was unblinded. We have also made progress in choosing the best drug for generalised seizures, an example being the rediscovery (30 years after the initial study) (Sato *et al*., 1982) that ethosuximide and valproate are equally efficacious for absence, and now that each is more efficacious than lamotrigine (Glauser *et al*., 2010).

What are the best drug combinations?

For clinicians, choosing the second drug is in fact more problematic than choosing the first drug. Practically, this means selecting the best combination. Even if the goal is conversion to a second monotherapy, patients will be on the combination for a time. It has not been practical with standard trial designs of add-on drugs for refractory partial-onset seizures to sort out which combinations work best (French and Faught, 2009). A retrospective analysis of a transition to monotherapy study suggested that the valproate/lamotrigine combination was better than other combinations with lamotrigine (Brodie and Yuen, 1997). There is also a retrospective study which suggests that lacosamide works better with non-sodium channel drugs (Sake *et al*., 2010), and a recent trial suggests that lamotrigine is superior to pregabalin as an adjunctive agent (Baulac *et al*., 2010). However, it takes a very large patient population, over 600 subjects in the lamotrigine/pregabalin comparative trial, to detect potential small differences in efficacy. Overall, we know little about other

combinations. It is now time to exploit clues from rodent studies of drug combinations (Luszczki *et al*., 2010), especially since we have more drugs with clearly-defined primary mechanisms of action. However, these results may not be directly applicable to our refractory epilepsy patients because the endpoint in the rodent studies is the ED50; it may be easier to find an ED50 than the ultimate clinical endpoint, the ED100!

We also have large populations of patients on certain baseline drugs. For example, the large numbers of patients on levetiracetam or lamotrigine monotherapy could be utilised, by randomising those who need a second drug to drugs with different, well-defined mechanisms; lacosamide, pregabalin, ezogabine, and perampanel could be considered. Head-to-head trials require a certain amount of courage on the part of commercial sponsors since the winners cannot be predicted, but there are precedents (Privitera *et al*., 2003; Baulac *et al*., 2010; Ramsay *et al*., 2010).

Tolerability: no surprises

Clinicians do not like unpleasant surprises. This eventuality can be made less likely by better surveillance during clinical trials. The usual procedure has been to ask open-ended questions at trial visits. There is a better way. Surely we now know enough about likely side effects of antiepileptic drugs (Perucca *et al*., 2009) to institute a more active search during early trials. However, this is not a common practice; of 56 AED trials in children, only six used a standard method of surveillance for side effects and often the method of collection of toxicity data was unspecified (Anderson and Choonara, 2010). There are published adverse effect scales (Gilliam *et al*., 2004). The common occurrence of depression should mandate the inclusion of appropriate measuring tools during trials (Gilliam *et al*., 2006). There are also validated scales for anxiety (Spitzer *et al*., 2006), and finally we should be able to anticipate and detect cognitive issues (Park and Kwon, 2008). It is especially important to assess the impact of a drug on cognition in children, for better or worse. Quality of life is probably related to a composite of all these factors and is also a valid secondary efficacy criterion.

Had we included these active probes, we would have characterised the adverse cognitive effects of topiramate and the personality problems with levetiracetam earlier. These negative effects were, for the most part, observed during clinical trials but a more accurate description of their nature and frequency would have been possible before open-label experience. The

rejoinder to this suggestion is that active pursuit of adverse effects will elevate their reported incidence. This is undoubtedly the case, but the playing field for future drugs would be level.

Safety: there will be surprises

Monitoring during trials

Safety is not the same as tolerability: it implies risk to permanent health or to life. The reality is that it is not possible to detect rare serious side effects with the usual population size of AED trials. Nevertheless, monitoring of laboratory tests, cardiac function, and the like should be maintained. A growing practice, which should be mandatory, is the use of an independent data-safety monitoring board with access to unblinded data throughout the trial. This committee may have the ability to detect a "signal" of a possible drug-related safety issue before formal statistical analysis, thus focusing attention on potential problems. This is not a universal practice: of 56 reviewed trials of AEDs in children, only three employed an independent safety monitoring committee (Anderson and Choonara, 2010).

Teratogenicity

Few issues are more important to the clinician treating large numbers of young women with epilepsy. It has taken agonisingly long to characterise the foetal effects of our new drugs. It is important to continue pregnancy registries. It is imperative for companies marketing a new AED to set up their own registry or to cooperate actively with established national or international registries such as the North American or European registries (Meador *et al*., 2008).

The ideal AED clinical trial program

Clinicians would like efficacy, tolerability, and safety information on a wide range of dosages for paediatric, adult, and older adult populations. Demonstration of adjunctive efficacy for refractory patients as a first step is reasonable, but even a hint of adjunctive efficacy should raise the possibility of monotherapy potential. Trials for specific seizure types or epilepsy syndromes should follow. Eventually, best combinations should emerge. No drug has been subjected to such an ideal program, which would require a long time and much money. We have much more data on drugs developed by large companies who enjoy a long patent life (*e.g.* topiramate) than drugs developed by small companies with only a few years of exclusive sales

(*e.g.* zonisamide). Some mechanism for extending the exploration of a drug's usefulness after its patent has expired must be found. We are almost certainly failing to exploit fully the drugs we have, as well as the drugs we shall have.

Conclusions

The system of clinical trials of antiepileptic drugs employed since the 1980s has, for the most part, served us well, but does not always yield the answers most relevant to clinicians. Recommendations for trial improvement may encompass these areas:
– Inclusion in clinical trials of populations more representative of those encountered in clinical practice (improved external validity);
– Measures to reduce the placebo response rate: careful selection of study sites, perhaps single-blind lead-ins or a return to crossover designs in some cases;
– Transparent quantification of the correlations between dosing, efficacy, and tolerability, with clear labelling in product information;
– Reporting of the seizure-free rate per dose and by seizure type;
– Clearer labelling guidance on appropriate target doses;
– Innovative end points, more parallel to clinical practice, including sustained seizure-freedom;
– Flexible dosing and possibly individually-determined endpoints in trials;
– Focused, standardised searching for adverse effects early in drug development;
– More direct comparative trials using active controls;
– Longer patient follow-up, with assessment of long-term drug efficacy and safety;
– Better matching of drug to seizure type, syndrome, and genotype, especially as drugs with more defined mechanisms of action become available;
– Many of these suggestions have been incorporated into ILAE guidelines for conduct of initial monotherapy trials (Glauser *et al.*, 2006) and could be extended to adjunctive and conversion to monotherapy trials.

Although significant preclinical groundwork and some important clinical trials have been financed by government agencies, the brunt of the clinical trial effort has been borne by pharmaceutical companies. We should therefore be grateful to the commercial sector for the explosive development of antiepileptic drugs over the past three decades, which required both enormous resources and the will to tackle a difficult disorder. Some improvements in trial design may be impractical or financially prohibitive, but many are feasible. The longer-term and comparative studies, essential as they are, have not been attractive to governmental funding agencies, especially in the United States. This attitude should change. Alternative mechanisms to address these questions may include consortia of investigators with indirect commercial or non-governmental funding. □

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