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Novel trial designs for monotherapy*

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ABSTRACT – Unlike many other areas of therapeutics, specific regulatory trial programmes are required to be undertaken in newly diagnosed epilepsy to support the licensing of novel antiepileptic drugs for use in drug-naïve patients. To complicate matters further, American and European regulators have taken markedly different approaches to this issue, with the FDA requiring withdrawal to monotherapy data comparing more than one dose of newer agents with historical controls, whereas the EMA recommends undertaking randomised head-to-head studies *versus* an established comparator. The former studies are designed to show superiority compared to previously published data, whereas the latter will accept a non-inferiority (equivalence) outcome. This paper discusses the positive and negative aspects of both designs and explores novel alternative options. Particular focus has been placed on placebo-controlled studies following a single seizure with supportive electroencephalographic and/or brain imaging evidence, in the hope of identifying a realistic design that will satisfy licensing authorities on both sides of the Atlantic Ocean.

Key words: antiepileptic drugs, epilepsy, clinical trials, historical controls, monotherapy

Over the years, there has been much discussion among European and American investigators and regulators regarding the best designs suitable for the granting of a monotherapy license for an antiepileptic drug (AED) that has previously been approved for use as adjunctive treatment in drug-resistant epilepsy (Porter *et al*., 2010). The US regulators support a withdrawal to monotherapy design with efficacy being measured by the proportion of patients meeting predefined escape criteria for seizure worsening compared with aggregated pseudoplacebo control data from eight previously conducted conversion-to-monotherapy trials (French *et al*., 2010). The European

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Medicines Agency prefers an active control design in patients with newly diagnosed epilepsy with a six-month, seizure-free primary endpoint and 12 months safety data on both drugs (Committee for Medicinal Products, 2011). They accept a non-inferiority (equivalence) outcome. Can we do better and find a novel design that satisfies all interested parties?

Patterns of response

A monotherapy license for an AED permits its use as first choice in newly diagnosed epilepsy. Arguably, it should be tested for that indication in the patient population for whom it will be prescribed. Patterns of drug response in adolescents and adults have been clearly delineated with around 60% of patients going into remission either immediately or after a short delay (Brodie *et al*., 2012). Around 90% of these patients, 50% of the complete population, will become seizure-free on their first AED, often on a modest or moderate dose (Kwan and Brodie, 2001). In around 25% of patients, the epilepsy will never come under control for a full year despite treatment with a range of AEDs prescribed singly or in combination. The remainder display fluctuations between periods of seizure freedom and relapse (Schiller, 2009; Callaghan *et al*., 2011; Neligan *et al*., 2011; Brodie *et al*., 2012). These patterns of response leave little leeway for identifying clinically relevant differences between AEDs in randomised head-to-head studies in this setting.

Withdrawal to monotherapy

The US Food and Drug Administration (FDA) does not accept equivalence as an appropriate end-point because of concerns regarding the "assay sensitivity" of the response with the established comparator in newly diagnosed epilepsy, which could result in the interpretation that both drugs were ineffective (Porter *et al*., 2010). Over the years, the alternative design of withdrawal to monotherapy in patients not seizure-free on one or two AEDs was developed (Perucca, 2010). Because placebo could not ethically be used in this setting, the comparator was traditionally a (sub-optimal) low dose of an established AED (Perucca, 2010). This design came under increasing criticism from the epilepsy community, largely because randomising patients with active epilepsy to a deliberately suboptimal treatment was increasingly regarded as ethically questionable (Chadwick and Privitera, 1999; Perucca and Tomson, 1999). Accordingly the FDA has now moved to accept the results of previous studies as "historical controls", with which to compare data from AEDs undergoing a withdrawal-to-monotherapy process in patients established but not seizure-free on a single AED (French *et al*., 2010). The first study with lamotrigine XR has recently been completed (French *et al*., 2012), with this controlled-released formulation of the drug subsequently being granted a monotherapy license in the US (Food and Drug Administration , 2011).

I have some problems with this design. Firstly, the trial drug will not have been shown to be effective and well-tolerated in patients with newly diagnosed epilepsy for whom it will be licensed. Eligible patients for the lamotrigine XR withdrawal to monotherapy study experienced >4 partial seizures during an eight-week baseline on a stable monotherapy regimen with a non-inducing AED. Two lamotrigine doses (250 mg and 300 mg) were included because of the requirement from the FDA that the study be blinded (French JA, personal communication). The assumption, presumably, is that there will be no important differences in efficacy between the lower and higher doses to maintain equipoise. In this study, both doses of lamotrigine XR successfully dipped below the 95% prediction limit for withdrawal (65.3%) of the combined historical control data with no overlapping by the upper confidence limit of either dose.

The escape criteria for this study included doubling of average monthly seizure rate, doubling of highest consecutive two-day seizure rate, emergence of new more severe seizures and clinically relevant prolongation of generalised tonic-clonic seizures (French *et al*., 2012). Adverse events were reported in 53 and 61% of patients randomised to lamotrigine XR at 300 mg/day and 250 mg/day, respectively. Overall, 25 (22.3%) and 24 (21.6%) patients "escaped" from the 250 mg and 300 mg doses, respectively. No important differences in outcome, perhaps not surprisingly, were documented between these doses. This may not be the case with wider dosage differences in other studies. Thus, a successful study depends on the number of patients reporting worsening seizure control on attempting to transfer onto the newer agent. One is also left to ponder how an appropriate dosing schedule for each drug successfully traversing this challenge can be identified using this design for newly diagnosed epilepsy and what sort of licence can reasonably be awarded that is relevant to its use in a markedly different patient population.

Active control trials

A range of randomised, double-blind comparative studies have been undertaken in Europe over the past 20 years (Kwan and Brodie, 2003; Brodie *et al*., 2007; Kwan *et al*., 2011; Baulac *et al*., 2012), which have resulted in the licensing (to date) of lamotrigine, oxcarbazepine, topiramate, levetiracetam, and in

some countries gabapentin, as first-line monotherapy in newly diagnosed focal epilepsy with or without secondary generalisation. The design of these trials has slowly evolved over the years with the European regulators now requesting data on six months' seizure freedom as the primary endpoint with comparative tolerability and safety data collected for at least a year on both drugs (Brodie *et al*., 2007). All recruited patients will have had the opportunity of control or failure with three doses of either drug. The vast majority of patients in these trials, who became seizure-free, did so at the lowest randomised dose (500 mg twice daily for levetiracetam, 150 mg twice daily for zonisamide *versus* controlled-release carbamazepine 200 mg twice daily and 300 mg twice daily, respectively; Brodie et al., 2007, Baulac et al., 2012). This design, therefore, requires time for all patients to have an appropriate trial of all three doses if necessary and, therefore, needs accurate matching of dosing of the new drug with the comparator. In the recently published pregabalin *versus* lamotrigine trial, neither of these goals was achieved and hence the data statistically favoured the established drug, particularly for secondary generalised seizures (Kwan *et al*., 2011).

The rationale for the above design is the expectation of non-inferiority between the drugs in this clinical setting and, therefore, the acceptance of equivalence as a suitable clinical endpoint. The specific requirements for equivalence has been discussed in an International League against Epilepsy guideline with the relative lower limit for non-inferiority being set at 20% between the new agent and the established comparator (Glauser *et al*., 2006). Following seizure-free patients for at least a year provides clinically useful safety information in the setting of often mild epilepsy, comparing the side-effect profile of the new AED as monotherapy with a year's treatment on the established agent. These data are relevant to the everyday use of the newer drug in the patient population for whom the license is being sought.

New designs

Can we develop a novel strategy that would satisfy investigators and regulators on both sides of the monotherapy design? We should surely be studying new AEDs in the setting for which the licence is being sought, *i.e*. monotherapy in newly diagnosed epilepsy. How can we increase the likelihood of demonstrating superiority in efficacy or effectiveness over the standard comparator, usually controlled-release carbamazepine? What endpoints do we need to support acceptable tolerability and safety for the new agent in this clinical setting? One possible way of refining the head-to-head monotherapy design is to explore pre-treatment seizure numbers as a possible variation in the inclusion criteria for the study. The likelihood of an optimal outcome in newly diagnosed epilepsy deteriorates with increasing pre-treatment seizure numbers (Macdonald *et al*., 2000; Kwan and Brodie, 2000; Leschziner *et al*., 2006) and, in particular, seizure density within the last 3, 6 and 12 months prior to starting a first AED (Mohanraj and Brodie, 2006). This observation was confirmed in the recent head-to-head study between levetiracetam and controlled-release carbamazepine where overall outcome was better ($p<0.001$) in patients reporting two or fewer seizures in the three months before starting treatment (levetiracetam/controlled-release carbamazepine: 82/80% seizure-free) compared to those experiencing three seizures or more over the same time period (levetiracetam/controlled-release carbamazepine: 64/63% seizure-free) (Brodie *et al*., 2007). Perhaps confining recruitment to patients with more active epilepsy will improve the chance of finding difference in efficacy or effectiveness between the drugs in this patient population?

Over the last decade, no drug has been tested or licensed as monotherapy for newly diagnosed idiopathic generalised epilepsy. Arguably, sodium valproate remains the drug of choice for this range of epilepsy syndromes (Marson *et al*., 2005). Concerns regarding valproate's teratogenic potential (Tomson *et al*., 2011) and its association with impaired cognitive development in infants exposed to the drug *in utero* (Meador *et al*., 2009) makes it important to identify a suitable and cost-effective alternative for this indication in young women. One possible design would be a placebo-controlled trial in patients reporting their first generalised tonic-clonic seizure, who had a surface electroencephalogram (EEG) consistent with the diagnosis of idiopathic generalised epilepsy. This fulfils the definition of epilepsy suggested by Fisher and colleagues as "a disorder of brain characterised by an enduring disposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition" (Fisher *et al*., 2005). The definition requires the occurrence of at least one epileptic seizure with an epileptiform EEG, abnormal brain magnetic resonance imaging (MRI), pre-existing neurological disorder or focal deficit appropriate to the seizure semiology. Thus, the same design could be applied to patients with focal epilepsy and a neurological or anatomical substrate relevant to their seizure semiology. Again, randomising such patients following their first seizure could be regarded as ethically justifiable.

The equipoise for this design is supplied by the MESS study in which 1,443 patients with a single seizure (56%), or in whom the diagnosis of epilepsy was in doubt (44%), were randomised to immediate or

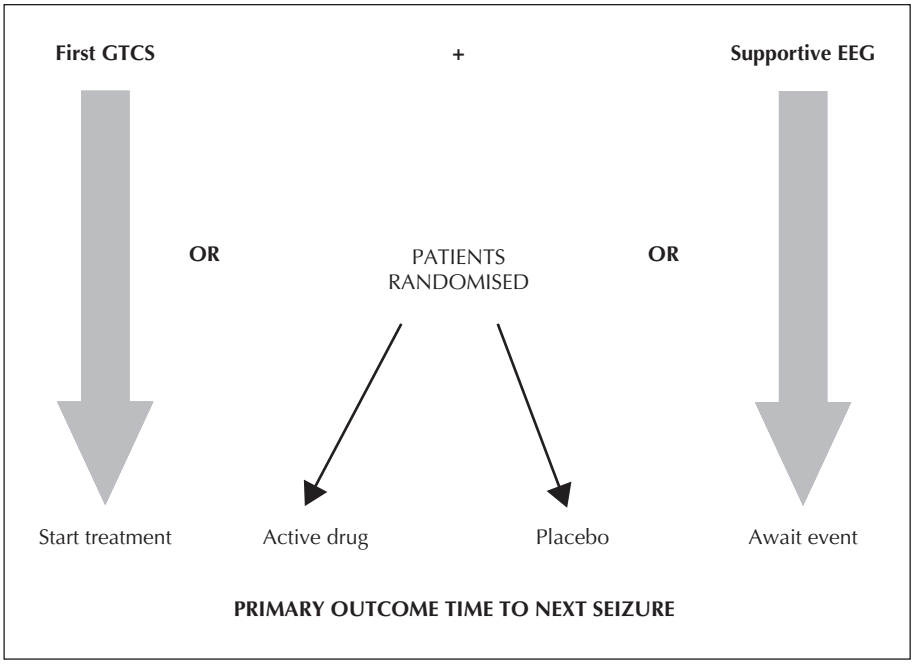

Figure 1. Suggested design for randomised trial in newly diagnosed idiopathic generalised epilepsy. GTCS: generalised tonic-clonic seizure; EEG: electroencephalogram.

deferred treatment (Marson *et al*., 2005). After three and five years of follow-up, outcomes were almost identical with 74 and 76% in the immediate and 71 and 77% in the deferred treatment groups achieving two years' remission. Fewer patients died in the deferred (23 deaths, 2 SUDEP) compared with the immediate (31 deaths, 4 SUDEP) treatment groups. Support for this strategy also comes from the Italian FIRST study (Musicco *et al*., 1997). Their recent analysis showed no difference in the probability of achieving five-year remission whether or not treatment was begun after the first unprovoked primary or secondary generalised tonic-clonic seizure (Leone *et al*., 2006). The primary endpoint for this design would be time to next seizure in patients randomised to a range of doses of the active drug or matched placebo (*figure 1*). Patients declining to take part, whether they decide to start treatment or not, could also be followed in the long-term, in parallel with those randomised in the studies.

In 2002, my colleagues and I reported a double-blind, flexible dosing study comparing remacemide hydrochloride to carbamazepine in patients with newly diagnosed partial and/or tonic-clonic seizures using a sequential design known as the *double triangular test* (Whitehead and Todd, 2004), which allowed the trial to be stopped as soon as the collected data were sufficient to draw a reliable conclusion (Whitehead, 2001). At the second planned interim analysis, carbamazepine was found to be more efficacious than remacemide (*figure 2*). The primary endpoint was taken as time to first seizure following the initial six-week titration phase. The study had 90% power to show superior efficacy of remacemide if the 54-week, seizure-free probability improved from 0.5 on carbamazepine to 0.6 on remacemide. Interim analyses were planned at 48 weeks, and then every 12 weeks thereafter. At each of these, a monitoring board comprising two clinicians and a statistician reviewed unblinded data concerning efficacy and safety. At the second interim analysis, 449 patients had been recruited, compared to the 1,000 that would have been needed for a fixed sample study of the same power. The evidence in favour of carbamazepine was sufficient to stop the trial. An analysis that allowed for its sequential nature found the treatment difference to be statistically significant (2-sided p=0.003). Overall, 50% of patients randomised to carbamazepine survived to 54 weeks, as predicted, compared with just 32% on remacemide. This study established carbamazepine as an ideal comparator for future active control comparisons in newly diagnosed epilepsy. Further refinement of this design is possible (Sooriyarachchi and Whitehead, 1998). This methodology can be simulated with real data sets for comparison with alternative approaches to explore the optimal conditions necessary for a successful study in patients with newly diagnosed epilepsy in whom a decision has been made to start treatment. Arguably, too, this would be the most efficient design for testing a new drug *versus* placebo or an established comparator in patients with a single partial-onset or generalised seizure and a suitable abnormal EEG, brain MRI and/or appropriate neurological substrate.

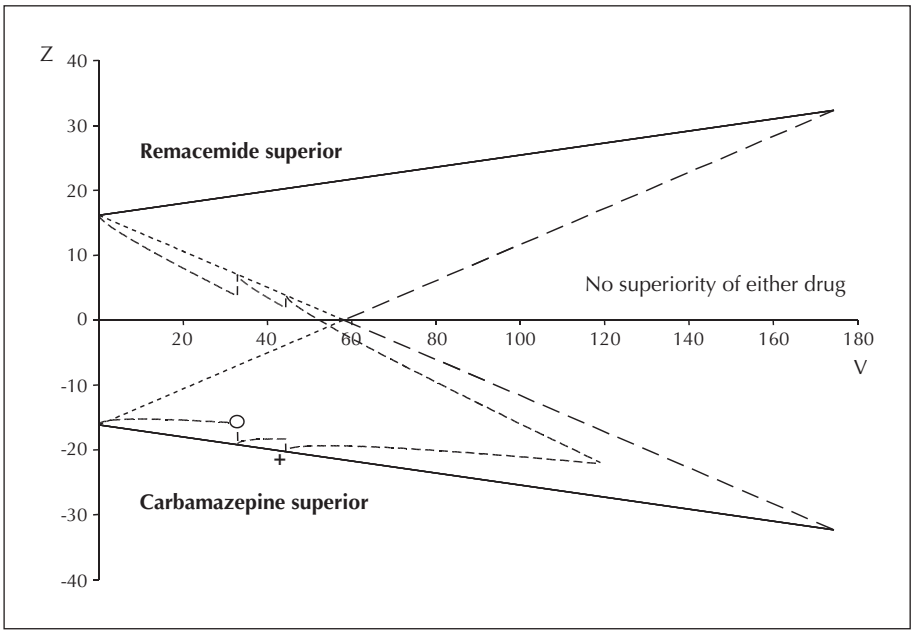

Figure 2. Double triangular sequential design and differences in time to first seizure.
The trial was stopped six weeks after randomisation for the two treatments because the second point was below the lower boundary. Z: logrank statistic expressing the advantage of remacemide over carbamazepine; V: null variance of Z; X: values (V, Z) at the interim analyses (taken from Brodie *et al*., 2002).

Conclusions: *Quo vadis?*

Where do we go from here? The historical control withdrawal to monotherapy design has been accepted by the FDA and already one drug, lamotrigine XR, has been licensed as monotherapy in the US. Further studies with pregabalin, lacosamide and eslicarbazepine acetate are ongoing. The European design, as published for levetiracetam *versus* controlled-release carbamazepine (Brodie *et al*., 2007), has arguably been "validated" by the "negative" pregabalin *versus* lamotrigine (Kwan *et al*., 2011) and the "positive" zonisamide *versus* controlled-release carbamazepine (Baulac *et al*., 2012) studies. Ongoing trials with lacosamide and eslicarbazepine acetate *versus* controlled-release carbamazepine follow a protocol similar to the design that resulted in the licensing of levetiracetam for newly diagnosed localisation-related epilepsy (Brodie *et al*., 2007). We also need to work on a design that provides a licensed alternative to sodium valproate for the idiopathic generalised epilepsies. This could be accomplished by randomising patients following a single tonic-clonic seizure with a supportive EEG to placebo or active treatment. This template could also be applied to patients with focal epilepsy following their first seizure who have an underlying neurological disorder or an appropriate abnormality on brain imaging.

Can we all agree on a version of the sequential analysis paradigm in newly diagnosed partial seizures with or without secondary generalisation and go forward in harmony? I doubt it! Together, these geographically, scientifically and clinically different concepts and designs provide complementary data on efficacy and safety. New AEDs are currently being tested and licensed as monotherapy in the US and Europe. Perhaps the job is done? □

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