

# Improving Development of Antiepileptic Drugs for Rare Forms of Epilepsy



Therapeutic development in rare diseases involves many challenges such as an incomplete understanding of the disease to inform trial design, requirements for new or more sensitive and specific outcome measures, and difficulties of recruiting a small sample to participation, among others. Rare diseases cover a broad range of diseases and patients, with about 50% of those affected being children. Many have a genetic component, while others arise from exposure to infections or toxins, from faulty immune responses, or occasionally from trauma or injury (e.g. traumatic brain injury (TBI)). For many rare conditions, the causes are frustratingly elusive. Many factors contribute to trial feasibility, but solid understanding of the epidemiology of the targeted condition is necessary to plan successful trials, but due to the small number of potential participants, a standard randomised controlled trial is often not feasible. Indeed this is the case with various forms of epilepsy syndromes. Although epilepsy affects approximately 1 in 100 people, many specific epilepsy syndromes are rare (<http://www.ninds.nih.gov/>).

Currently there are several incentives in place to encourage the development of new therapies for the rare epilepsy syndromes, and particularly those that do not respond well to the marketed antiepileptic drugs (AEDs). These disorders meet the requirements of orphan indications, for which tax incentives are provided and investments are smaller, with a potentially less demanding path for approval in Europe and the USA. For example, the USA Orphan Drug Act guarantees market exclusivity to the sponsor for seven years, as well as 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 American National Institutes for Neurological Disorders and Stroke (NINDS) Anticonvulsant Screening Program (ASP), which provides free screening of antiepileptic compounds for commercial and academic institutions and sophisticated pre-clinical characterisation of promising molecules (Smith et al., 2007). Another opportunity may involve the repurposing of drugs from other therapeutic areas that possess either relevant disease-modifying properties for epilepsy or a novel mechanism of action with substantial synergistic efficacy against refractory epilepsy when combined with an existing AED therapy. This route would markedly reduce the level of investment necessary for discovery and development, and potentially decrease the regulatory data requirements.

As these types of new epilepsy therapies address a major unmet medical need, they also offer a promising incentive for future AED development. Indeed, the urgency to discuss innovative AED drug development was highlighted at the recent ILAE/AES Working Groups

joint meeting in London in which a call for the discovery of disease-modifying treatments that prevent the development of epileptogenesis in at-risk populations and importantly, drug development in specific rare refractory subgroups that would qualify for the much coveted “orphan drug designation” (Wilcox et al., 2013; Simonato *et al.*, 2013). Below we discuss various ways to improve the development of antiepileptic drugs for rare forms of epilepsy.

## Innovative Study Designs

Epilepsy, by its nature, poses challenges to clinical development, and with the presence of over 20 AEDs on the market and a low success rate for Phase III epilepsy trials, enthusiasm for traditional antiepileptic drug (AED) development has decreased (French, 1997; Simonato *et al.*, 2012; Simonato *et al.*, 2013). However, the need for development of new therapies is as urgent as ever, with ~30% of the epileptic patients continuing to have poorly controlled seizures despite therapy (French, 1997). Given the presence of numerous approved AEDs for seizure control, conducting pure placebo-controlled designs is considered unethical in the epilepsy population, exposing the patients to unnecessary risk. Most AEDs are tested using the traditional Phase III, add-on, placebo-controlled clinical trial design in refractory patients who have frequent partial seizures. This population is usually heterogeneous, with patients maintained at a given dose for a fixed duration (usually 8 – 12 weeks), followed by open-label extension studies. This design has several hurdles for the development of new therapies in rare epilepsy syndromes. They usually require fairly large populations and the presence of the background AEDs can complicate the interpretation of the results. A “superiority” trial design in rare diseases is often not possible, as these trials usually require larger sample sizes. The “pure-placebo” controlled designs are accepted as gold standard in many disease areas, but in diseases such as epilepsy, where a single event can have serious consequences, and there are other therapeutic options, these trials are considered unethical by regulatory agencies, and have faced steep recruitment challenges.

To better understand the role of the investigational drug’s effect as monotherapy, an alternative design that “converts” the patients to monotherapy has also been approved by both FDA and EMA (Sachdeo, 2007; Wilcox *et al.*, 2013). In this design, patients who continue to have seizures despite being maintained on background AEDs are randomised initially to placebo and study drug (often two doses). Following achievement of a maintenance period, the background AEDs are withdrawn, and patients are titrated to monotherapy or placebo. Once patients have an event (which can be pre-defined as one or the *n*th seizure of specific characteristics), patients are



withdrawn from the study and treated with alternative standard of care AEDs. In this time-to-event design, the primary endpoint is retention time in the study following discontinuation of background AED. One other option is to have pseudo-placebo studies, with low and high doses of the study drug that has shown some efficacy in Phase II trials, compared to an active control. This design may be better suited for newly-diagnosed epilepsy patients, who have not yet been tried on any AEDs. Similar to the “conversion” studies above, the study duration in these trials also do not need to be fixed. Rather, these trials can also have the time-to-event design, where the patients receive rescue therapy and transition to an open-label trial following the first or  $n^{\text{th}}$  seizure (Simonato *et al.*, 2013).

In some very rare diseases, with no prior experience of the drug, companies have been successful securing initial approvals with small open-label studies (specifically if there is a well understood and clinically relevant biomarker for treatment response), or use of historical baseline data (French *et al.*, 2012). For epilepsy, that may necessitate the study of epilepsy syndrome with clearly defined EEG signature that relates to the specific seizures, or another blood/imaging biomarker, and well documented prior seizure frequency/severity (historical control). One can also design longer-term initial studies to understand the natural course of the disease, in order to use as historical controls. This can be done as an observational study, but also can be incorporated as a lead-in arm in a controlled study, where patients are treated with a known AED for several weeks and the seizure frequency and severity are well-documented.

Finally, there are currently no feasible controlled trial designs to study therapies that may prevent the development of epilepsy (epileptogenesis) in at-risk populations (e.g. post-traumatic seizures, those with developmental lesions, febrile seizures etc). These patients are most-often studied only after the seizure pattern has been developed. Development of early-stage disease-modifying or preventative therapies for epileptogenesis will be challenging, but necessary, if we are to get in front of the disease process. Taken together, for new epilepsy therapies, and specifically in the refractory or rare epilepsy syndromes, innovative clinical trial designs are still needed.

#### Homogeneity of Sub-populations

Another major problem with current AED study designs is implicit in the patient population included which could lead to many false negatives (Simonato *et al.*, 2012). More specifically, the majority of randomised clinical trials for AEDs include patients with complex partial seizures, with or without secondary generalised seizures. This heterogeneous population of epileptic patients includes a wide variety of and diverse epileptogenic and ictogenic mechanisms. Potential compounds tested in a traditional randomised controlled trial (RCT) against any one subset of these seizure types could go unnoticed if it were not effective against any and all the others. As discussed by Simonato and colleagues (2012), these observations raise several important issues related to clinical trial design. First, the patients studied in these trials have medical characteristics that render them treatment-resistant, which may not be relevant to various different target populations. In addition, this concept of a “lump sum enrolment” may lead to ineffective treatment as the

underlying etiology and pathophysiology of the disease is so discrepant from one epilepsy syndrome to another.

Given the nature of rare disease clinical trials, in that these are much smaller studies with only a few patients per study site, it is imperative that the patient population is more homogeneous. One possibility is through target identification based on a specific etiology (e.g. TBI), genetic or other biomarker (e.g. EEG or MRI signature, specific antibody etc). For example, among refractory epilepsy subgroups, MRI can be used to identify subgroups of patients with hippocampal sclerosis or developmental cortical lesions. Many of these patients can achieve freedom from seizures only after a successful respective neurosurgery, and as such there is a clear need for development of effective non-surgical therapies. Among the paediatric epileptic population, approximately 4% suffer from Lennox-Gastaut syndrome (LGS), a severe form of epilepsy that is notoriously difficult to treat (Shields, 2004; Markand, 2003). This population can also be reliably identified based on a well-recognized triad of multiple generalized seizure types, a slow spike-and-wave pattern (less than 2.5 Hz) on EEG and cognitive dysfunction (Markand, 2003). Taken together, further research is needed to more carefully characterise fundamental neuronal mechanisms underlying different types of epilepsy syndromes and ictogenesis that might influence their response to specific antiepileptic compounds.

### Future Directions

Despite the development and availability of more than 20 anti-seizure drugs, current medications still fail to control seizures in 20-30% of patients. However, our understanding of the mechanisms mediating the development of epilepsy and the causes of drug resistance has grown substantially over the past decade, providing opportunities for the discovery and development of more efficacious anti-epileptic and anti-epileptogenic drugs. New strategies for the discovery and development of AEDs that also offer a compelling case for industry investment must be pursued in order to provide new and improved treatment options for patients with epilepsy and, importantly, rare epilepsy syndromes.

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