CLINICAL INVESTIGATION

The trials of antiepileptic drug trials

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Studies of new antiepileptic drugs (AED) present challenges unique to the treatment of seizures and epilepsy. Perhaps the most prominent of these challenges is the ethical concern of using an unproven medication alone in a study of patients with diagnosed epilepsy. As a result, the focus in the design of current methods of evaluating AED has been on patient safety. Given the constraints of the Helsinki Declaration in preventing undue risk to the patient and requiring equipoise, the use of 'add-on' trial designs has been adopted for AED development [101]. Patients with existing epilepsy are entered into a study and maintained on at least one approved AED [1]. The new AED or placebo is added to the patient's current therapy. Often, these studies will use a crossover design to increase the power of the study and reduce the number of patients enrolled. For most studies, the primary efficacy outcome is a reduction in seizure frequency over a defined period of time, usually a month, after the new AED is added. Reduction in seizure frequency is usually evaluated by a responder rate, defined as a >50% reduction in seizure frequency [2]. The common duration of a study is 3 months for the active arm and 3 months for the placebo arm. Over the past 2–3 decades, these study designs have led to the approval of 13 new AED in the USA. In general, add-on study designs have been effective in achieving the goal of obtaining regulatory approval for a new drug.

From a regulatory perspective, add-on study designs have been used successfully and maintained ethical standards for clinical trials. However, these designs have complicated the interpretation of study results and left many important clinical questions unanswered. The results of these complications have directly impacted drug approvals, the approach to treating patients with epilepsy, and our thought processes about AED therapy [3]. Additionally, the limits of our understanding of epilepsy and its treatment have made the development of other approaches to evaluation of AED therapy difficult.

Several examples can be given to illustrate these problems. When a new AED is added to an existing therapy in a patient, evaluation of efficacy and toxicity of the new agent is difficult at best. It is never clear if the decrease in seizure frequency resulted from an interaction with the approved agent the patient continues to take throughout the study. Pharmacokinetic and pharmacodynamic interactions may provide the explanation for improved control of seizures. Use of serum concentration data can help in determining the role of pharmacokinetic interactions in efficacy results from a study, but pharmacodynamic interactions are nearly impossible to detect. Most studies have an insufficient number of subjects to evaluate all possible combinations of the new AED with the maintenance AED. The result of this reality is that new AED approvals are for adjunct therapy with other AED. Add-on studies also promote the idea of combination or polytherapy in managing patients with epilepsy, when little solid scientific evidence exists to support this approach to treatment of epilepsy. Additionally, it creates disparities between results of add-on efficacy studies and effectiveness studies [102].

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Likewise, the adverse-event profile of a new AED is difficult to determine based upon results from an add-on trial. Definite statements can be made about adverse events that occurred with combination therapy, but the individual adverse-event profile of the new AED, and adverse events that occur as a result of specific AED combinations, cannot be determined.

Time limitations also play a role in confounding the interpretation of most add-on studies. Epilepsy is a chronic disorder that requires ongoing treatment; however, clinical trials must be done in a timely fashion, making prolonged treatment schemes impractical when the main goal of an add-on study is to determine efficacy and safety. As stated previously, treatment arms in a typical add-on trial have durations of 3 months. This length of time allows for sufficient data collection to determine reductions in seizure frequency, responder rates, and acute adverse events. On the other hand, the short time span does not allow for evaluation of durability of response, development of tolerance, and detection of adverse events likely to occur later in therapy [4].

Sample size and recruitment of study participants are also major issues in add-on trials. Powering studies to detect a 50% reduction in seizures, results in sample sizes of a few hundred subjects. Even with the requirement of two to three clinical studies demonstrating efficacy prior to US FDA approval, there are usually fewer than 5000 individuals who have taken a new AED prior to the marketing of the drug. With this size of study, there are too few individuals to accurately detect rare adverse events. The case of felbamate is an excellent example of this concept [5]. Recruitment of subjects for trials is also problematic. With the primary outcome of efficacy being reduction of seizures, it is assumed that patients are having seizures when they enter an add-on study. For most protocols, subjects are required to average two to four seizures per month during a 2–3 month baseline period. As new AED have come to the market, potential study participants have been placed on these drugs in attempts to control seizures. Other treatment modalities have been developed and are frequently used; for example, epilepsy surgery and vagal nerve stimulation. This process results in filtering of study participants in current add-on AED trials to patients who are extremely refractory to a variety of treatments, lessening the possibility of a response to the new AED [4]. From one perspective this is preferred, because it means that only the most efficacious AED in the most difficult patients get approved. However, it also means that some new AED that are potentially useful in certain patients do not get approved for use.

Other concerns impact add-on AED studies. Most add-on studies are designed to evaluate efficacy in partial seizure types, leaving little rigorous evidence for efficacy in other seizure types. Diagnosis of partial seizures and criteria for inclusion in an add-on study revolve around clinical parameters and do not consider growing information on the differences in the underlying pathophysiology for similar clinical seizure presentations. Thus, new AED with highly targeted mechanisms of action are more difficult to evaluate using current add-on trial strategies. Handling of data from study participants who do not complete an add-on study is also problematic. Use of the commonly used last observation carried forward technique in an 'intent-to-treat' analysis for new AED studies has been shown to result in overestimations of efficacy [6]. While seizures are the main clinical symptom of epilepsy, it is well known that patients with epilepsy experience other symptoms, such as psychological, psychiatric or cognitive problems [7]. Current add-on designs usually do not consider these aspects of epilepsy and are not fully capable of providing useful data. Finally, measures of efficacy in add-on trials rely on individual patient or caregiver reporting of seizures, and are not a reliable methodology. Each of these issues makes application and interpretation of add-on trial data difficult at best.

While add-on trial designs have resulted in the availability of numerous new AED, there has not been a corresponding improvement in the effectiveness of newer AED compared with older AED. Whether this is due to the limitations of add-on study designs or other factors is unclear. However, it is clear that the add-on study design has profound impact and implications for the treatment of epilepsy [8]. There is a great need for the development and exploration of new trial designs that maintain patient safety, while providing more useful data on efficacy and effectiveness [7]. Designs that involve time to an event, use of validated historical controls, other indicators of effectiveness beside seizure frequency, or rigorous escape criteria that limit risk to the patient may provide alternatives to the current standard of add-on trial design [7]. Alternative study designs that are more consistent with the clinical realities of managing and treating epilepsy will greatly aid in advancing AED therapy for patients with epilepsy.

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