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REVIEW

# Anti-epileptogenic Clinical Trial Designs in Epilepsy: Issues and Options

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**Abstract** Although trials with anti-seizure drugs have not shown anti-epileptogenic or disease-modifying activity in humans, new compounds are on the horizon that may require novel trial designs. We briefly discuss the unique challenges and the available options to identify innovative clinical trial designs that differentiate novel anti-epileptogenic and disease-modifying compounds, preferably early in phase II, from current anti-seizure drugs. The most important challenges of clinical testing of agents for epilepsy prevention include having sufficient preclinical evidence for a suitable agent to proceed with a human trial of an anti-epileptogenic drug, and to demonstrate the feasibility of doing such a trial. Major challenges in trial design to assess agents for disease modification include the choice of suitable study parameters, the identification of a high-risk study population, the type of control, the time and duration of treatment, and a feasible follow-up period.

**Keywords** Anti-epileptogenic drugs · Disease-reversal · Disease-modification · Antiepileptogenic drug trial design · Disease-modifying drug trial design · Disease-reversing drug trial design · Feasibility of trial design · Human biomarkers · Novel epilepsy trial design · Epilepsy

## Introduction

Although approximately 70–80 % of humans with new-onset epilepsy eventually enter sustained seizure remission during treatment with current anti-seizure drugs (ASDs) [1, 2], important, unmet needs exist in the drug treatment of epilepsy, including the development of more effective and safer ASDs [3]. Currently, we have no drugs that, when administered to patients immediately following brain insult for a limited time period, have been shown to have anti-epileptogenic activity after washout [3]. Although, in its broadest definition, anti-epileptogenic activity will prevent or reduce the long-term consequences of the insult, including the development of epilepsy, drug-resistant epilepsy, neurodegeneration, and cognitive or behavioral alterations [4, 5], we will limit our discussion on preventing epilepsy in this article. In addition, we need disease-modifying agents in the treatment of established epilepsy [3]. Disease-modifying compounds, when given for a limited time period in patients with established epilepsy, are able to alter the long-term development or progression of the disease after washout. The scope of disease modification includes effects on the underlying pathophysiology, the natural history or the severity of the epilepsy, the development of pharmacoresistance, neurodegeneration, and cognitive or behavioral alterations in the course of the disorder [6]. Here, we will focus the effects of disease modification on seizure outcome.

Although past trials of available ASDs have not shown anti-epileptogenic or disease-modifying activity in humans [7, 8], there is hope. Our understanding of the mechanisms mediating epilepsy development has grown substantially over the last decade [6, 9], offering the opportunity to discover and develop anti-epileptogenic and disease-modifying drugs for the future. In this article, we briefly discuss the unique challenges to identify innovative clinical trial designs that differentiate novel anti-epileptogenic and disease-modifying compounds, preferably early in phase II, from current ASDs.

## Lessons from Epilepsy Prevention Trials Using ASDs

A large number of clinical trials have been performed over the last 2–3 decades dedicated to determining whether > 15 ASDs

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are both safe and effective for treatment of seizures in patients that already have developed epilepsy. The regulatory requirements for approval of ASDs has been well established all over the world, although there is still some room for re-evaluation and modification of these protocols, especially for the indication of these drugs as monotherapies [10]. At most levels, the development of new drugs for seizure suppression can be called a moderate success; we have a number of new agents that are less toxic and better tolerated than many of the older generation ASDs [3, 11]. But, despite all the advances in this domain, about 30–40 % of patients with epilepsy continue to have seizures and suffer from some of the common "comorbidities" connected to chronic epilepsy, such as cognitive issues, memory problems, and depression. In addition, for many patients, even for those who become seizure free, their ASDs are not without bothersome side effects.

The story is very different for anti-epileptogenic drugs. First, we start out with no "older" drugs that are effective (even partially) that we are attempting to improve upon. Second, there have been, until very recently, no animal models in which successful seizure prevention has occurred upon which to build a platform for drug screening. Third, until the last 10–15 years there has been very limited basic or clinical research in this area, and even now there is no on-going clinical trial of an agent to prevent epilepsy after any of the many identified high risks.

That's not to say that there have not been many years of clinical trials that focused on preventing epilepsy. Almost all of these utilized already established ASDs with the hypothesis that the initial precipitating risk produced a condition in which "small" seizures occurred and that, if left untreated, these "small" seizures or some hyperexcitable facsimile of such, would produce increased excitability that ultimately resulted in clinical epilepsy, some of which would be "intractable" for conventional anti-seizure therapy. Thus, the argument went, suppressing the early seizures or seizure-like events would prevent the later epilepsy. It was also recognized that epilepsy might be prevented if the brain injury associated with a given risk, for example stroke, traumatic brain injury (TBI), or status epilepticus, could be significantly reduced, and it was hypothesized that some anti-seizure agents, especially those that were also highly sedative, might prevent brain injury by other mechanisms.

It must be realized that part of this rationale was also based on a lack of other hypotheses about epileptogenesis that might have pointed to other neurobiological phenomena that resulted in epilepsy, and also because many efforts in the ischemia and TBI fields to produce neuroprotection had failed.

For the purposes of this review, we will not consider trials that attempt to prevent provoked seizures, such as those occurring in young children with high fevers (febrile seizures) or those after alcohol withdrawal. Most would consider such studies as not part of anti-epileptogenesis, and are reviewed elsewhere [12].

Attempts have been made to prevent epilepsy after TBI and craniotomy, or in the presence of brain tumors or cortical dysplasias. Most of the studies have been relatively poorly performed by current clinical trial standards. They involved relatively few patients, had poor (or no concurrent) controls, were not blinded, and the participants may not have been randomized. In addition, in some of the blood levels in the trials were not monitored, so compliance with the medication regimens was uncertain. There are several exceptions to this, and these will be highlighted in the ensuing discussion.

The development of epilepsy after TBI has been best studied. There are 13 clinical trials of epilepsy prevention after TBI listed in a comprehensive review by Temkin [13]. The number of participants range from 49 to 404. Five studies used phenytoin (PHT) alone, 5 used PHT and phenobarbital, and 1 each used phenobarbital, carbamazepine, or valproic acid. Only the 2 performed at the University of Washington (1 PHT [14] and 1 valproic acid [15]) were randomized, double-blind, controlled trials, and these were the 2 trials with the largest number of enrolled participants. Neither of these trials was able to identify an anti-epileptogenic effect. A number of the early studies purported to show positive effects of phenobarbital and PHT, but more recent randomized controlled trials (RCTs) have demonstrated no useful effects [14] and even suggested that there were additional cognitive side effects associated with these treatments [16]. Similarly, the 1 well-performed RCT with valproic acid also failed to show any beneficial effect [15].

The 2 recent RCTs performed at the University of Washington illustrate how these trials are performed in the most careful and statistically rigorous forms. Participants with moderate TBI that were judged to have a ≥ 20 % risk for developing late epilepsy were randomized to active treatment or placebo within 24 h of injury and loaded with the appropriate drug with serum concentration monitoring. Participants were followed for 2 years after TBI. The results indicated that PHT reduced early post-TBI *clinical* seizures (as had been demonstrated by other studies), but did not prevent the development of subsequent epilepsy [14]. In fact, more participants in the PHT group developed epilepsy than in the control group. As continuous electroencephalography monitoring was not performed, the development of early subclinical seizures in the 2 groups could not be compared.

The second trial using a very similar protocol was performed comparing 1 or 6 months of valproic acid therapy with 1 week of PHT followed by placebo. Again, the results showed no antiepileptogenic effect [15].

The earlier studies discussed in Temkin's review [13] using either phenobarbital or carbamazepine did not demonstrate statistically significant positive effects, even when performed less rigorously than those discussed earlier. Similarly, the

study using a combination of phenobarbital and PHT was not as rigorously performed, and although it appeared to show a positive effect, it was not statistically significant.

Thus, both very well-performed RCTs and less rigorously performed studies failed to demonstrate anti-epileptogenic effects of these "older" ASDs. Similar negative results were seen in epilepsy prevention trials after craniotomy, even when the drugs were given before surgery, and in patients with brain tumors who were treated with either PHT or valproic acid before experiencing seizures.

The conclusion from the meta-analysis of trials employing ASDs to prevent epilepsy is that none of these treatments has been demonstrated as positive. This does not prove that these drugs would be ineffective under other circumstances, such as earlier or more persistent treatment, different doses than are commonly used for seizure suppression, closer attempts at ensuring compliance with frequent blood tests, and so on. However, the overall impression in the field is that PHT, phenobarbital, carbamazepine, and valproic acid are not useful for clinical anti-epileptogenesis.

There were many problems identified in these studies that could prove useful in the future. First, the lack of good preclinical data on a successful anti-epileptogenic treatment in any animal model is very limiting. Second, there is significant lack of knowledge about the process of epileptogenesis and this limits the choice of appropriate drugs to try in the clinic. This also limits rational decisions about how quickly after the initial precipitating event treatment needs to be started, how long to treat, and what to do about nonclinical seizures that might be occurring that are not detectable without electroencephalography monitoring (or better, prolonged ambulatory intracranial monitoring). Biomarkers that may be used to monitor epileptogenesis and the effects of therapy are also lacking so that prolonged studies with careful long-term follow-up are needed.

Many well-established precipitating causes of epilepsy also produce additional brain damage and it is critical to make sure that any anti-epileptogenic treatment does not hamper recovery of function after the damage. Thus, careful functional, cognitive, and behavioral testing needs to be performed during the trial in addition to monitoring for seizures. This adds quite a lot of additional expense, as well as additional difficulty of maintaining patients in the study.

Designing a good clinical trial for seizure prevention is not impossible, but it may be more difficult than disease modification in epilepsy (see below), and it is more difficult than comparable prevention or disease modification trials in other important neurologic diseases. However, the importance of developing a therapeutic intervention that would reduce or eliminate epilepsy in those known to be at high risk (a population often easy to identify) would be a major contribution to reducing the burden of one of the most disabling neurologic conditions, and research in this endeavor is clearly too valuable to stop because of either the cost or difficulty. In the following sections, we will elaborate on the challenges and attempt to point towards practical solutions to some of these issues in order to encourage and facilitate future research in anti-epileptogenesis.

## Challenges to Clinical Testing of Agents for Epilepsy Prevention

The most important challenges of clinical testing of agents for epilepsy prevention are 2-fold. We need to have sufficient preclinical evidence for a suitable agent to proceed with a human trial of an anti-epileptogenic drug, and we need to examine the feasibility of doing such a trial.

### Finding the Preclinical Evidence for a Suitable Anti-epileptogenic Agent

One of the most crucial early steps in planning a human study of an anti-epileptogenic agent is determining if the weight of preclinical evidence supports proceeding with a costly trial. This not only includes preclinical evidence for efficacy in preventing epilepsy, but also determining whether there are sufficient data to guide the dosing, timing, and duration of treatment in early human trials [17]. As, as discussed below, trials may long and complex, minimizing the risk of falsely rejecting a promising preclinical compound is critical when embarking on early clinical trials [6]. The proposed early phase II trial designs for assessing prevention of epilepsy and disease reversal need to be based on results of comparative, preclinical proof-of-concept studies. Appropriate biomarkers are needed to identify suitable high-risk human populations for early, small, phase II trials. Comparative phase II trials will determine differences from standard of care before investment in larger and much more costly confirmatory phase III studies. A major incentive to embark into early phase II studies will be the discovery of valid and drug-able targets, of target-related biomarkers, and of diagnostic methodology to identify the specific patient populations at high risk of developing epilepsy for prevention trials or having severe epilepsy for disease reversal studies. However, the animal data are not always clear. Issues of inadequate sample size, unblinded assessments, publication bias, and lack of methodological transparency have limited the interpretability of preclinical results in many diseases [11, 18, 19]. After many costly failed trials for stroke neuroprotection and amyotrophic lateral sclerosis using drugs that showed promise in animal models, these research communities have come together to create guidelines for preclinical studies increase the assurance of preclinical efficacy, and to determine the optimal dosing and the therapeutic window [20, 21]. Similar guidelines for anti-epileptogenic therapy were recently proposed as part of a joint

American Epilepsy Society/International League Against Epilepsy workshop on preclinical therapy discovery [19]. These guidelines stress preclinical studies beyond initial proof-of-concept stage should be adequately powered, randomized, and employ blinded assessment. The trials should report clinically relevant primary endpoints, easily assessed in human trials, such as seizure frequency. The results should be reproducible across laboratories and, if feasible, across models. Finally, both positive and negative results should be published.

In assessing the preclinical data, it is also important to understand the limitations of the animal model in replicating the human condition of interest, which is almost always more heterogeneous. Commonly-used models for post-traumatic epilepsy, such as the lateral fluid-percussion model [22], employ precisely delivered pressure waves to epidural space [23]. Human TBI is much more complex, often with effects distant to the site of injury and variable co-occurrence of potentially epileptogenic pathology, such as intraparenchymal hemorrhage and ischemia [24]. Therefore, until there is a particular model that has been validated for human anti-epileptogenic therapy, demonstrating efficacy in multiple models may increase the odds of translational success.

Understanding the drug target will also provide guidance in designing anti-epileptogenesis trials. The development of spontaneous seizures after an epileptogenic insult has been theorized to result from cascade of events that occur in response to the injury [4]. Each putative event in such a cascade, such as activation of immune cells, disruption of the blood–brain barrier, induction of apoptosis, and changes in gene transcription, may have a predictable time course. Some processes may be constitutively altered during the entire latent period, while others may only transiently increase and decrease. Drugs acting on a transient process will therefore be expected to have a therapeutic window outside of which administering the therapy will be ineffective in preventing epilepsy. Unless there is adequate understanding of the timing of target expression in humans following an epileptogenic insult, the therapeutic window used in human clinical trials will have to be extrapolated from the preclinical literature. However, if this initial guess is incorrect, the result may be a failed trial of a potentially beneficial drug. Assessment for target expression, if relevant, could be performed in parallel to tests of tolerability and efficacy in early (phase II) trials.

Special consideration should be given towards drug efficacy in preclinical trials. As no studies have shown anti-epileptogenic effects in humans, the degree to which the magnitude of response in preclinical studies (as measured by percent reduction in seizure frequency, delay to seizure onset, or proportion of treated animals remaining seizure-free) is correlated to response in clinical trials is unknown. It is likely that the heterogeneity of the epileptogenic insult significantly affects the degree to which preclinical response rates can be used to estimate clinical response rates for the purpose of designing a trial; results from models of extremely variable insults such as TBI may be less informative than those in monogenic disorders such as tuberous sclerosis.

Finally, there is a distinction between compounds that have never been tested in humans *versus* repurposing drugs approved for other indications. Novel compounds will require additional animal and then human testing to determine safety and pharmacokinetics prior clinical trials for epilepsy prevention. A thorough understanding of the safety profile of a drug is needed to adequately assess the risk of therapy because, as discussed below, many participants will need to be exposed to the experimental drug to prevent one case of epilepsy after some injuries. Understanding the pharmacokinetics of a compound, novel or repurposed, is also instrumental in designing a human clinical trial. It is obvious that effective serum and brain drug concentrations seen in preclinical trials should be attainable in humans during the therapeutic window. However, determining pharmacokinetic feasibility may not be straightforward. Acute neurologic injury itself can alter drug metabolism and clearance [25]. In addition, following an acute injury, patients are often treated with many different medications and their effect on the experimental drug should be anticipated if it to be administered soon after the epileptogenic insult.

## Finding Feasible Designs for Anti-epileptogenic Trials

Once there is sufficient biologic evidence to proceed with a human trial of an anti-epileptogenic drug, one must examine the feasibility of doing such a trial. Many factors contribute to trial feasibility, but solid understanding of the epidemiology of the targeted condition is necessary to plan successful trials. For compounds targeting a common epileptogenic insult, such as moderate-to-severe TBI (incidence 20–118 per 100,000 [26]), identifying eligible participants is not likely to be a significant problem. However, less common epileptogenic insults, such as unprovoked status epilepticus, have lower incidence rates (estimated at 6.5 per 100,000 [27]) requiring more trial sites or longer trial duration in order to accrue enough participants for a clinical trial. For trials of epilepsy prevention in genetic disorders with high rates of epilepsy, such as tuberous sclerosis, mechanisms by which pre-symptomatic individuals are identified need to be well worked out in advance.

Determining the sample size and duration of follow-up for an anti-epileptogenesis trial requires an understanding of the rate and time-course of unprovoked seizures following the injury. Insults with relatively low rates of epilepsy, such as stroke where as few as 2–12 % of individuals develop late unprovoked seizures [28], will require large trials to demonstrate even large effect sizes. Conditions with a long latent period for epilepsy development require long follow-up periods, which increase trial costs and increase the risk for dropouts and loss to follow-up [29]. As it is not feasible to

show that a test compound prevents epilepsy for the remaining life-time of the patient, a reasonable strategy would be to follow patients for several years and compare rates of epilepsy onset between anti-epileptogenic and control treatments. The duration of follow-up should be long enough to maximize the proportion of individuals expected to develop epilepsy. This will reduce sample size requirements.

The rate and time course of acquired epilepsy are also important contributors to number needed to treat (NNT) for a particular condition. Even before undertaking a trial, it is important to estimate what the expected NNT is as this will inform both the trial feasibility and, if the trial is successful in demonstrating an anti-epileptogenic effect, the likelihood a treatment will be clinically useful. An acceptable NNT is determined by careful consideration of burden of therapy compared with the burden of disease. Burden of therapy includes the risks of serious side effects related to anti-epileptogenic drug treatment, the duration and manner of treatment, and treatment cost. The burden of disease may include the risk of developing epilepsy and the severity of epilepsy that develops after an insult, age at which epilepsy develops, the proportion of individuals who develop pharmacoresistance, and the effect of epilepsy-related comorbidities. For example, for a condition resulting in a 5 % rate of late, unprovoked seizures and a treatment that reduces the risk by 30 %, 67 patients would need to be exposed to treatment to prevent 1 case of epilepsy. If the treatment had a rate of serious adverse effects of 1/500, 1 patient who would have been unlikely to develop epilepsy would be harmed for about every 8 patients in whom epilepsy was prevented. This figure may be acceptable if the resulting epilepsy was severe or difficult to treat as pharmacoresistant epilepsy is associated with significant risks for morbidity and mortality [30, 31]. However, if the resultant epilepsy was easy to manage with standard anti-seizure medications, clinical trials of the experimental drug for this condition may be inappropriate because, even if positive, the treatment will be of limited clinical utility because patients and doctors will likely find the standard of care preferable.

Other factors that may influence the feasibility of a study include the mortality after an epileptogenic insult. If the trial is targeting epilepsy after an acute neurologic injury such as TBI and the intervention occurs soon after the insult, many participants will die after getting treatment, but before they have an opportunity to develop epilepsy because of high 30-day case fatality. While this should not have an effect on interpretation of the results unless the treatment has an effect on mortality, early deaths increase sample size requirements and trial costs.

## Improving Trial Feasibility Through Biomarkers and Surrogate Endpoints

As discussed above, the proportion of patients who develop epilepsy after neurologic injury is relatively low for the many of the common causes of acquired epilepsy (Fig. 1). One potential method to reduce the size of anti-epileptogenesis trials, limit the NNT, and enhance feasibility is to identify subpopulations that are high risk for developing epilepsy. For many acute neurologic injuries, epidemiologic studies have identified clinical features that increase risk of subsequent epilepsy. For instance, while the risk of developing epilepsy following viral encephalitis is about 10 %, patients who have acute seizures at onset have a 20 % chance of developing epilepsy [32]; an epilepsy prevention trial enrolling this subset of individuals would need only be half the size as a trial studying all encephalitis patients. Biological markers, such as gene polymorphism, neuroimaging characteristics, or electrophysiological markers, may also be employed to select the subset of patients most likely to develop epilepsy [33]. While there are no validated human biomarkers to predict who will develop epilepsy, early results are promising. In moderate-to-severe TBI, a small study suggested that the presence of the apolipoprotein ε4 allele was associated with elevated risk of late unprovoked seizures with nearly half of the participants carrying the allele developing epilepsy [34]. Neuroimaging biomarkers to predict epilepsy risk are currently the subject of active clinical and preclinical investigation [35, 36], but none

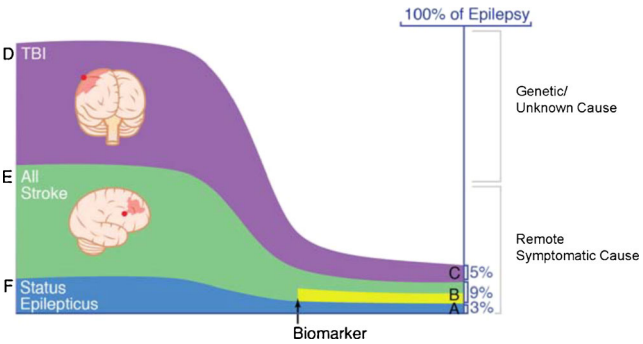


**Fig. 1** Proportion of individuals for 3 common causes of acquired epilepsy, traumatic brain injury (TBI), stroke, and status epilepticus who develop epilepsy and the contribution of these conditions to the overall burden of epilepsy. To prevent epilepsy due to status epilepticus (A) or TBI (C), patients (F or D, respectively) would need to be treated with an anti-epileptogenic drug after the insult. For patients who have TBI, the rates of subsequent epilepsy are low (C and D is approximately 10 % for all moderate-to-severe TBI at 3 years [46]) and the majority of individuals exposed to anti-epileptogenic treatment would not have developed epilepsy anyway. In this case, the number needed to treat (NNT) to prevent 1 case of epilepsy is high. In contrast, a higher proportion of patients develop epilepsy after status epilepticus (A and F is approximately 68 % [47]). The number of patients with status epilepticus exposed to an anti-epileptogenic drug to prevent on case of epilepsy is much lower. However, the effect of preventing epilepsy due to status epilepticus on the overall incidence of epilepsy is relatively low because it is a rare cause of epilepsy (A=3 %). Finally, the proportion of individuals who develop epilepsy after a stroke (B, E) is also relatively low and the NNT to prevent 1 case of post-stroke epilepsy if all patients who present after a stroke are treated would be high. However, if a biomarker identified after stroke associated with onset of epileptogenesis (shown in the schematic in yellow) can be used to select patients for anti-epileptogenic treatment, the NNT to prevent post-stroke epilepsy could be reduced significantly

have been validated. Molecular biomarkers for epileptogenesis in humans, including transcriptional products that can be easily detected in the serum, have so far been elusive, but are theoretically appealing because they may also identify targets for intervention or markers of efficacy. Conducting anti-epileptogenesis trials that include a clinical risk factor or biomarker as inclusion criteria should be performed cautiously though because of potential threats to generalizability of the study results.

Surrogate endpoints are commonly used in assess treatments where the clinically meaningful endpoint is expected to have a long latency. Glycolated hemoglobin or low-density lipoprotein levels are well-known surrogate endpoints for clinical outcomes in diabetes and atherosclerosis trials, respectively. This approach is valid if levels of a putative surrogate endpoint are highly predictive for development of the clinical meaningful outcome [37]. Identification of a surrogate marker for epilepsy that manifests long before the first clinical seizure would make anti-epileptogenesis trials for conditions with a long latent period more feasible and less costly by shortening the observation period and reducing dropout risk. However, no such surrogate endpoint has yet to be identified and validated in humans.

In order to further highlight the impact of epidemiology of acquired epilepsies on anti-epileptogenesis trial feasibility, we have summarized the incidence of the insult, rates, and latency of subsequent epilepsy and estimate the required sample size and NNT for a trial of a hypothetical agent that is 30 % effective in preventing epilepsy for some common conditions that have been proposed as candidates for intervention in Table 1. We have also highlighted some potential benefits and pitfalls to targeting particular conditions for anti-epileptogenesis trials. While it is difficult to propose designs for epilepsy prevention trials without knowledge of the timing and duration of experimental treatment, we highlight some possible designs for clinical trials to assess anti-epileptogenic effects (Fig. 2). Potential designs may include administration of an anti-epileptogenic drug or control treatment (ASD or placebo) for a period of time after the insult followed by withdrawal of treatment. For conditions with a short latent period to epilepsy onset, participants could be followed until they develop unprovoked seizures (Fig. 2A). A strategy whereby participants are monitored for seizures after epilepsy is typically established could be employed for conditions associated with a longer latent period provided there are adequate methods for participant retention during this time period (Fig. 2B). Another strategy is to employ a delayed start of an experimental anti-epileptogenic treatment as a comparison group (with or without a third placebo or anti-seizure arm; Fig. 2C). Delayed-start designs could be useful for treatments that have a window of time during which they most effectively engage the anti-epileptogenic process. Such delayed-start protocols have been employed to assess for disease modification in other neurologic disorders such as Parkinson's disease [38].

## Challenges of Clinical Trial Design to Assess Agents for Disease Modification

In order to assess disease modification, clinical trial designs need to demonstrate, after washout, changes of the long-term development or progression of epilepsy, such as development of pharmacoresistance, neurodegeneration, and cognitive or behavioral alterations compared with a control. Major challenges in trial design include the choice of suitable study parameters, the identification of a high-risk study population, the type of control, the time and duration of treatment, and a feasible follow-up period. In several ways, a trial of a disease modification would be easier to perform and present a more realistic and practical trial design than a trial of epilepsy prevention. Several studies have provided some preliminary information regarding the natural history of epilepsy, including rates of pharmacoresistance and patterns of remission during treatment with ASDs [1, 2, 39, 40], which could inform study design and sample size determination. Furthermore, such studies may be easier to recruit participants for because, in essence, the target population is similar to that of conventional ASD trials and individuals could easily be identified at epilepsy centers. In addition, because the target population already has (or is at risk for) treatment-resistant epilepsy, patients and clinicians may tolerate an unknown or higher risk–benefit ratio in disease modification trials than in the epilepsy prevention studies discussed above. Furthermore, disease modification study may have broader ability to reduce the overall burden of epilepsy as the majority of people with epilepsy do not have acquired disease. Finally, the duration and the effect size of disease modification trials may be similar to that seen in add-on trials of ASDs. A 50 % reduction of seizure frequency *versus* baseline for 12 months after washout, for example, may be seen as evidence of efficacy similar to that observed in conventional ASD trials. A word of caution: as long we do not know the pharmacological features of the disease-modifying compound to be tested, it will be difficult to offer individual trial design solutions tailored to the specifics of the compound. Here we will offer general considerations on the options and limitations of trial designs for disease-modifying pharmacological therapy.

### Trial Designs to Assess Disease-Modifying or Disease-Reversing Effects in Pharmacoresistant Epilepsy

Prospective long-term observations have shown that 3 subgroups exist among patients with pharmacoresistant epilepsy: those who have pharmacoresistant epilepsy continually since their first seizure and those who develop pharmacoresistant

**Table 1** Examples of common conditions and neurologic injuries that are associated with a high risk of developing epilepsy and associated epidemiology factors that affect the design of anti-epileptogenesis trials in humans targeting these conditions. An estimate of numbers needed to treat and sample size are provided for each condition assuming a hypothetical treatment that is 30 % effective at reducing the risk of developing epilepsy

| Injury/condition [ref.] | Annual incidence (per 100,000) | % Of overall epilepsy etiology [incident (I)/prevalent (P)] | 30-d case fatality | High risk biomarker/ clinical feature | % With high risk feature | Cumulative incidence of unprovoked seizure | Cumulative incidence of epilepsy | | | | NNT* assuming 30 % efficacy (epilepsy incidence rate used for estimate) | Est. sample size per group† assuming 30 % efficacy | Pros/cons |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1–3 y | 3–5 y | 5–10 y | > 10 y | | | |
| Moderate-to-severe TBI [26, 34, 46, 48, 49] | 20–118 | I: 4.6–8.8 % P: 5 % | 11–15 % | | | — | — | 11 % | — | — | 30 (11 %) | 1196 | **Pros**: High rate/burden of epilepsy; hx of past trials for infrastructure; existing preclinical models; few comorbid medical problems; available animal models with demonstration of anti-epileptogenic effect **Cons**: Variable injury; high case fatality and loss to follow-up, long latency to epilepsy, consent issues |
| | | | | Severe TBI | 18 | — | 6 % | 10 % | 14 % | 16 % | 34 (10 %) | 1354 | |
| | | | | Contusion/ICH | 10 | — | 2 % | — | — | 35 % | 16 (21 %) | 579 | |
| | | | | ApoE4 | 9 | 47 % (@ 6 mo f/u) | — | — | — | — | 8 (47 %) | 205 | |
| Febrile status epilepticus [50–54] | 1.2 | — | 0 | | | — | 7 % | — | — | — | 48 (7 %) | 1989 | **Pros**: High risk for epilepsy, ascertainment can be made during initial hospitalization; potential biomarkers (FEBSTAT); existing animal models **Cons**: Variable etiology, long latent period, rare |
| | | | | Focal features for seizure | 42–48 | — | — | — | — | 21 % | 48 (7 %) | 1989 | |
| | | | | Focal features and repetitive | 19 | — | — | — | — | 49 % | 21 (16 %) | 780 | |
| Ischemic stroke [28, 55–57] | 76–170 | I: 18 % P: ? | 12 % | | | 2.7–35.0 % | 2.5§–3.2 % | 3.8 % | 3.1§–5.4 % | 5.4 % | 88 (3.8 %) | 3771 | **Pros**: Epilepsy important comorbidity in survivors; ascertainment can occur during the initial hospitalization **Cons**: Variable injury; medical comorbidities; patients at risk for recurrent stroke during study period; animal models for spontaneous seizures are limited |
| | | | | Acute seizure | 2–9 | — | — | 10 % | — | — | 34 (10 %) | 1354 | |
| | | | | Cortical location | 36 | — | 14 %§ | — | — | — | 24 (14 %) | 931 | |
| Neonatal seizures [58–62] | 1.0–3.5 per 1000 live births | — | 23–28 % | | | — | 13–22 % | — | 18–56 %¶ | — | 20 (17.5 %) | 720 | **Pros**: High risk of epilepsy, ascertainment can occur during the initial hospitalization; high burden of epilepsy; available animal models **Cons**: Heterogeneous etiology, high mortality |
| | | | | Hypoxic–ischemic encephal-opathy | 66 | — | 50 % | — | — | — | 7 | 87 | |
| Encephalitis [32, 63] | 3.5–7.4 | I: 1–3 % P: ? | — | | | 10 % | — | — | — | 10 % | 67(5 %) | 2950 | **Pros**: High rate of subsequent epilepsy; short latent period, high burden of disease; easy to identify patients via state laboratories/hospitalizations **Cons**: Variable etiology and severity, limited animal models assessing epilepsy |
| | | | | Acute seizure | 43 | 22 % | 6 % | 10 % | 16 % | 22 % | 34 | 1354 | |

**Table 1** (continued)

| Injury/condition [ref.] | Annual incidence (per 100,000) | % Of overall epilepsy etiology [incident (I)/prevalent (P)] | 30-d case fatality | High risk biomarker/ clinical feature | % With high risk feature | Cumulative incidence of unprovoked seizure | Cumulative incidence of epilepsy | | | | NNT* assuming 30 % efficacy (epilepsy incidence rate used for estimate) | Est. sample size per group† assuming 30 % efficacy | Pros/cons |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 1–3 y | 3–5 y | 5–10 y | > 10 y | | | |
| Tuberous sclerosis [64–68] | 0.56‡ | — | n/a | | | 53 % | 65 % | — | 50–97 % | — | 6(65 %) | 101 | **Pros**: High risk of epilepsy, significant comorbidity and burden of disease, multiple animal models with anti-epileptogenesis demonstrated in some<br>**Cons**: Difficult to ascertain cases before they develop epilepsy, many come to medical attention owing to seizures |
| | | | | *TSC2* mutation | 50 | 62 % | 82 % | — | — | — | 5(82 %) | 54 | |

NNT = number needed to treat; n/a = not applicable; TBI = traumatic brain injury; ICH = Intracranial hemorrhage; ApoE4 = apolipoprotein E4; f/u = follow-up; hx = history; FEBSTAT = FEBSTAT study [54]

*A theoretical number needed to treat was calculated for a hypothetical intervention that reduces incidence of epilepsy at 3 years by 30 %. The number in parentheses represents the incidence figure used for the calculation if a range of incidence rates are reported in the literature. When no 3-year incidence rate was available in the literature, an estimate was made using linear extrapolation using available data.

† A theoretical sample size per group was estimated for 30 % reduction in epilepsy incidence at 3 years assuming 80 % power and 5 % level of significance using an unadjusted sample size calculation for comparing 2 binomial proportions. The same incidence rate of epilepsy at 3 years used to calculate NNT is used to determine sample size. Sample size estimates do not account for case fatality. ‡ Likely an underestimate as it does not account for asymptomatic cases. § Prospective. ¶ Prospective study ~20 % incidence

epilepsy after years of being seizure-free [1]. In addition, there is a third subgroup of patients who will become seizure-free after years of having seizures that could not be controlled with ASDs [1]. Careful clinical observations have shown that the response and, correspondingly, the rate of pharmacoresistance to newly administered ASD treatments is highly dependent on the number of prior life-time ASDs [2, 41, 42], and the number of seizures in the months prior to ASD initiation and in the first year after starting ASD treatment [39, 41, 42]. The seizure-free rates decreased from 61.8 % for the first ASD to 41.7 %, 16.6 %, and 0 % after 1, 2–5, and 6–7 past ASDs proved inefficient [41]. Thus, for every 1.5 ASDs that proved ineffective in the past the seizure-free rates decreased by 50 % [41]. Likewise, the percentage of patients with a > 50 % seizure frequency reduction to the newly administered ASD treatment dropped to 69.3 % after failure of 1 past ASD, 47 % after failure of 2–5 past ASDs, and 31 % after failure of 6–7 past ASDs [41]. Although participants entering randomized controlled add-on trials are not routinely stratified according to the number of prior life-time ASDs, post-hoc analysis is needed to confirm that the rate of nonresponse depends on the number of life-time ASDs in clinical trials. Based on this data from clinical observations, if confirmed in the analysis of RCTs, the chance of becoming seizure free is clearly reduced in patients relative to the number of ASDs that they have tried and which failed to eliminate seizures. While the response rate is clearly very low after so many anti-seizure drugs, the implication should not be that patients should not be tried on new anti-seizure drugs when they become available. Many experienced clinicians have a few patients that respond well to a new compound, despite many drug failures. This does not mean in itself that the epilepsy is progressing in all patients. One might argue that at the first presentation there are individuals that will not respond to any current ASDs and that it takes a certain number of attempts to identify those individuals, not because they are progressing during treatment. Regardless of whether the pharmacoresistant epilepsy exists from the start or has developed later, it might be advantageous to develop a disease-modifying therapy. A disease-modifying treatment, if successful, would transform pharmacoresistant epilepsy into ASD-responsive epilepsy. If ASDs can be successfully withdrawn following sustained seizure freedom for several years, the disease-modifying treatment may even turn out to have disease–reversing properties.

Based on these observations, a comparative early-phase II trial design is proposed to assess a disease-reversing effect of a novel agent. Patients with focal seizures unresponsive to their first two lifetime ASDs would be randomized to either a standard 3-month add-on ASD plus placebo for a limited time or a standard add-on ASD plus the experimental disease-modifying agent for a limited time before washout. Prior treatment with 2 lifetime ASDs were chosen as an example, as this is the minimum definition of pharmaoresistance

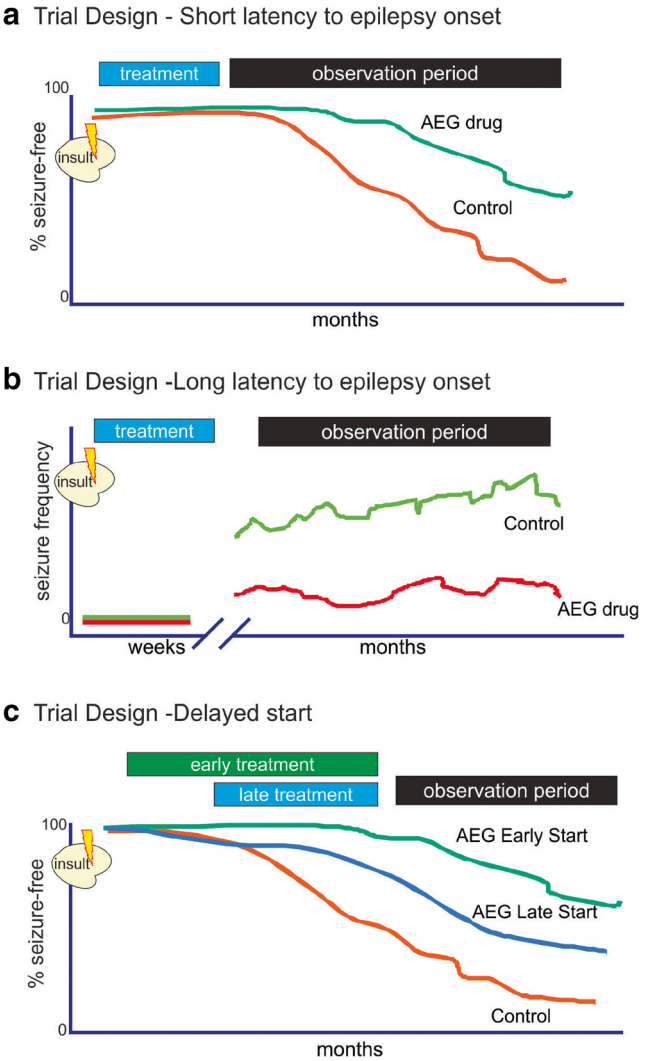


**Fig. 2** Schematics for possible design of epilepsy prevention trials. (A) For an epileptogenic insult with a short latent period for the onset of epilepsy, participants could be randomized to receive anti-epileptogenic (AEG) treatment or control (standard anti-seizure treatment or placebo) for a period of time after the insult. Participants would be followed for the onset of seizures during and after the treatment period. If anti-epileptogenic treatment is effective, the rate of developing unprovoked seizures would be lower in the AEG-treated group. (B) For an insult associated with a long latent period, the observation period could be delayed and participants could be assessed for seizure occurrence months to years after the insult provided few individuals are lost to follow-up during the delay. (C) An alternate strategy to demonstrate the disease-modifying properties of an experimental treatment is a delayed start design where participants are randomized to receive AEG treatment early after an insult or after some delay and then observed following the discontinuation of therapy. If the experimental treatment is truly disease-modifying, the proportion of participants who develop epilepsy will be higher in the late-treated group and early-treatment group will never "catch up" at the end of the observation period. A third comparison group that received standard anti-seizure drug or placebo could be employed to improve the internal validity of the study

recently proposed by the International League Against Epilepsy [43]. Depending on the preclinical profile of the disease-modifying agent, suitable entry criteria, for example failure for up to 5 prior ASDs, or psychiatric or cognitive comorbidity, can be chosen. In addition, the participants should be screened for psychiatric comorbidity to assess a potential effect of the test compound on comorbidity. The duration of disease-modifying treatment would be based on extrapolation from preclinical data that take into account the proposed mechanism of action and pharmacokinetic parameters of the agent. Seizure outcome would be monitored as in a standard anti-seizure trial with an open 24-month extension period with unchanged study medication.

Patients with active epilepsy randomized to either arm would be compared for 50 % and 100 % seizure reduction *versus* baseline at 3 months or failure for any reason at the end of the 24-month extension (Fig. 3).

Depending on the expected profile of the disease-modifying agent, suitable study parameters may include measures of general health, reversal of pharmacoresistance, development of tolerance to the effect of the disease-modifying agent, and changes in behavioral comorbidity such as anxiety, major depression, and interictal dysphoria [44, 45].

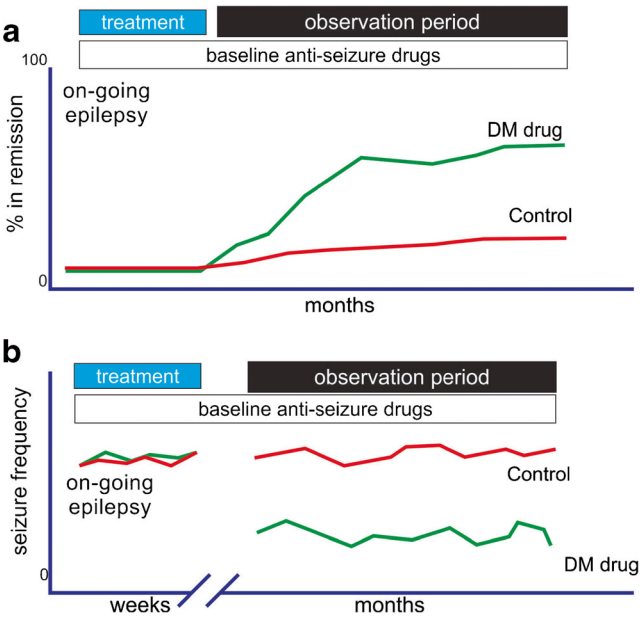


**Fig. 3** Schematics for possible design of disease modification trials in ongoing epilepsy. To assess a compound for its ability for disease modification, patients with epilepsy could be randomized to receive disease modification (DM) treatment or control (standard anti-seizure treatment) for a period of time. Patients would be followed for change of the chosen parameter, for example entering seizure remission (A) or change in seizure frequency (B) during DM treatment and following DM treatment withdrawal. If DM is effective, the rate of seizures would be lower in the DM group. The observation period could be prolonged and patients could be assessed for seizure occurrence months to years after the treatment provided enough patients are remaining in follow-up. If the experimental treatment is truly disease-modifying, the proportion of patients in remission will be higher at the end of the observation period

## Looking Ahead

Although it is admittedly difficult to address specific challenges and options of drugs for anti-epileptogenesis and disease modification, or even disease reversal, if these compounds are not currently available, it may be useful to address general issues and options for trial design that the novel compounds for epilepsy treatment pose for clinical trialists once we have them. Given the challenges for preclinical testing of suitable compounds, the issues to find suitable biomarkers for high-risk populations and the extended follow-up that may be required to assess anti-epileptogenesis and disease modification, it may be worthwhile to remind us why we need to undertake such costly and time-consuming trials. The clinical answer is that we are probably at the end of our wits with conventional ASD treatment. No substantial advances have been made for adult patients with common seizure types and for the many patients with catastrophic childhood onset epilepsies [3]. One possible explanation why we did not advance dramatically with conventional ASDs in the cure of epilepsy is that we need to get away from purely symptomatic seizure treatment to epilepsy treatments that favorably affect the underlying disease [6]. Considering what kind of novel trial designs we may need once we have the novel anti-epileptogenesis and disease-modification compounds is one aspect of ushering in a new era of epilepsy treatment which may be around the corner, we hope.

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## References

1. Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 2006;129:617–624.
2. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012;78:1548–1554.
3. Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia 2011;52:657–678.
4. Pitkänen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol 2011;10:173–186.
5. Löscher W, Brandt C. Prevention or modification of epileptogenesis after brain insults: experimental approaches and translational research. Pharmacol Rev 2010;62:668–700.
6. Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nat Rev Drug Discov 2013;12:757–776.
7. Mani R, Pollard J, Dichter MA. Human clinical trails in antiepileptogenesis. Neurosci Lett 2011;497:251–256.
8. Temkin NR. Preventing and treating posttraumatic seizures: the human experience. Epilepsia 2009;50:10–13.
9. Bialer M, White HS. Key factors in the discovery and development of new antiepileptic drugs. Nat Rev Drug Discov 2010;9:68–82.
10. Friedman D, French JA. Clinical trials for therapeutic assessment of antiepileptic drugs in the 21st century: obstacles and solutions. Lancet Neurol 2012;11:827–834.
11. French JA, White HS, Klitgaard H, Holmes GL, Privitera MD, Cole AJ, et al. Development of new treatment approaches for epilepsy: Unmet needs and opportunities. Epilepsia 2013;54:3–12.
12. Dichter MA, Temkin N. Management of patients at high risk for seizures and epilepsy after traumatic brain injury and other risks (the Risk of Epilepsy Development (RED) syndrome). In: Shorvon S, Perucca E, Engel J, Jr (eds) Treatment of epilepsy. 3rd ed. Oxford, John Wiley, 2009; 249–258.
13. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. Epilepsia 2001;42:515–524.
14. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323:497–502.
15. Temkin NR, Dikmen SS, Anderson GD, Wilensky AJ, Holmes MD, Cohen W, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. J Neurosurg 1999;91:593–600.
16. Dikmen SS, Temkin NR, Miller B, Machamer J, Winn HR. Neurobehavioral effects of phenytoin prophylaxis of posttraumatic seizures. JAMA 1991;265:1271–1277.
17. Schmidt D. Is antiepileptogenesis a realistic goal in clinical trials? Concerns and new horizons. Epileptic Disord 2012;14:105–113.
18. Hackam DG, Redelmeier DA. Translation of research evidence from animals to humans. JAMA 2006;296:1731–1732.
19. Pitkänen A, Nehlig A, Brooks-Kayal AR, Dudek FE, Friedman D, Galanopoulou AS, et al. Issues related to development of antiepileptogenic therapies. Epilepsia 2013;54:35–43.
20. Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, et al. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke 2009;40:2244–2250.
21. Ludolph AC, Bendotti C, Blaugrund E, Chio A, Greensmith L, Loeffler J-P, et al. Guidelines for preclinical animal research in ALS/MND: A consensus meeting. Amyotroph Lateral Scler 2010;11:38–45.
22. D'Ambrosio R, Fairbanks JP, Fender JS, Born DE, Doyle DL, Miller JW. Post-traumatic epilepsy following fluid percussion injury in the rat. Brain 2004;127:304–314.

23. McIntosh TK, Vink R, Noble L, Yamakami I, Fernyak S, Soares H, et al. Traumatic brain injury in the rat: Characterization of a lateral fluid-percussion model. Neuroscience 1989;28:233–244.
24. Pitkänen A, Immonen RJ, Gröhn OH, Kharatishvili I. From traumatic brain injury to posttraumatic epilepsy: what animal models tell us about the process and treatment options. Epilepsia 2009;50:21–29.
25. Boucher BA, Hanes SD. Pharmacokinetic alterations after severe head injury. Clinical Pharmacokinet 1998;35:209–221.
26. Bruns J, Hauser WA. The epidemiology of traumatic brain injury: a review. Epilepsia 2003;44:2–10.
27. Hesdorffer D, Logroscino G, Cascino G, Annegers J, Hauser W. Incidence of status epilepticus in Rochester, Minnesota, 1965–1984. Neurology 1998;50:735–741.
28. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. Stroke 2004;35:1769–1775.
29. Herman ST. Clinical trials for prevention of epileptogenesis. Epilepsy Res 2006;68:35–38.
30. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology 2002;58(8 Suppl. 5):S21-S26.
31. Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. Seizure control and mortality in epilepsy. Ann Neurol 1999;46:45–50.
32. Annegers J, Hauser W, Beghi E, Nicolosi A, Kurland L. The risk of unprovoked seizures after encephalitis and meningitis. Neurology 1988;38:1407.
33. Engel J. Biomarkers in epilepsy: introduction. Biomarkers 2011;5:537–544.
34. Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, et al. Increased risk of late posttraumatic seizures associated with inheritance of APOE 4 Allele. Arch Neurol 2003;60:818.
35. Gomes WA, Shinnar S. Prospects for imaging-related biomarkers of human epileptogenesis: a critical review. Biomark Med 2011;5:599–606.
36. Mishra AM, Bai H, Gribizis A, Blumenfeld H. Neuroimaging biomarkers of epileptogenesis. Neurosci Lett 2011;497:194–204.
37. Atkinson AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, Hoth DF, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89–95.
38. Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009;361:1268–1278.
39. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–319.
40. Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively. Epilepsia 2011;52:619–626.
41. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs Effect of past treatment history. Neurology 2008;70:54–65.
42. Sillanpää M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain 2009;132:989–998.
43. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–1077.
44. Brooks-Kayal AR, Bath KG, Berg AT, Galanopoulou AS, Holmes GL, Jensen FE, et al. Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. Epilepsia 2013;54:44–60.
45. Kanner AM. The treatment of depressive disorders in epilepsy: What all neurologists should know. Epilepsia 2013;54:3–12.
46. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20–24.
47. Hesdorffer DC, Logroscino G, Cascino G, Annegers JF, Hauser WA. Risk of unprovoked seizure after acute symptomatic seizure: effect of status epilepticus. Ann Neurol 1998;44:908–912.
48. Annegers JF, Grabow JD, Kurland LT, Laws ER. The incidence, causes, and secular trends of head trauma in Olmsted County, Minnesota, 1935–1974. Neurology 1980;30:912.
49. Pitkänen A. Therapeutic approaches to epileptogenesis—hope on the horizon. Epilepsia 2010;51(Suppl. 3):2–17.
50. Annegers JF, Hauser WA, Shirts SB, Kurland LT. Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987;316:493–498.
51. Maytal J, Shinnar S. Febrile status epilepticus. Pediatrics 1990;86:611–616.
52. Shinnar S, Pellock JM, Berg AT, O'Dell C, Driscoll SM, Maytal J, et al. Short-term outcomes of children with febrile status epilepticus. Epilepsia 2001;42:47–53.
53. Dubé CM, Ravizza T, Hamamura M, Zha Q, Keebaugh A, Fok K, et al. Epileptogenesis provoked by prolonged experimental febrile seizures: mechanisms and biomarkers. J Neurosci 2010;30:7484–7494.
54. Shinnar S, Bello JA, Chan S, Hesdorffer DC, Lewis DV, MacFall J, et al. MRI abnormalities following febrile status epilepticus in children The FEBSTAT study. Neurology 2012;79:871–877.
55. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, et al. Stroke incidence among white, black, and hispanic residents of an urban community the Northern Manhattan Stroke Study. Am J Epidemiol 1998;147:259–268.
56. Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000;57:1617.
57. Lossius MI, Rønning OM, Slapø GD, Mowinckel P, Gjerstad L. Poststroke epilepsy: occurrence and predictors—a long-term prospective controlled study (Akershus Stroke Study). Epilepsia 2005;46:1246–1251.
58. Holden KR, Mellits ED, Freeman JM. Neonatal seizures I. Correlation of prenatal and perinatal events with outcomes. Pediatrics 1982;70:165–176.
59. Legido A, Clancy RR, Berman PH. Neurologic outcome after electroencephalographically proven neonatal seizures. Pediatrics 1991;88:583–596.
60. Ortibus E, Sum J, Hahn J. Predictive value of EEG for outcome and epilepsy following neonatal seizures. Electroencephalogr Clin Neurophysiol 1996;98:175–185.
61. Saliba RM, Annegers JF, Waller DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992–1994. Am J Epidemiol 1999;150:763–769.
62. Mizrahi EM, Clancy RR. Neonatal seizures: Early-onset seizure syndromes and their consequences for development. Ment Retard Dev Disabil Res Rev 2000;6:229–241.
63. Beghi E, Nicolosi A, Kurland LT, Mulder DW, Hauser WA, Shuster L. Encephalitis and aseptic meningitis, Olmsted County, Minnesota, 1950–1981: I. Epidemiology. Ann Neurol 1984;16:283–294.
64. Wiederholt W, Gomez MR, Kurland LT. Incidence and prevalence of tuberous sclerosis in Rochester, Minnesota, 1950 through 1982. Neurology 1985;35:600.
65. Webb D, Fryer A, Osborne J. On the incidence of fits and mental retardation in tuberous sclerosis. J Med Genet 1991;28:395–397.
66. Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: a population study. Dev Med Child Neurol 1996;38:146–155.
67. Zeng LH, Xu L, Gutmann DH, Wong M. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol 2008;63:444–453.
68. Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010;51:1236–1241.