CLINICAL INVESTIGATION

Designing better trials for epilepsy medications: the challenge of heterogeneity

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Despite the expanding treatment options in the past two decades, a third of patients with epilepsy remain treatment resistant, and there is a continued need for new therapies. After many years of repeated success, several late-stage clinical development programs for antiseizure drugs have seen unexpected failures to demonstrate superiority of the experimental drug over placebo, which has led to a re-examination of how clinical trials are conducted in this heterogeneous and often unpredictable condition. There are numerous sources of variability in epilepsy trials that can reduce effect size. Methods to improve diagnostic accuracy and outcome assessment are needed to ensure that promising compounds have the best chance to get to patients.

Keywords: anti-epileptic drugs • clinical trials • epilepsy • placebo response rate • seizure

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A recent report from the Institute of Medicine estimated that one in 26 individuals will have epilepsy at some point in his or her lifetime [1]. At present, two-thirds of individuals suffering from epilepsy can achieve complete control of their seizures by use of appropriate medication [2]. These medicines traditionally are called antiepileptic drugs (AEDs). The name implies that the drugs treat the underlying disease, whereas in fact they only effectively treat the symptom (epileptic seizures). Thus, a more accurate name for these medications is antiseizure drugs (ASDs). In the 1970s and 1980s, there was clearly a dearth of available ASDs. At that time, there were only five ASDs in common use, and patients with treatment-resistant epilepsy would quickly fail these medications and be left with limited or no options. ASD development has been extremely productive over the last two decades; now healthcare providers have over 20 ASDs from which to select. These options include drugs that are appropriate for use in patients with newly diagnosed epilepsy, patients with treatment-resistant epilepsy, and many epilepsy syndromes including the generalized and focal epilepsies. Yet, in most estimations, new ASDs are still greatly needed. The current options suffer from a number of problems, including relatively common shared side effects (impacting psychiatric, CNS and somatic function), a high potential for drug interactions, and impact on reproductive functioning [3]. Even more concerning is the fact that the large increase in available drugs in most estimations has not significantly reduced the proportion of patients with epilepsy (estimated at ~1/3) who are treatment resistant and who continue to experience seizures despite best medical therapy [2,4]. In addition, patients suffering from certain epileptic syndromes (e.g., Lennox-Gastaut syndrome, Dravet syndrome) have little to no chance of obtaining seizure control with currently available ASDs. Therefore, new treatments are still urgently needed.

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Strategy for ASD development & recent ASD trials

The strategy for testing ASDs has not substantially changed in the last 30 years. Typically, drugs will be tested initially as adjunctive therapy in patients with treatment-resistant partial (focal) epilepsy. This patient population is studied first, because it comprises the largest population of adult patients with treatment-resistant epilepsy, making trial enrollment feasible. The add-on design is selected because it is the requirement of the US FDA that these studies demonstrate superiority. It is much easier to demonstrate superiority when placebo is used as the comparator. Since epilepsy is a serious condition, a placebo-control would not be possible in any design other than adjunctive therapy, for ethical reasons (active epilepsy should not go untreated with few exceptions). A schema of the traditional ASD trial is shown in Figure 1.

The adjunctive placebo-controlled design provided some challenges (e.g., patients might already have some of their seizures suppressed by their ongoing therapy, and drug–drug interactions were often challenging). Nonetheless, drugs that had already been demonstrated to have an antiseizure effect in animal models, or in human proof-of-concept studies, almost never failed in these types of trials. When drugs did not ultimately make it to the clinic, it was because the treatment effect was considered to be too small, there was a significant safety or side-effect issue, or the company developing the drug made a strategic decision to stop development. This was exemplified by the number of drugs that were approved in the USA from 1998 to 2010 (Figure 2).

Changes were seen in the mid-2000s, when drugs that had demonstrated substantial promise in early stages of development began to fail in large Phase III clinical trials. Two eagerly anticipated ASDs (carisbamate and brivaracetam) were in the forefront of this wave of failure. Carisbamate was an interesting case study, as two Phase II studies were performed at similar sites. The first demonstrated a significant treatment effect, while the second, performed at identical doses, failed to demonstrate an effect [5]. A subsequent study also failed [6]. Brivaracetam demonstrated very good efficacy with minimal side effects in a Phase II study [7], but was variably effective in larger Phase III studies, and replication of efficacy at specific doses could not be achieved [8,9]. There were also difficulties encountered in trials of a new ASD, perampanel. Efficacy was demonstrated at 8- and 12-mg doses [10,11]. However, in study 304 [101], the outcome that had been prespecified as pivotal for European regulators (50% responder rate, defined as the proportion of patients who had a 50% reduction in seizures) was not significantly different from the unexpectedly high placebo responder rate of 24%. Further analysis uncovered an even higher placebo responder rate in Central and South American study centers (33.3%) [10,11]. Most recently, a trial of pregabalin extended release failed and again a very high placebo responder rate of 35.8% was seen [12]. By comparison, a pooled analysis of all four similarly designed placebo-controlled add-on trials of the immediate release form of pregabalin (performed a decade earlier) showed a pooled placebo responder rate of 10.1% [13].

There are a number of theories regarding the source of higher placebo responder rates and lower effect sizes that are observed over time. These take into consideration that, at least in some instances, higher placebo responder rates are observed in some geographic regions and not others (although this is not always the case) and even within a single trial, rates can vary based on patient population characteristics [14]. It is also notable that this problem seemed to amplify as trials were performed more globally and also as the number of centers needed to recruit the appropriate number of patients increased markedly. As an example, the original pregabalin studies were performed predominantly in the USA, Canada and western Europe, whereas recent ASD studies recruit in such diverse geographic locations as eastern Europe, South America, Mexico, South Africa, China and Malaysia. Moreover, whereas studies a decade or more ago were performed predominantly at academic epilepsy centers, many of whom could enrol ten patients or more, study centers now include groups that perform neurology clinical trials in multiple indications, who may not have followed patients for as long or know them as well. Issues that may contribute to rising placebo rates and/or dropping effect sizes may include enrollment

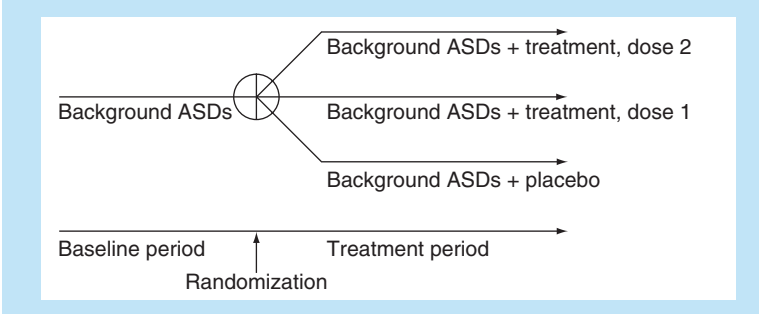

Figure 1. Typical add-on antiseizure drug trial design. In this design, subjects with treatment-resistant epilepsy who meet trial inclusion criteria are randomized to receive placebo or experimental treatment in addition to their usual ASDs, following a period of time to establish their baseline seizure frequency. Typically, there are several treatment arms with different fixed doses of the experimental ASD.
ASD: Antiseizure drug.

of patients for whom there is diagnostic uncertainty. Epilepsy is a complex disorder. Unlike conditions such as Alzheimer's disease and multiple sclerosis, there are no established and accepted diagnostic criteria, and this can amplify diagnostic uncertainty. Enrollment of patients that do not have epilepsy or the specific epilepsy syndrome under investigation into therapeutic trials can lead to increased variability in mean treatment response. Furthermore, unequal distribution of these inherent nonresponders among the study arms of a clinical trial can lead to diminished effect sizes. In addition, even if the patient has the epilepsy syndrome of therapeutic interest, it is possible that not all of the events reported by the patient or family as seizures, the primary outcome of epilepsy clinical trials, are epileptic. Coexistence of episodes expected and unexpected to respond to the experimental treatment in the same subject can further add variability to clinical trials. Below we explore diagnostic uncertainty in epilepsy and how this may affect the conduct and outcome of therapeutic trials.

Uncertainty regarding diagnosis & classification

Epilepsy remains a clinical diagnosis defined by the occurrence of two or more unprovoked seizures more than 24 h apart. The current operational definition of a seizure is a "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [15]. The behavioral manifestations of seizures are protean. This is especially true among partial-onset seizures where semiology, the observable and experiential features of a seizure, vary based on the cortical location of the seizure onset zone. Diagnostic testing, such as electroencephalography (EEG) or brain imaging, serve only supportive roles in epilepsy diagnosis and patients often have unequivocal epilepsy despite a normal EEG and MRI. Therefore, clinical history is critical for the diagnosis of epilepsy. It is important to thoroughly interview a patient about the nature of their paroxysmal events. However, because seizures often leave people unaware, observer descriptions, where available, are even more critical. This may be a complex process and a complete understanding about the nature of a patient's events may evolve over repeated interviews and visits. For a minority of patients, however, despite careful history taking the diagnosis of epileptic seizures is often incorrect. In many resource-rich healthcare systems, patients who have episodes that are suspected of being seizures but are not responding to ASD are admitted to epilepsy monitoring units where behavior, through audio–visual recording, and EEG can be recorded during their paroxysmal spells. It is estimated that

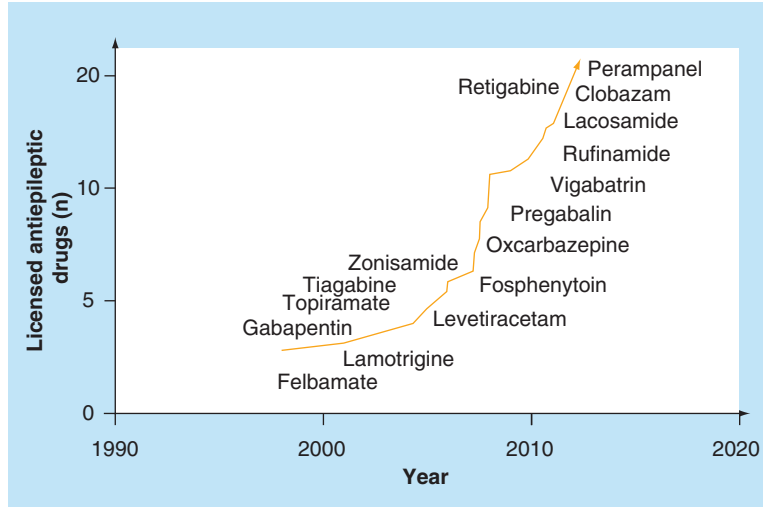

Figure 2. Antiepileptic drugs approved in the USA between 1998 and 2013.

approximately 25–30% of patients admitted to such video-EEG units will have events that are not epileptic [16,17], although many of these patients would have been treated with AEDs for many years [16]. The majority of these nonepileptic events are found to be psychogenic events termed nonepileptic attack disorders. Other paroxysmal events that may be mistaken for seizures include syncope, hypoglycemia, movement disorders and parasomnias [18]. A further difficulty for many physicians is that both epileptic seizures and nonepileptic attack disorders can coexist in the same patient [19]. Another situation that can lead to misclassification of nonepileptic events as epileptic occurs in epilepsy patients with moderate or severe developmental delay. These patients (often children) may have repetitive stereotypic behaviors such as hand flapping or hyperventilation. In the absence of video-EEG monitoring, these may be very difficult to distinguish from the stereotyped behavior caused by seizures [20]. Children in general can have events that are difficult to characterize as epileptic. In one study of children in a video-EEG monitoring unit (where true seizures were identified by video-EEG), parents only correctly counted seizures in 38% of children, whereas they over-reported seizures in 12%, and under-reported in 50% [21]. They were more likely to count motor seizures (generalized tonic–clonic convulsions [GTCC], atonic, complex partial seizures [CPS]) than nonmotor seizures (absence).

In addition, video-EEG monitoring can correct epilepsy syndrome diagnosis; some patients thought to have focal epilepsy by clinical history or based on a brief EEG demonstrating focal discharges are subsequently found to have generalized epilepsy syndromes [22]. Even a good clinical history may lead the physician to the wrong conclusion regarding the epilepsy syndrome; in one series approximately 70% of patients

with confirmed generalized epilepsy reported 'auras', a feature typically associated with focal epilepsy [23].

Clearly, misclassification of seizures and misdiagnosis of epilepsy can affect trial results in a number of important ways. The most significant and problematic situation would be enrolling a patient who did not have epilepsy into a trial of an epilepsy therapeutic intervention. If enrolled patients' events were not epileptic in nature, the events would not be expected to be impacted by the intervention, and the effect size would be reduced. This would also occur if patients were enrolled who had a combination of epileptic and nonepileptic events. For example, as noted above, distinguishing seizures from other events can be challenging in children with developmental delay, and this is particularly true of nonmotor seizures. In studies of Lennox-Gastaut syndrome, a syndrome seen in children with developmental delay and multiple motor and nonmotor seizure types, it is common to count only motor seizures such as tonic/atonic when they cause falls (known as 'drop' seizures) and GTCC. In a recent study of clobazam, the responder rate for drop seizures was 12.1% in the placebo group, and 41.2, 49.4 and 68.3% in the low-, medium- and high-dose drug group (all highly statistically significant differences from placebo), respectively. However, there was a very different result for nondrop seizures. This type of seizure increased by 76% in the placebo group, and also increased in the low- and medium-dose drug group, neither of which separated statistically from placebo. Thus, if the seizure types that are less reliably counted by parents had been included, the trial would have failed [24].

Enrolling patients who do not have the epilepsy syndrome that is being studied can also be problematic. Epilepsy syndromes usually fall into two groups – those that are considered to be of focal or localized onset in the brain (also known as focal epilepsy) and those that are of generalized onset (either genetic generalized or with broad epileptic networks, as in Lennox-Gastaut syndrome) [25]. Drugs tend to be either 'broad spectrum', working in both focal and generalized epilepsies, or 'narrow spectrum', working either only in focal epilepsy syndromes only or generalized epilepsy syndromes. Studies tend to enrol patients belonging to either only one syndrome, or several closely related syndromes (e.g., GTCC upon awakening and juvenile myoclonic epilepsy with GTCC). Ideally, patients with less heterogeneity (e.g., those with only juvenile myoclonic epilepsy, or only a specific etiology of focal epilepsy such as hippocampal sclerosis) would be enrolled. However, this would not only limit generalizability of the results, but would also make recruitment into the study extremely difficult. Enrolling misclassified patients, particularly those who have been misclassified as to whether focal or generalized, could have two possible deleterious effects. Enrolling a large number of patients who have focal syndromes in a study of a generalized epilepsy could cause the study to fail if the therapeutic intervention only works in generalized syndromes. Alternatively, if the drug is not effective in generalized epilepsy, but is effective in focal epilepsy, then enrolling a large number of patients with focal epilepsy could cause the drug to erroneously appear to be effective.

Uncertainty regarding outcome

The outcome of interest for most therapeutic trials in epilepsy is based on seizure frequency. This is typically specified as median seizure reduction from baseline, number of subjects with a greater than 50% seizure reduction or both; preferences vary depending on the regulatory agency. While this outcome is obviously clinically relevant, it is notoriously difficult to measure reliably [26]. In epilepsy trials, subjects are asked to complete seizure diaries using paper calendars in which they note the date of their seizure and the type of seizure they had. However, studies have shown that patients with epilepsy are often not reliable reporters of their seizures. In one study of patients in an epilepsy monitoring units, only 26% of subjects were aware of all of their seizures and 30% of subjects recalled none of their seizures [27]. Even when subjects are aware of the seizure, they may fail to log it contemporaneously as diaries are often not completed in real time. The diary may not be available at the time of the seizure or the postictal state may be prolonged. Although a single study in subjects with epilepsy has noted good reliability of a paper diary compared with random subject interview [28], studies in other fields have demonstrated very poor compliance with daily diary completion [29]. Backfilling – retroactive completion of the diary just prior to the study visit – is a common practice and can lead to inaccurate recollection of seizure frequency and type. It is also not known whether subjects can reliably distinguish among their seizure types. In clinical practice, it is common that subjects often mistake CPS for simple partial seizures because they are amnestic for part of the seizure. This phenomenon has significant implications for the accuracy of reported outcomes in clinical trials. Therefore, a reduction in seizure severity (e.g., from CPS to SPS) can be missed because subjects are unable to reliably distinguish between the seizure types. Tonic–clonic seizures are less likely to be misidentified or forgotten because they are less frequent and often associated with characteristic signs, such as muscle soreness or tongue biting, that are obvious to the patient even if he or she is amnestic for the event.

They are also more likely to be apparent to observers who can aid the subject in recollection. Indeed, when GTCCs are examined in *post hoc* analysis of lacosamide clinical trials, placebo response rates were significantly lower than when all seizures were considered [30].

The use of seizure diaries may be even more problematic in pediatric epilepsy trials. Children are often unable to report their seizure symptoms and recognition of a seizure requires that an observer be available. If subjects are not under constant observation, seizures may be missed and not counted accurately. In children with severe epilepsy, such as Lennox-Gastaut syndrome, in which seizures can occur multiple times daily, lack of constant observation can lead to significant under-reporting of seizures [26].

Variability in seizure frequency can add significant heterogeneity to epilepsy clinical trials. Seizure frequency is not uniform even in a single patient, as many subjects tend to have exacerbations in seizure frequencies and seizure clusters [31]. Furthermore, even subjects with treatment-resistant epilepsy can experience periods of spontaneous remission that can last months or years [32]. In pooled analyses of the placebo arms of levetiracetam clinical trials, a shorter duration of epilepsy was found to be a predictor of placebo response [33], suggesting that subjects with a shorter duration of epilepsy may not have 'established' a stable seizure frequency and could potentially have a spontaneous remission during the course of a trial. In a separate analysis of lacosamide add-on trials, subjects with a higher number of failed ASDs or high seizure frequency at baseline, consistent with a more severe epilepsy, were less likely to have a placebo response [14]. Subjects enrolled in a clinical trial during an exacerbation of their epilepsy may spontaneously improve over the course of the observation period. When disease severity is used as criteria for entry into a study, there is a statistical tendency, termed 'regression to the mean', for a subject's disease severity to approach the mean severity of the group over time. This may be especially problematic when considering subjects who barely exceed the minimum number of seizures necessary to enter a study. There is a high chance that these subjects are experiencing a transient exacerbation of seizures and their mean seizure frequency is typically below the threshold required to qualify for the study. Therefore, a desire by sponsors to enrol subjects earlier in the course of their disease with the hope that these subjects will be more likely to be sensitive to the experimental treatment than patients with a long history of treatment-resistant epilepsy may inadvertently contribute to diminishing effect sizes by selecting for patients who are most likely to improve by chance alone.

Finally, most epilepsy trials are add-on trials where the experimental ASD or placebo is given in addition to the subject's baseline ASD regimen. In many trials, subjects are permitted up to two to three background AEDs. In many parts of the world, there are upwards of 20 commercially available ASDs, which creates the potential for complex and unpredictable pharmacokinetic and pharmacodynamic interactions that can affect response to treatment and tolerability. Possible interactions include induction and inhibition of hepatic metabolism and displacement of free drug from serum protein or from the drug target [34]. In addition to background drugs, trial subjects may have pharmacogenetic heterogeneity. Polymorphisms in genes encoding hepatic enzymes and drug transporters can lead to significant variability to serum and CNS concentrations of ASDs [35]. Therefore, under the typical fixed dosage paradigm of ASD trials, subjects in the same treatment arm may differ significantly in the amount of the drug that reaches its target in the brain due to differences in genetics and background medications. This would not be expected to impact placebo responder rates, but could reduce effect sizes.

Possible solutions to reduce heterogeneity & variability in epilepsy trials

Due to the issues described above, there is a need for greater attention to classification and diagnosis, not only at the patient level, but at the individual seizure level, as patients can have both epileptic and non-epileptic seizures. Training has been undertaken in recent epilepsy therapeutic studies in order to instruct investigators on how to take a history that will allow appropriate diagnosis and classification. In some trials, seizure descriptions have been provided for central review to ensure that only seizures that are highly likely to be epileptic are counted in the primary outcome. Since these practices are relatively new, their ability to improve trial results and prevent trial failure is as yet unknown.

Methods to circumvent patient report to determine seizure frequency altogether may reduce the variability in epilepsy trials. More reliable and accurate measures of seizure frequency that do not rely on patient recall, caregiver observation or subject effort are necessary. Potential methods may include devices that detect and log seizures. Currently, several simple seizure detection devices are available or in development that employ accelerometers to detect seizure-related movements [36,37] or physiological changes associated with seizures [38]. However, these devices are of limited utility for clinical trials because they are designed to detect convulsive seizures and may not readily detect more subtle CPS. It is possible that newer devices using multiple

modalities including motion, ECG, skin conductance and even simple EEG recordings may be able to detect a broader range of seizure types and could provide a more objective seizure count. Other possibilities to improve the reliability of outcome measurement in epilepsy trials are surrogate biomarkers. However, the identification of a serum proteins or metabolites highly correlated with seizure frequency has been elusive. While imaging techniques may also prove useful to assess seizure frequency, practical matters of cost and access to sophisticated equipment may limit utility in large clinical trials.

There is a pressing need to decrease variability in epilepsy therapeutic trials due to misclassification and inaccurate outcome reporting. Additional research is needed to identify additional factors that contribute to diminishing effect size in epilepsy trials, and identify strategies to circumvent them to improve trial efficiency and maximize the likelihood that effective drugs will reliably separate from placebo. New strategies are needed to objectively measure seizure outcomes to overcome the inherent uncertainty of patient or caregiver report. Reducing the variability and heterogeneity in trials might reduce the risk of unexpected negative trials and possibly encourage industry to continue to develop novel therapies for people with epilepsy.

Future perspective

This review highlights several sources of heterogeneity that complicate trials of therapies for people with epilepsy. The authors anticipate that in the next 5–10 years, improved access to technology intended to improve seizure diagnosis, such as video-EEG monitoring, and more accurate assessment of patient outcomes might reduce the growing variability in epilepsy clinical trials. In addition, we will improve our understanding of the contribution of patient, investigator and regional contributions to trial heterogeneity and be able to perform smaller, more efficient and less costly trials and reduce the risk that promising therapies will fail in late stage clinical development.

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Executive summary

Background

- Novel therapies for epilepsy are needed for treatment-resistant epilepsy because a third of patients continue to have seizures despite the availability of over 20 drugs.

The role of heterogeneity in the results of recent antiseizure drug trials

- Recent promising treatments have failed to demonstrate efficacy in late-stage clinical development because of higher than expected placebo response rates.

Potential sources of variability

- Epilepsy is a challenging condition for clinical trials because of multiple sources of heterogeneity and variability that can diminish effect size.
- Diagnostic uncertainty, exacerbated by variability in access to diagnostic tools, investigator experience with epilepsy and the manifestation of the disease may contribute to heterogeneity of subject response to placebo and experimental treatment.

Reliance on patient-reported seizure outcomes may contribute to additional variability

- Strategies addressing sources of variability are needed to improve the likelihood that efficacious treatments will make it to the clinic.

References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 Institute of Medicine. *Epilepsy Across the Spectrum: Promoting Health and Understanding*. The National Academies Press, Washington, DC, USA (2012).

2 Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 78(20), 1548–1554 (2012).

3 Chong DJ, Bazil CW. Update on anticonvulsant drugs. *Curr. Neurol. Neurosci. Rep.* 10(4), 308–318 (2010).

4 Loscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. *Epilepsia* 52(4), 657–678 (2011).

■■ **Comprehensive review detailing the history and impact of antiseizure drug development and addresses potential reasons why a substantial number of patients remain treatment resistant despite the availability of over 20 drugs.**

5 Sperling MR, Greenspan A, Cramer JA *et al.* Carisbamate as adjunctive treatment of partial onset seizures in adults in two randomized, placebo-controlled trials. *Epilepsia* 51(3), 333–343 (2010).

■ **Discusses the results of two identical Phase III clinical trials of a compound that demonstrated promising efficacy in earlier clinical development. One of the studies failed to demonstrate a statistical difference from placebo while the other study, performed in similar geographic regions, showed a significant treatment effect. This was one of the first late-stage failures in antiseizure drug (ASD) clinical delevopment after two decades of successful Phase III trials.**

6 Halford JJ, Ben-Menachem E, Kwan P *et al.* A randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of adjunctive carisbamate treatment in patients with partial-onset seizures. *Epilepsia* 52(4), 816–825 (2011).

7 Van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a Phase IIb, randomized, controlled trial. *Epilepsia* 54(1), 89–97 (2013).

8 French JA, Costantini C, Brodsky A, von Rosenstiel P, Group NS. Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. *Neurology* 75(6), 519–525 (2010).

9 Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Eleventh Eilat Conference (EILAT XI). *Epilepsy Res.* 103(1), 2–30 (2013).

10 French JA, Krauss GL, Steinhoff BJ *et al.* Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global Phase III study 305. *Epilepsia* 54(1), 117–125 (2013).

11 French JA, Krauss GL, Biton V *et al.* Adjunctive perampanel for refractory partial-onset seizures: randomized Phase III study 304. *Neurology* 79(6), 589–596 (2012).

■ **Global Phase III study that demonstrated efficacy of a novel ASD over placebo in only one of the two prespecified end points. *Post hoc* analysis revealed a significant difference between placebo and each dose tested for both end points (median seizure reduction and responder rate) among subjects enrolled at North American sites, whereas there was no difference among all groups for either end point among subjects enrolled at South and Central American sites. These findings suggest that regional differences may affect trial performance.**

12 French JA, DiVentura B, Posner H, Zangrilli Z. Real-time central patient review improved quality in a once-a-day trial of pregabalin for partial epilepsy in adults (A0081194). *Neurotherapeutics* 10(3), 539–550 (2013).

13 Gil-Nagel A, Zaccara G, Baldinetti F, Leon T. Add-on treatment with pregabalin for partial seizures with or without generalisation: pooled data analysis of four randomised placebo-controlled trials. *Seizure* 18(3), 184–192 (2009).

14 Schmidt D, Beyenburg S, D'Souza J, Stavem K. Clinical features associated with placebo response in refractory focal epilepsy. *Epilepsy Behav.* 27(2), 393–398 (2013).

■ **Pooled analysis of three randomized controlled trials of lacosamide. The authors examined factors associated with a greater than 50% responder rate for subjects receiving placebo. Longer duration of epilepsy, more frequent seizures at baseline, and prior epilepsy surgery were all associated with a lower chance of placebo response supporting the theory that diagnostic uncertainty and regression to mean seizure frequency influence ASD trial results.**

15 Fisher RS, van Emde Boas W, Blume W *et al.* Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 46(4), 470–472 (2005).

16 Alsaadi TM, Thieman C, Shatzel A, Farias S. Video-EEG telemetry can be a crucial tool for neurologists experienced in epilepsy when diagnosing seizure disorders. *Seizure* 13(1), 32–34 (2004).

17 Benbadis SR, O'Neill E, Tatum WO, Heriaud L. Outcome of prolonged video-EEG monitoring at a typical referral epilepsy center. *Epilepsia* 45(9), 1150–1153 (2004).

18 Morrell MJ. Differential diagnosis of seizures. *Neurol. Clin.* 11(4), 737–754 (1993).

19 Martin R, Burneo JG, Prasad A *et al.* Frequency of epilepsy in patients with psychogenic seizures monitored by video-EEG. *Neurology* 61(12), 1791–1792 (2003).

■ **Comprehensive study of 1590 patients undergoing video-electroencephalography monitoring, 32% were found to have psychogenic, nonepileptic seizures (PNES). Of these, 5% had both PNES and epileptic seizures, demonstrating that PNES is common, and there is overlap between epileptic and nonepileptic seizures.**

20 Chapman M, Iddon P, Atkinson K *et al.* The misdiagnosis of epilepsy in people with intellectual disabilities: a systematic review. *Seizure* 20(2), 101–106 (2011).

■ **In this systematic review, six cohort and two case studies were included. Overall, when this information was provided, 32–38% of patients with intellectual disability suspected to have epilepsy, upon expert evaluation either did not have epilepsy, or had nonepileptic events. The cause was usually a misinterpretation of behavioral events (e.g. staring, stereotypic blinking and swallowing, self stimulatory tics) as seizures.**

21 Akman CI, Montenegro MA, Jacob S, Eck K, Chiriboga C, Gilliam F. Seizure frequency in children with epilepsy: factors influencing accuracy and parental awareness. *Seizure* 18(7), 524–529 (2009).

22 Benbadis SR. Observations on the misdiagnosis of generalized epilepsy as partial epilepsy: causes and consequences. *Seizure* 8(3), 140–145 (1999).

- **A review was performed on 16 patients who had been monitored by video-electroencephalography, and who had been diagnosed with 'partial' epilepsy, but whose seizures sounded generalized. Six patients were rediagnosed as having idiopathic generalized epilepsy. This suggests that even in expert hands, misdiagnosis may occur.**

23 Boylan LS, Labovitz DL, Jackson SC, Starner K, Devinsky O. Auras are frequent in idiopathic generalized epilepsy. *Neurology* 67(2), 343–345 (2006).

24 Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA; Investigators OVS. Randomized, Phase III study results of clobazam in Lennox-Gastaut syndrome. *Neurology* 77(15), 1473–1481 (2011).

25 Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 42(6), 796–803 (2001).

26 Fisher RS, Blum DE, DiVentura B *et al.* Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav.* 24(3), 304–310 (2012).

27 Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. *Neurology* 47(1), 260–264 (1996).

- **This study performed in an epilepsy monitoring unit suggested that only 26% of all patients were able to accurately report all seizures, and 30% were unaware of all seizures.**

28 Neugebauer R. Reliability of seizure diaries in adult epileptic patients. *Neuroepidemiology* 8(5), 228–233 (1989).

29 Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient compliance with paper and electronic diaries. *Control. Clin. Trials* 24(2), 182–199 (2003).

30 Chung S, Sperling MR, Biton V *et al.* Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. *Epilepsia* 51(6), 958–967 (2010).

31 Haut SR. Seizure clustering. *Epilepsy Behav.* 8(1), 50–55 (2006).

32 Callaghan B, Schlesinger M, Rodemer W *et al.* Remission and relapse in a drug-resistant epilepsy population followed prospectively. *Epilepsia* 52(3), 619–626 (2011).

33 Niklson I, Edrich P, Verdru P. Identifying baseline characteristics of placebo responders versus nonresponders in randomized double-blind trials of refractory partial-onset seizures. *Epileptic Disord.* 8(1), 37–44 (2006).

34 Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol.* 2(6), 347–356 (2003).

35 Szoeke CE, Newton M, Wood JM *et al.* Update on pharmacogenetics in epilepsy: a brief review. *Lancet Neurol.* 5(2), 189–196 (2006).

36 Lockman J, Fisher RS, Olson DM. Detection of seizure-like movements using a wrist accelerometer. *Epilepsy Behav.* 20(4), 638–641 (2011).

37 Kramer U, Kipervasser S, Shlitner A, Kuzniecky R. A novel portable seizure detection alarm system: preliminary results. *J. Clin. Neurophysiol.* 28(1), 36–38 (2011).

38 Poh MZ, Loddenkemper T, Reinsberger C *et al.* Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. *Epilepsia* 53(5), e93–e97 (2012).

Website

101 ClinicalTrials Database: NCT00699972. http://clinicaltrials.gov/show/NCT00699972