Epilepsia, 54(Suppl. 4):3–12, 2013
doi: 10.1111/epi.12294

PRECLINICAL THERAPY DISCOVERY

Development of new treatment approaches for epilepsy: Unmet needs and opportunities

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Abstract

A working group was created to address clinical "gaps to care" as well as opportunities for development of new treatment approaches for epilepsy. The working group primarily comprised clinicians, trialists, and pharmacologists. The group identified a need for better animal models for both efficacy and tolerability, and noted that animal models for potential disease-modifying or antiepileptogenic effect should mirror conditions in human trials. For antiseizure drugs (ASDs), current animal models have not been validated with respect to their relationship to efficacy in common epilepsy syndromes. The group performed an "expert opinion" survey of perceived efficacy of the available ASDs, and identified a specific unmet need for ASDs to treat tonic–atonic and myoclonic seizures. No correlation has as yet been demonstrated between animal models of tolerability and adverse effects (AEs), versus tolerability in humans. There is a clear opportunity for improved therapies in relation to dose-related AEs. The group identified common and rare epilepsy syndromes that could represent opportunities for clinical trials. They identified opportunities for antiepileptogenic (AEG) therapies in both adults and children, acknowledging that the presence of a biomarker would substantially improve the chances of a successful trial. However, the group acknowledged that disease-modifying therapies (given after the first seizure or after the development of epilepsy) would be easier to study than AEG therapies.

KEY WORDS: Antiseizure therapy, Epilepsy syndromes, Antiepileptogenic therapy, Animal models.

This workshop group focused on determining the preclinical pathways toward the development of novel therapeutics. To this end, the group specifically addressed the ability of any development pathway to lead to new therapeutic options that would ultimately be of benefit to the epilepsy community,

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As each new drug is placed into clinical development, it is introduced to clinical trials with great enthusiasm. Typically, preclinical data are presented that raise the hope of "better" efficacy than previous therapeutics, or excellent tolerability. Yet, to date, the "magic bullet," or anything close to it, escapes us. In discussion with members of this and other working groups who are currently involved in discovery and development of novel therapeutics a clear message emerged: There would likely be a surge in new therapeutic development, and in resources to capitalize these developments, if preclinical testing were better able to reduce the risks of clinical development by more accurately predicting the extent of impact that a new therapy would have (antiseizure, antiepileptogenic, or disease modifying) in specific populations with epilepsy or at risk for developing epilepsy, and also in determining the tolerability–benefit ratio. We therefore addressed the following questions:

1 Can preclinical data differentiate whether a novel therapeutic agent will have clinical benefit over present drugs?
2 Has this been the case in the past?
3 If so, is there any way to specifically predict what epilepsy syndromes will be most likely to be benefitted?
4 Moreover, can preclinical tests determine likelihood for dose-related and/or serious adverse effects (AEs) and their impact on the cost–benefit ratio of treatment?

For the task of finding improved epilepsy therapies it is also critically important to understand how clinicians determine the value of therapeutic interventions: Do clinicians select the drug they believe will be most efficacious for a given syndrome? How much of a role does tolerability play?

Another important element of addressing the potential opportunities in epilepsy care is to look at unmet needs. To do this, we first looked at the number of individuals affected by different types of epilepsy. What syndromes are more or less common? We addressed the likelihood that patients within those syndromic groups, and the doctors who care for them, would currently be "satisfied" with available treatments. This is important for two reasons. The first is to target treatments to the areas with the highest unmet need. The second is to understand how easy or difficult it would be to recruit patients within a given syndrome. We addressed this issue not only for antiseizure drugs (ASDs), but also for putative antiepileptogenic and disease-modifying agents.

Using Animal Models to Evaluate Antiseizure Efficacy

Seventy-five years after phenytoin was successfully identified using the cat maximal electroshock (MES) model (Putnam & Merritt, 1937), the MES test remains an important gatekeeper for the National Institute of Neurological Disorders and Stroke (NINDS)-Anticonvulsant Screening Program (ASP). The MES test is quick, requires minimal technical expertise, and can be used to screen a large number of investigational ASDs. In addition, the MES test possesses a pharmacologic profile that supports its use as a model of human generalized tonic–clonic seizures (GTCS) (Table 1). The limitations of the MES test as a gatekeeper have been argued, however, as it failed to identify the efficacy of levetiracetam (Löscher & Schmidt, 2011). That said, the MES test is just one of several animal models that have demonstrated utility as an early and efficient screen for antiseizure activity (Table 1). The subcutaneous metrazol (s.c. Met) test and various rodent kindling models have emerged as useful models of generalized myoclonic seizures and focal seizures secondarily generalized, respectively (Table 1). The pharmacologic profiles of the genetic absence epileptic rat

Table 1. Correlation of ASD efficacy in animal models and human epilepsy (Löscher & Schmidt, 2011; White, 2011)

Animal Model	Seizure phenotype	Human correlate	ASDs active in the model
Maximal electroshock	Tonic-extension seizure	Generalized tonic–clonic seizures, focal seizures	PHT, CBZ, OXC, VPA, PB, FBM, GBP, LTG, LCM, TPM, ZNS, EZG/RTG
s.c. Metrazol	Minimal clonic seizure	Generalized myoclonic seizures	ESM, VPA, BZD, EZG/RTG, FBM, GBP, PB,[a] TGB,[a] VGB[a]
6 Hz (32/44 mA)	Limbic seizures secondarily generalized	Pharmacoresistant limbic seizures	CLZ, FBM, LCM, LEV, EZG/RTG, VPA
GAERS, Lethargic mouse, and Wistar rat	Spike-wave discharges (SWD)[b]	Absence seizures	ESM, VPA, BZD, LTG, TPM, LEV [SWD worsened by PHT, CBZ, OXC, and GABAmimetics]
Kindled rodent	Limbic seizures secondarily generalized	Limbic seizures	CBZ, OXC, PHT, VPA, PB, BZD, FBM, GBP, PGB, LCM, LTG, TPM, TGB, ZNS, LEV, VGB, EZG

s.c., sub-cutaneous; GAERS, generalized absence epilepsy rat of Strasbourg; BDZ, benzodiazepines; CBZ, carbamazepine; CLZ, clonazepam; ESM, ethosuximide; EZG, ezogabine; FBM, felbamate; GBP, gabapentin; LCM, lacosamide; LTG, lamotrigine; LEV, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; RTG, retigabine; TGB, tiagabine; TPM, topiramate; VPA, valproic acid; VGB, vigabatrin; ZNS, zonisamide.

[a]PB, TGB, and VGB block clonic seizures induced by s.c. metrazol but are inactive against generalized absence seizures and may exacerbate spike-wave seizures.

[b]Models of spike-wave seizures not routinely employed in initial evaluation of investigational drugs.

of Strasbourg (GAERS), the WAG/Rij rat, and the Lethargic mouse support their use as important and validated models of human absence seizures (Table 1). These models not only identify efficacious compounds, they have also become important tools for assessing whether a particular pharmacologic intervention will aggravate spike-wave seizures, for example, similar to the aggravation associated with the use of phenytoin, carbamazepine, oxcarbazepine, vigabatrin, tiagabine, and phenobarbital. Of interest, the WAG/Rij rat test demonstrated the ability of ethosuximide to prevent epilepsy in this model of human childhood absence epilepsy in one lab (Blumenfeld et al., 2008). This preclinical finding is of great interest as it suggests that, if confirmed, antiepileptogenesis may be a future therapeutic option for idiopathic (genetic) generalized epilepsies and that at least some of the older ASDs may also have antiepileptogenic mechanisms. In recent years, the 6 Hz test has reemerged as an acute seizure model with a unique pharmacologic profile that differentiates it from other acute seizure models such as the MES and s.c. Met tests. High doses of phenytoin, carbamazepine, lamotrigine, and levetiracetam are required to block seizures induced by high (i.e., 44 mA) current stimulation. The 6 Hz test is responsive to a number of clinically available ASDs including valproic acid, felbamate, clonazepam, ezogabine/retigabine, and the investigational ASD carisbamate (Löscher & Schmidt 2011; Wilcox et al., 2013). As such, the 6 Hz test is perhaps best suited as an acute seizure model that can be used to evaluate promising investigational ASDs.

The primary criticism that is often levied against the animal models employed in the current NINDS ASP is that they have yet to "bring forth" a novel therapy that has led to a dramatic reduction in the incidence of pharmacoresistant epilepsy (Wilcox et al., 2013). Nonetheless, the current approach has proven useful by identifying well over a dozen mechanistically unique new ASDs for the treatment of human epilepsy, thus providing important new treatment options to the patients and their caregivers.

Using Animal Models to Evaluate Adverse Effects and Tolerability

Often, dose-limiting AEs preclude reaching a dose that is both fully efficacious (i.e., 100% seizure control) and devoid of AEs. Most, if not all, of the currently available therapies are associated with one or more AEs that may include ataxia and/or incoordination, dizziness, sedation, irritability and/or agitation, cognitive disturbance, and depression. Because these AEs can limit the overall utility of a potentially highly effective ASD, the question emerges whether ASD-induced AEs could be predicted using animal models in much the same manner that animal models are used to assess potential efficacy. There are at least one or more laboratory tests that could be used to evaluate the presence or absence of a particular AE; however, none of these tests are routinely employed in the early evaluation of AEs. As such, the currently available models suffer in a large part from a lack of demonstrated predictive validity. For example, it is not known whether impairment of performance in rodent models of learning and memory such as the Morris water maze predicts drug-induced cognitive disturbance, or any other AE analogous to those reported in human clinical studies. Therefore, observations obtained in a rodent behavioral test/model should be used as a cautionary guide until that particular test/model has been shown to possess construct and predictive validity.

It is important to note that the initial animal efficacy and tolerability studies are conducted following acute (not chronic) administration of a single drug (monotherapy) in nonepileptic and noninduced animals; an approach that would miss AEs that result from a drug–disease interaction, drug accumulation, or emerge after chronic exposure. Albeit conducted as part of the licensing process required by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA), the toxicology studies and chronic dosing studies are always conducted in neurologically intact animals rather than in animals with epilepsy. It is notable that the AE profile associated with an acute dose in a neurologically intact animal would/should not be expected to be the same as that which might be observed in an epileptic animal after chronic drug administration; nor would the AE profile necessarily be predictive of what might be observed in a patient with epilepsy. For example, preclinical testing of *N*-methyl-D-aspartate (NMDA) antagonists revealed a minor induction of psychotomimetic AEs in normal rodents but an exaggerated expression of these behaviors in fully amygdala kindled rats, a pattern that was confirmed with clinical testing of the competitive NMDA antagonist dCCPene in healthy volunteers and patients with epilepsy (Klitgaard et al., 2002). Complicating our ability to predict AEs using animal models is the fact that patients with epilepsy display a number of comorbidities that can be exacerbated, or lessened, by currently available drug therapies, a finding that is rarely considered in early preclinical development (see Brooks-Kayal et al. in this supplement for further discussion; Brooks-Kayal et al., 2013).

Where are We Now? Clinical Efficacy and Tolerability of Available Antiseizure Drugs

The majority of people with new-onset epilepsy achieve seizure freedom with the available ASDs, and response is

particularly favorable for some syndromes, such as idiopathic (genetic) generalized epilepsies. However, about one third of patients have pharmacoresistant seizures, and the newer ASDs have only minimally improved outcome in patients whose seizures are refractory to older agents (Löscher & Schmidt 2011; Brodie et al., 2012). In a recent study, the proportion of patients achieving seizure freedom rose only from 64% to 68% with an expanded armamentarium of new ASDs (Brodie et al., 2012).

One way of assessing the predictive value of preclinical tests for ASD discovery is to contrast the preclinical activity profile of existing ASDs with their comparative clinical efficacy across different syndromes, and their relative potential for causing specific side effects.

Comparative efficacy

Ideally, comparative efficacy should be established through randomized head-to-head trials in newly diagnosed patients. Regrettably, most monotherapy trials conducted to date have major methodologic limitations, including open-label design, inclusion of heterogeneous populations, suboptimal dose flexibility, suboptimal duration of follow-up, and inadequate power to detect potential clinically meaningful differences in efficacy (Glauser et al., 2006, 2013; Perucca and Tomson, 1999). Keeping these limitations in mind, available evidence suggests that, for the treatment of focal seizures, (1) carbamazepine and phenytoin have comparable efficacy; (2) phenobarbital, primidone, and, possibly, valproic acid have lower efficacy than carbamazepine; (3) oxcarbazepine, lamotrigine, topiramate, levetiracetam, and zonisamide are not more efficacious than carbamazepine; and (4) vigabatrin is probably less effective than carbamazepine (Perucca & Tomson, 1999; Baulac et al., 2012; Glauser et al., 2013). Based on the few monotherapy trials in patients with primarily generalized seizures, valproic acid is comparable in efficacy to ethosuximide, and superior to lamotrigine, for the treatment of absence seizures (Glauser et al., 2010, 2012). Most new-generation ASDs have also been tested in placebo-controlled adjunctive- therapy trials. These trials, however, typically do not involve head-to-head comparisons with other drugs, and methodologic difficulties do not permit any meaningful conclusions about comparative efficacy (Rheims et al., 2011).

Because of the lack of well-controlled monotherapy trials in most seizure types, an "expert opinion" about perceived efficacy was sought among nine physicians from our group with broad experience using old and new ASDs. We assessed only ASDs that had been available for a period sufficient to acquire meaningful perceptions of relative efficacy. The raters included adult and pediatric epileptologists from America and Europe, and each provided scores independently, without discussion with the other raters. Raters were asked to score each ASD separately, without any ranking, on the following scale: −1 (worsening), 0 (no effect), 1–3 (mild, moderate, or marked efficacy). This exploratory survey was aimed at (1) comparing perceived efficacy in clinical practice with results of standard and future animal models, and determining whether efficacy can be predicted for specific seizure types; and (2) identifying seizure types where few or no drugs are rated as efficacious, thus highlighting an area of significant need.

Although this small, subjective survey has numerous limitations, a comparison of the scores (Table 2) provides interesting insights. For one, new ASDs are not perceived as more efficacious than older agents. In fact, carbamazepine scored higher than any other ASD for efficacy in focal seizures, having been rated as a "3/3" by all but one rater; valproic acid had the highest score for GTCS (2.8) and myoclonic seizures (2.6), and was tied with ethosuxi-

Table 2. "Perceived" efficacy of ASDs in different seizure types[a]

Drug	Focal seizures	Absence seizures	Tonic/atonic seizures	Myoclonic seizures	Primary GTCS
Phenytoin	2.5	−0.2	0.8	−0.2	2.0
Carbamazepine	2.9	−0.8	0.6	−0.8	1.5
Valproic acid	2.0	2.9	1.9	2.6	2.8
Ethosuximide	0.1	2.9	0.1	0.5	0.4
Phenobarbital	2.4	0.1	1.0	0.8	2.4
Zonisamide	2.3	1.0	0.9	1.4	1.6
Gabapentin	1.1	−0.6	−0.1	−0.8	0.8
Lamotrigine	2.4	2.0	1.6	1.1	2.1
Topiramate	2.4	1.3	1.8	1.3	2.1
Tiagabine	1.3	−0.9	−0.1	−0.4	0.5
Oxcarbazepine	2.8	−0.9	0.4	−0.8	1.6
Levetiracetam	2.6	1.1	1.0	1.8	2.1
Felbamate	2.1	0.8	1.8	0.9	1.5
Pregabalin	1.8	−0.7	−0.1	−0.8	0.8

[a]Mean scores based on ratings by nine different clinicians. As for the scoring system, −1 indicates worsening, 0 indicates no effect, and 1–3 indicates mild, moderate, or marked efficacy, respectively.

mide for absence seizures (2.9). Of interest, despite these high scores, carbamazepine and valproate are not consistently selected by clinicians as first-line drugs for focal seizures and generalized seizures, respectively. This might be due to their AE profile, including potential for drug interactions. In the case of valproic acid, weight gain and teratogenicity may discourage first-line use, at least in selected populations. Indeed, efficacy is not always the primary consideration in drug selection.

Another message that emerges from Table 2 is that there is dissatisfaction concerning most available treatment options for drop attacks (i.e., tonic and atonic seizures) and for myoclonic seizures. Except for valproic acid, all ASDs received scores below 2 for each of these seizure types. It should be noted that clobazam, an ASD recently approved in the United States for the adjunctive treatment of drop attacks, was not included in the survey.

Adverse Effects

AEs are common in ASD therapy, and they have been estimated to affect the quality of life of 30–60% of patients (Perucca & Meador, 2005). To the extent that intolerable AEs prevent achievement of efficacious doses, side effects also have negative effects on drug efficacy.

The AEs of ASDs include idiosyncratic reactions, central nervous system (CNS) and metabolic effects, chronic disorders affecting many systems, drug interactions, and teratogenic effects. Although all ASDs can cause significant toxicity at therapeutic doses, the patterns of AEs differ considerably from one drug to another. Occurrence of these effects depends not only on the type of prescribed ASD, but also on a variety of factors such as the rate of uptitration, dosage and dosing schedule, pharmaceutical formulation, duration of treatment, and patient-specific features including genetic background, age, gender, comorbidities, and comedications.

A review comparing the AE profiles of available ASDs based on the published literature was recently published (Perucca & Gilliam, 2012). Although for some AEs, such as drug–drug interactions, preclinical tests with good predictive value have been developed and are widely used in drug development, there is opportunity for a concerted effort to identify improved animal models to predict common CNS dose-limiting toxicity, as well as idiosyncratic reactions.

Opportunities for Treatment of Epilepsy: How Big Is the Opportunity?

In this section, we address the prevalence of common epilepsy syndromes, as a consideration of unmet need.

Epilepsies are heterogeneous. Although some neurologists have an understanding of this issue, most of the general population has little appreciation for the diversity of syndromes in epilepsy.

In a continuing effort to educate physicians and lay persons, the community of epileptologists needs to set forth the most common syndromes and to define them clinically and epidemiologically.

The rough, tentative assessment listed below is intended for reference by those who might at a later date undertake the full task of clinical and epidemiologic definitions. This task should include, besides the careful clinical definitions, the prevalence and incidence of these syndromes—which may vary by region. We also provide a rough estimate of the number of patients available for clinical trials, which would also be of great assistance to investigators and companies with potential ASDs. These estimates need validation or modification from published evidence or future epidemiologic studies. Neither etiology nor therapy responsiveness is considered in this assessment; the list (using the latest classification) is roughly in the order of world prevalence. Virtually all of these syndromes are in enormous need of new therapies.

Epilepsy syndromes and seizure types with >1,000,000 affected persons worldwide

1. Febrile seizures in children—Usually benign, febrile seizures are common, occurring in 2–4% of the world's population (higher in Japan). Only a very small number of children (<1%) with febrile seizures have sequelae, but the outcome can be severe for those affected (S. Shinnar, personal communication). Febrile seizures are often not included in prevalence figures for epilepsy.
2. Focal seizures in adults and children—This specific type is the most prevalent of all the seizure types. The associated seizure manifestations, the focal seizure with dyscognitive features (previously the "complex partial seizure"), and the focal seizures ending in a GTCS are the most-often studied seizure type for almost all therapies. GTCS are often more easily controlled than are the other forms of focal seizures. Both the device and the pharmaceutical industries have concentrated on focal seizures in hopes of achieving success in the largest epilepsy market.
3. GTCS associated with idiopathic (genetic) generalized epilepsies in adults and children—these GTCS occur in the setting of a number of unique genetic syndromes, including juvenile myoclonic epilepsy, GTCS upon awakening, and juvenile absence epilepsy. This seizure type has been studied in a number of ASD trials. Whether most of these attacks are really "generalized" from onset is uncertain (Theodore et al., 1994).
4. Juvenile Myoclonic Epilepsy—This is one of the more common of the idiopathic (genetic) generalized epilepsies. Most patients will also have GTCS in addition to myoclonia.

Epilepsy syndromes and seizure types with between 100,000 and 1,000,000 affected persons worldwide

1 Lennox-Gastaut syndrome—This syndrome is a heterogeneous disorder usually beginning in early childhood with varying disabilities, often with both severe seizures (multiple seizure types) and substantial subnormal mental function.
2 West syndrome (infantile spasms)—This syndrome has its onset most often before the age of one year. The seizures can sometimes be controlled, but many patients have substantial sequelae.
3 Childhood/juvenile absence epilepsy—These syndromes are often rewarding to treat with available medications, although some patients remain intractable.
4 Benign epilepsy with centrotemporal spikes (BECTS)—This syndrome is a frequent childhood epilepsy, usually seen between the ages of 3 and 13 years. A benign course is typical, although not present in all patients.
5 Status epilepticus—This is a heterogeneous grouping. Generalized tonic–clonic status is life-threatening, with a substantial morbidity and mortality. Some forms of nonconvulsive status can cause permanent memory loss. Other kinds of status vary in their severity and potential sequelae.
6 Neonatal seizures—Neonatal seizures are heterogeneous, both in presentation and in long-term implications. Many patients have substantial sequelae or associated problems.

Epilepsy syndromes and seizure types with <100,000 affected persons worldwide

1 Early infantile epileptic encephalopathies
2 Severe myoclonic epilepsy of infancy (Dravet syndrome)
3 Landau-Kleffner syndrome
4 Rasmussen's syndrome
5 Progressive myoclonic epilepsies (will overlap with genetic list)
6 Benign neonatal convulsions
7 Benign myoclonic epilepsy of infancy
8 Myoclonic astatic epilepsy (Doose syndrome)
9 Epilepsy with Grand Mal on Awakening
10 Photosensitive epilepsies (will overlap with many other categories)
11 Autosomal dominant nocturnal frontal lobe epilepsy

We need validation and modification of the above list. To properly accomplish such a goal, careful and precise clinical definitions need to be paired with expert epidemiologic investigations. Much of the needed data may appear to exist, but may be tainted, for example, by less than rigorous clinical definitions—or worse, the inadequate application of such definitions during the studies. If epilepsies are to emerge as disorders that receive the full attention of the public and receive the support needed for research funding consistent with their high prevalence, we all need to work to carefully define these syndromes.

Antiepileptogenic Therapies

Opportunities for early antiepileptogenic (AEG) interventions

Although we do not have a full understanding of what occurs during the epileptogenic process, a successful therapeutic intervention in this process holds the potential to either prevent the development of seizures or alter the course of the disease. Biomarkers for epilepsy risk prior to the first seizure, which we do not have at the moment, would greatly facilitate our ability to identify candidates for presymptomatic AEG treatment, whereas treatments with the potential to modify epilepsy severity after presentation could be delivered based on clinical information available at the time of presentation.

AEG treatment prior to the first seizure (presymptomatic AEG treatment)

As shown in Figure 1, only a fraction of patients presenting with first seizures have an identifiable etiology (for example, trauma, stroke, CNS infection, or tumor) that could have been reasonably foreseen to increase the risk of developing epilepsy, thereby allowing the option of presymptomatic treatment, for example, trauma, stroke, CNS infection, or tumor. Unfortunately clinical trials of ASDs as AEGs have been repeatedly negative (Temkin, 2009). Although disappointing, it seems likely that these trials failed because of problems with trial designs and because ASDs were not designed or selected to have AEG activity. This highlights the importance of focused AEG strategies. No well-controlled trials of AEG treatment have been conducted in conditions thought to confer an increased risk of developing seizures such as infarct, hemorrhage, or tumor. Although these groups of patients have traditionally been thought to represent the opportunity for AEG treatment, a broader view suggests that other presymptomatic opportunities exist. For example, new opportunities to prevent epilepsy may exist in situations where genetic testing could identify subjects at risk, for example, childhood absence epilepsy (Blumenfeld et al., 2008). Similarly new opportunities to prevent symptomatic, immune-mediated epilepsy with antiinflammatory or immunologic intervention (Dalmau et al., 2011; Maroso et al., 2011) may be just over the horizon.

AEG treatment following the first seizure (postpresentation AEG treatment)

Even if a patient has experienced a first seizure, the opportunity for AEG treatment may exist. It remains

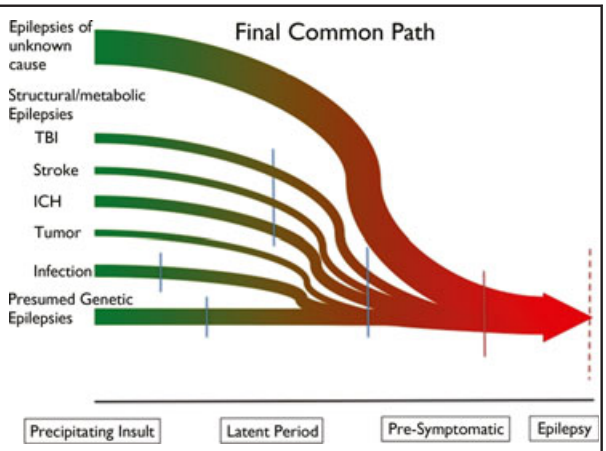

Figure 1.
Schematic diagram representing opportunities for AEG therapy. Epilepsy etiologies are represented by curves with varied thickness indicating relative incidences (not to scale). Opportunities to intervene are represented as vertical bars indicating that some interventions may be specific for a single etiology, whereas others likely act further down a final common path and alter development of epilepsy of varied etiologies. Blue vertical bars represent presymptomatic treatment that may be antiseizure or AEG. Red vertical dashed line represents appearance of epilepsy. Conceptual features of the time course of development are identified on the x-axis. Note that the majority of epilepsies have unknown etiology, and therefore offer little opportunity to intervene in the epileptogenic process or presymptomatic period, although if genetic epilepsies can be addressed, this could change. Final common path does not imply that the mechanisms of epileptogenesis for all epilepsies are similar (see text).
Epilepsia © ILAE

unproven that the ultimate severity of epilepsy is predetermined at the time of initial presentation, and extensive clinical and animal data suggest that the severity of epilepsy may be determined, in part, by the number and severity of seizures experienced early in the course, as well as other presently unidentified factors (Schmidt & Sillanpää, 2012). In a French study, 485 (52.3%) of 926 patients presenting with a first unprovoked seizure went on to satisfy the epidemiologic criteria for epilepsy (Jallon et al., 2001). Therefore, in the broadest sense, more than half of all patients could be candidates for an AEG treatment that works in all types of epilepsies when given after the first seizure. Taking the broad view, the opportunity for AEG therapy is far greater than that presented by the population with easily identifiable proepileptic antecedents (162 [17.5%] of 926 in the study of Jallon et al.). Whether it is reasonable to treat a large number of people at risk for epilepsy with an AEG treatment also depends on the expected toxicity of the compound being studied, that is, the benefit to those who might develop epilepsy must be balanced against the risk to those who would not have developed epilepsy if left untreated.

Interim summary: opportunities for early AEG interventions

Despite negative results from trials of ASDs for prevention of severe posttraumatic epilepsy, opportunities to prevent the development of nongenetic epilepsies surely exist given the latency of seizure onset after initial insult in many patients. Likewise, new opportunities arise for AEG intervention in genetic epilepsies prior to the first seizure and in those who just had their first seizure. In addition, a majority of patients presenting after a first seizure may be candidates for AEG treatment aimed at modifying disease severity, even if a specific antecedent cannot be discovered. If we had suitable AEG molecules or nondrug AEG interventions, major challenges include finding biomarkers for epilepsy risk prior to the first seizure and defining suitable preclinical proof of concept studies with trial designs enabling valid conclusions with predictive value.

Opportunity for Antiepileptic and Disease-Modifying Syndromes in Children

Having an effective and safe AEG agent would be an important advance in children. At this point it cannot be assumed that the process of epileptogenesis is the same in the mature and immature brain and that the wide variety of epilepsy syndromes in children share the same pathophysiologic mechanism. In addition, long-term safety of an AEG therapy—whether a drug, device, or dietary therapy—will have to be shown in the developing brain.

A prime group who could be targeted for AEG therapy are children with prolonged febrile seizures that have been reported in retrospective studies in 30–80% of patients with temporal lobe epilepsy due to hippocampal sclerosis (Cendes et al., 1993; French et al., 1993; Mathern et al., 1995). However, in prospective studies, fewer children developed epilepsy (Nelson & Ellenberg, 1976; Verity & Golding, 1991; Verity et al., 1993). The true incidence may come from the findings of The "Consequences of Prolonged Febrile Seizures in Childhood" (FEBSTAT) study, a prospective, longitudinal study of the development of epilepsy (Hesdorffer et al., 2012). Temporal lobe epilepsy may take over a decade to develop following the initial prolonged febrile seizure. Until it is determined that a short treatment phase following the seizure was effective, children might have to be treated for over a decade to prevent epilepsy. Even if one assumed a risk of temporal lobe epilepsy as high as 25% following a prolonged febrile

seizure, many children will receive unnecessary treatment. However, if the FEBSTAT study finds a biologic marker identified at the onset that is highly predictive of subsequent epilepsy, a more restricted group of vulnerable children could be targeted for therapy.

Prevention of epilepsy after head trauma has some of the same issues as prolonged febrile seizures. The risk of developing posttraumatic epilepsy in children is around 10–20% (Annegers et al., 1998; Emanuelson & Uvebrant, 2009). Because epilepsy may take years to develop, many children might have to be treated for years to prevent epilepsy in a relatively small group.

Although >30 genetic disorders in childhood are associated with epilepsy (Fig. 2), those in which seizures occur above rates in the general population comprise only 0.01% of the patients (E. Quay & G. Holmes, unpublished data). Furthermore, seizures may precede diagnosis or occur early in the course of the genetic disorder making AEG agents irrelevant. Other genetic conditions are severe, for example, nonketotic hyperglycinemia, with a high morbidity and mortality, and treating with an AEG agent is likely to be futile.

Relatively common genetic disorders that are associated with a high risk of epilepsy are listed in Figure 2. Conditions most attractive for AEG agents would include disorders that are readily diagnosed before seizures occur and have a high incidence of severe epilepsy that develops early in life. Tuberous sclerosis complex (TSC) would fit this requirement as a disorder caused in the majority of patients by mutations in either *TSC1* or *TSC2*. The condition is common (1 in 6,000 live births) and is associated with epilepsy in 80% of the patients. The molecular signaling pathway responsible for the condition is well known and the condition can be diagnosed at birth. Seizures occur within the first year in 70% of those who develop epilepsy. The initial seizures are often infantile spasms, and there is evidence that infantile spasms adversely alter outcome. Because of the high risk of developing severe epilepsy within a short time of diagnosis, efficacy and safety of an AEG agent could be determined with a small cohort of patients within a relatively short period.

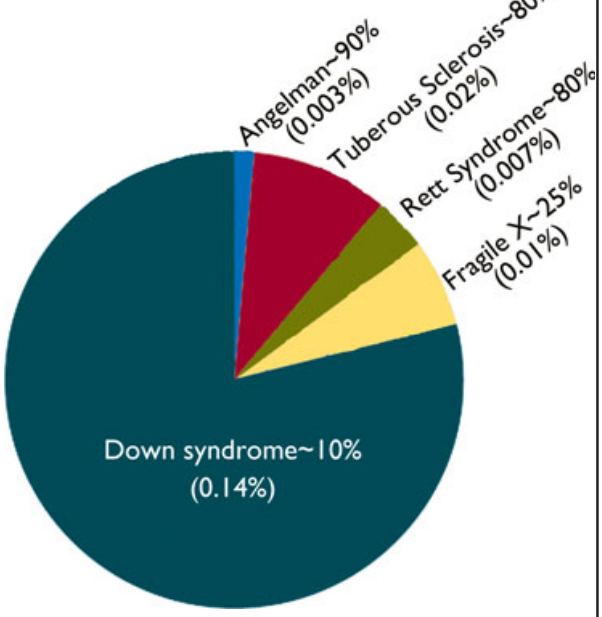

Figure 2.
Estimated incidence of seizures in common genetic disorders. The incidence of the disorder in the general population is provided in parentheses. (From unpublished data from E. Quay & G. Holmes).

Conclusion

We identified a substantial clinical gap of care in 4 areas (1) one-third of patients with epilepsy will not achieve seizure freedom and/or will experience tolerability problems with currently available ASDs; (2) there is a dearth of studies on specific epilepsy syndromes, such benign epilepsy of childhood with centrotemporal spikes (BECTS), or juvenile myoclonic epilepsy (JME); (3) currently all antiepileptogenesis trials using classical ASDs have failed; and (4) there have been no trials for disease modification.

The current pathway for drug development in epilepsy still relies on acute seizure models as a gatekeeper. Enrichment of the armamentarium of preclinical testing with models of drug-resistant epilepsies offers new potentials for better therapies, but increases costs substantially. Early human proof of concept studies could derisk the investments at an early stage in the drug development process. Better modeling of AEs of ASDs would help identify better tolerated drugs. Clinicians and epide-miologists must strive to better delineate the syndromes and their underlying pathophysiology. Development of individualized treatments in epilepsy demand deep knowledge of the pathophysiology of the specific syndrome, shared pathomechanisms between the syndromes, and the frequency of occurrence in the population in order to allocate the resources to the areas of highest needs. Although AEG and disease-modifying trials have been disappointing with current ASDs, new mechanisms and innovative drugs seem to have rekindled interest in them. Successful trial designs must include valid biomarkers to predict (1) development of seizures after an insult or an identified genetic defect, and (2) predict the severity of epilepsy and associated comorbidities. Valid biomarkers, which would need a joint effort from the research community, would enable antiepileptogenesis/disease-modifying trials, derisk development of innovative drugs, and allow smaller sized trials in various epilepsy syndromes.

Acknowledgment

We thank Anne Berg for critical input to an earlier version of the manuscript.

Disclosures

Jacqueline French serves as the president of The Epilepsy Study Consortium, a nonprofit organization. New York University, where Dr. French is employed, receives a fixed amount from the Epilepsy Study Consortium toward Dr French's salary. The money is for work performed by Dr. French on behalf of The Epilepsy Study Consortium, for consulting and clinical trial–related activities. Dr French receives no personal income for these activities. Within the last year, The Epilepsy Study Consortium received payments from the following: Cyberonics, Eisai Medical Research, EntraPharmaceuticals, GlaxoSmithKline, Icagen, Inc., Johnson & Johnson, Marinus, Neuro-therapeutics, NeuroVista Corporation, Ono Pharma U.S.A., Inc., Lundbeck, Pfizer, Sepracor, Sunovion, SK Life Science, Supernus Pharmaceuticals, UCB Inc/Schwarz Pharma, Upsher Smith, Valeant, and Vertex. Dr. French also received funding from NINDS, Milken Foundation, and the Epilepsy Therapy Project.

Samuel Wiebe holds the Hopewell professorship of clinical neurosciences research, funded by the University of Calgary, and receives research funding from Canadian Institutes of Health Research.

Elinor Quay has nothing to declare.

Roger J. Porter, MD, is a consultant to Civitas, Lilly, Medivation, NeuroPace, SK Pharma, Upsher-Smith, and Zalicus. He is also a consultant to the Epilepsy Foundation, Landover, MD.

Emilio Perucca received research grants from the European Union, the Italian Medicines Agency, the Italian Ministry of Health, and the Italian Ministry for Education, University and Research. He also received speaker's or consultancy fees and/or research grants from Bial, Eisai, GlaxoSmithKline, Medichem, Pfizer, Sun Pharma, Supernus, UCB Pharma, Upsher-Smith, and Vertex.

Eugen Trinka has acted as a paid consultant to Eisai, Biogen-Idec, Medtronics, Bial, and UCB. He has received research funding from UCB, Biogen-Idec, Sanofi-Aventis, and speakers' honoraria from Bial, Cyberonics, Desitin Pharma, Eisai, Gerot, Böhringer, Sanofi, Medis, and UCB. He has received research grants from FWF—Fond zur Wissenschaftsförderung, Österreich, Jubiläumsfond der Österreichischen Nationalbank und Red Bull.

H. Steve White has received research grants and a contract from the National Institute of Neurological Disorders and Stroke (NINDS). He has also received speaker's or consultancy fees from Insero Health, Janssen Pharmaceuticals, Inc., Upsher-Smith Laboratories, UCB Pharma, and Citizen's United for Research in Epilepsy. Dr. White is also one of two scientific co-founders of NeuroAdjuvants, Inc., Salt Lake City, UT.

Michael Privitera has received grant funding from the U.S. Food and Drug Administration, the American Epilepsy Society, the Epilepsy Foundation, Eisai, UCB, and Neuren and has been a Consultant (DSMB) for Upsher-Smith and Lilly.

Andrew Cole has been a consultant for Clarus Ventures, Concert Pharmaceuticals, Sage Pharmaceuticals, and Eisai Pharmaceuticals. He has received grant funding from NINDS.

Alexis Arzimanoglou has received speaker's or consultancy fees from Cyberonics, Eisai, GlaxoSmithKline, UCB Pharma, and Viropharma. He also sits on a safety monitoring board for UCB and received educational and European Community grants for which remuneration was made to University Hospital of Lyons or to a research association of his department.

Dieter Schmidt has received hospitality and speaker fees from Eisai, GSK, Novartis Pharma, Sun Pharma, and ViroPharma, in the past three years.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

Annegers JF, Hauser WA, Coan SP, Rocca WA. (1998) A population-based study of seizures after traumatic brain injuries. *N Engl J Med* 338:20–24.

Baulac M, Brodie MJ, Patten A, Segieth J, Giorgi L. (2012) Efficacy and tolerability of zonisamide versus controlled-release carbamazepine for newly diagnosed partial epilepsy: A phase 3, randomised, double-blind, non-inferiority trial. *Lancet Neurol* 11:579–88.

Blumenfeld H, Klein JP, Schridde U, Vestal M, Rice T, Khera DS, Bashyal C, Giblin K, Paul-Laughinghouse C, Wang F, Phadke A, Mission J, Agarwal RK, Englot DJ, Motelow J, Nersesyan H, Waxman SG, Levin AR. (2008) Early treatment suppresses the development of spike-wave epilepsy in a rat model. *Epilepsia* 49:400–409.

Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. (2012) Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 78:1548–54.

Brooks-Kayal AR, Bath KG, Berg AT, Galanopoulou AS, Holmes GL, Jensen FE, Kanner AM, O'Brien TJ, Whittemore VH, Winawer MR, Patel M, Scharfman HE. (2013) Issues related to symptomatic and disease-modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia*, 54(Suppl. 4): 44–60

Cendes F, Andermann F, Dubeau F, Gloor P, Evans A, Jones-Gotman M, Olivier A, Andermann E, Robitaille Y, Lopes-Cendes I, Peters T, Melanson D. (1993) Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: An MRI volumetric study. *Neurology* 43:1083–1087.

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. (2011) Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 10: 63–74.

Emanuelson I, Uvebrant P. (2009) Occurrence of epilepsy during the first 10 years after traumatic brain injury acquired in childhood up to the age of 18 years in the south western Swedish population-based series. *Brain Inj* 23:612–616.

French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, Spencer DD. (1993) Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. *Ann Neurol* 34:774–780.

Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. (2006) ILAE treatment guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 47:1094–1120.

Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Capparelli EV, Adamson PC. (2010) Childhood Absence Epilepsy Study Group. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 362:790–9.

Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC, for the Childhood Absence Epilepsy Study Team. (2012) Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: Initial monotherapy outcomes at 12 months. *Epilepsia* 54:141–55.

Glauser T, Ben-Menachem E, Arya R, Bourgeois B, Cnaan A, Guerreiro C, Kalviainen R, Mattson R, French JA, Perucca E, Tomson T. (2013) Evidence-based analysis of antiepileptic drug efficacy and

effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013:551–63.

Hesdorffer DC, Shinnar S, Lewis DV, Moshe SL, Nordli DR, . Jr, Pellock JM, MacFall J, Shinnar RC, Masur D, Frank LM, Epstein LG, Litherland C, Seinfeld S, Bello JA, Chan S, Bagiella E. (2012) Sun S Design and phenomenology of the FEBSTAT study. *Epilepsia* 53:1471–1480.

Jallon P, Loiseau P, Loiseau J. (2001) Newly diagnosed unprovoked epileptic seizures: Presentation at diagnosis in CAROLE study. Coordination Active du Réseau Observatoire Longitudinal de l' Epilepsie. *Epilepsia* 42:464–75.

Klitgaard H, Matagne A, Lamberty L. (2002) Use of epileptic animals for adverse effect testing. *Epilepsy Res* 50:55–65.

Löscher W, Schmidt D. (2011) Modern antiepileptic drug development has failed to deliver: Ways out of the current dilemma. *Epilepsia* 52:657–78.

Maroso M, Balosso S, Ravizza T, Iori V, Wright CI, French J, Vezzani A. (2011) Interleukin-1β biosynthesis inhibition reduces acute seizures and drug resistant chronic epileptic activity in mice. *Neurotherapeutics* 8:304–15.

Mathern GW, Pretorius JK, Babb TL. (1995) Influence of the type of initial precipitating injury and at what age it occurs on course and outcome in patients with temporal lobe seizures. *J Neurosurg* 82:220–227.

Nelson KB, Ellenberg JH. (1976) Predictors of epilepsy in children who have experienced febrile seizures. *N Engl J Med* 295:1029–1033.

Perucca P, Gilliam FG. (2012) Adverse effects of antiepileptic drugs. *Lancet Neurol* 11:792–802.

Perucca E, Meador KJ. (2005) Adverse effects of antiepileptic drugs. *Acta Neurol Scand Suppl* 181:30–5.

Perucca E, Tomson T. (1999) Monotherapy trials with the new antiepileptic drugs: Study designs, practical relevance and ethical implications. *Epilepsy Res* 33:247–62.

Putnam TJ, Merritt HH. (1937) Experimental determination of the anticonvulsant properties of some phenyl derivatives. *Science* 85:525–6.

Rheims S, Perucca E, Cucherat M, Ryvlin P. (2011) Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. *Epilepsia* 52:219–33.

Schmidt D, Sillanpää M. (2012) Evidence-based review of the natural history of the epilepsies. *Curr Opin Neurol* 25:159–63.

Temkin NR. (2009) Preventing and treating posttraumatic seizures: The human experience. *Epilepsia* 50(Suppl. 2):10–3.

Theodore WH, Porter RJ, Albert P, Kelley K, Bromfield E, Devinsky O, Sato S. (1994) The secondarily generalized tonic-clonic seizure: A videotape analysis. *Neurology* 44:1403–1407.

Verity CM, Golding J. (1991) Risk of epilepsy after febrile convulsions: A national cohort study. *Br Med J* 303:1373–1376.

Verity CM, Ross EM, Golding J. (1993) Outcome of childhood status epilepticus and lengthy febrile convulsions: Findings of national cohort study. *BMJ* 307:225–228.

White H.S. (2011) Antiepileptic drug development and experimental models. In Wyllie, Cascino, Gidal, Goodkin (Eds) *Wylies Treatment of Epilepsy*. Lippincott Williams & Wilkins, Philadelphia, PA, pp. 506–512, .

Wilcox KS, Dixon-Salazar T, Sills GJ, Ben-Menachem E, White HS, Porter RJ, Dichter MA, Moshé SL, Noebels JL, Privitera MD, Rogawski MA (2013) Issues related to development of new antiseizure treatments. *Epilepsia* 54(Suppl. 4):24–34.