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Is antiepileptogenesis a realistic goal in clinical trials? Concerns and new horizons*

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ABSTRACT – Any attempt to make antiepileptogenesis a realistic goal in clinical trials should be based on the experience of failures of the past. A wide variety of experimental studies and clinical trials using chronic antiseizure drug therapy during the extended post-injury period have had minimal success. The disappointing results of these studies may be due to several factors including the possibility that antiseizure drugs, despite the fact they suppress seizure activity, do not interfere in any substantial way with the "epileptogenic" process of focal epilepsies. Although the reasons for the failure are not entirely clear, it may be that the antiseizure drugs may have been tested at the wrong doses, for the wrong duration, or at the wrong time after brain injury. Surprisingly, the anti-absence drug ethosuximide has also been shown to be antiepileptogenic in several experimental models of absence epilepsy. In addition, clinical trials aimed at preventing focal post-injury epilepsy have suffered from poor enrolment and other issues related to the comorbidity of severe epilepsies that follow overt brain injury. Testing specific anti-inflammatory and immunological antiepileptogenic agents to prevent focal epilepsies, as well as prevention trials for genetic epilepsies, possibly with anti-absence drugs, may be a way to resolve the dilemma. Although more evidence is needed, there is hope on the horizon for antiepileptogenic therapy that works.

Key words: antiepileptic drug, antiepileptogenic treatment, disease-modifying treatment, preclinical antiepileptogenesis model, clinical trial

Although the current treatment of epilepsy with antiseizure drugs (ASDs) is able to abort symptoms (*i.e.* seizures) in two of three patients with new-onset epilepsy, there are no antiepileptogenic drugs (AEGs) that ameliorate or stop the disease process in patients at risk of epilepsy

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or in those with epilepsy (Temkin, 2009; Pitkänen, 2010). Diverse brain insults, including traumatic brain injury, stroke, infections, tumours, neurodegenerative diseases, and prolonged acute symptomatic seizures, such as complex febrile seizures or, uncommonly, status epilepticus, can induce "epileptogenesis", a process by which normal brain tissue is transformed into tissue capable of generating spontaneous recurrent seizures (Löscher and Brandt, 2010). Although it has received less attention, epileptogenesis is also operative in genetic and cryptogenic epilepsy. Clinical trials to assess AEG treatment to prevent epilepsy have largely been performed in the extended seizure-free post-injury phase of patients at risk of focal epilepsies caused by moderate-to-severe brain injury, which is a common cause of epilepsy. It has been estimated that 15% of all epilepsy is due to an acute, acquired CNS insult, with traumatic brain injury, stroke and CNS infection each representing 5% of the cases (Hauser and Hesdorffer, 1990). The urgent need to solve this problem has been acknowledged and the development of treatments to prevent epileptogenesis has been identified as a major objective for epilepsy research (Baulac and Pitkänen, 2009; Kelley *et al*., 2009; Galanopoulou *et al*., 2012). There is general agreement that blocking epileptogenesis has the potential to provide large benefits to patients by avoiding the negative medical and social consequences that occur with epilepsy and lifelong therapy.

Despite the unquestionable need for antiepileptogenic treatments, there is widespread concern that we currently do not have suitable preclinical and clinical strategies to successfully develop antiepileptogenic drugs. Several researchers have, somewhat pessimistically, suggested that "*the development of more AEDs with novel pharmacological properties may be a better strategy for the future than placing our bets on identifying antiepileptogenic agents, an untested scenario that is hampered by lack of validated preclinical models, formidable obstacles in clinical testing, and likely substantial regulatory hurdles*" (Brodie *et al*., 2011). It may therefore be useful to critically review whether antiepileptogenesis is a realistic goal for clinical trials and discuss new horizons that may offer hope.

Definitions

It may be useful to briefly define antiepileptogenic treatments/drugs and how they differ from antiseizure drugs (Pitkänen, 2010):

– *Antiepileptogenic drugs (AEG)* prevent, stop, and reverse the development or ameliorate the epileptic condition, if given after the onset of an epileptogenic insult. Antiepileptogenic treatments are assessed by their impact on the enduring predisposition to generate epileptic seizures (modified from Pitkänen [2010]);

– *Disease or syndrome modifying treatments (DMTs/SMTs)* alter the development of epilepsy or prevent or delay or reduce the progression of existing epilepsy, associated pathology and comorbidities, if given after the insult precipitating the onset of the disease/syndrome. Antiepileptogenic treatments are also DMT/SMTs (Pitkänen, 2010);

– *Antiseizure treatments (ASTs) or antiseizure drugs (ASDs)* stop or reduce the frequency or severity of seizures, independent of any effects on disease progression. These serve to differentiate between treatments for epileptogenesis (modified from Pitkänen [2010]).

Clinical antiepileptogenic trials have failed to deliver

Did we use the wrong drugs?

Efforts to abort the epileptogenic process using chronic antiseizure therapy during the extended post-injury period have had minimal success (Temkin, 2009; Pitkänen, 2010; Löscher and Brandt, 2010). A brief survey of recent antiepileptogenesis trials is given in *table 1*. Several trials with new antiseizure drugs have been terminated before completion, while the results of some completed trials have not been reported.

The disappointing results of these studies may be due to several factors including the possibility that antiseizure drugs, despite the fact they suppress seizure activity, do not interfere in any substantial way with the "epileptogenic" process (*table 2*). Alternatively, the "right" drugs may have been tested at the wrong doses, for the wrong duration, or at the wrong time (too late) after brain injury (Sloviter, 2011).

Do we need better preclinical models?

To identify pharmacological interventions that prevent, interrupt or reverse the epileptogenic process in people at risk, two groups of animal models, kindling and status epilepticus-induced recurrent seizures, have been recommended as potentially useful tools as models of acquired focal epilepsy (Löscher and Brandt, 2010; Galanopoulou *et al*., 2012). Furthermore, genetic rodent models of epileptogenesis are increasingly used in assessing antiepileptogenic treatments for absence epilepsy (see Löscher and Brandt, 2010; Pitkänen, 2010; Galanopoulou *et al*., 2012). Epileptogenesis is unlikely to be a single process across epilepsy syndromes. Models representing other important epilepsy syndromes and developmental ages, which address the unmet needs of certain patients, should be

Table 1. Brief summary of recent clinical antiepileptogenesis trials (ClinicalTrials.gov Identifier are given in brackets).

Terminated trials	*Traumatic brain injury*: phase III levetiracetam (TRACK, NCT01463033) *Traumatic brain injury*: phase II, topiramate, phenytoin (NCT00598923) *Stroke*: phase III levetiracetam (van Tuijl *et al*., 2011) **Comment (DS):** according to the authors, poor enrolment was the main reason for termination.
Completed trials	Levetiracetam to prevent post-traumatic epilepsy phase II, non-randomised endpoint *Classification*: safety study *Primary outcome measures*: adverse effect profile, AE outcome measures of abnormal scores on mood questionnaires using the Achenbach system of empirically based assessment and CSCD depression. (ClinicalTrials.gov Identifier: NCT01463033) **Comment (DS):** study is completed; study results are not posted or published.
Ongoing trials	Comparison of short duration levetiracetam to extended course for seizure prophylaxis after subarachnoid haemorrhage (SAH) (DOPAST); recruiting. *Study design*: randomised, open label, parallel, phase III, levetiracetam safety/efficacy study (ClinicalTrials.gov Identifier: *NCT01137110*) Early treatment of infants at high risk of developing West syndrome (WS) with low-dose adrenocorticotropin hormone (ACTH) *Purpose*: detect pre-hypsarrhythmia in infants at high-risk for WS and determine whether treatment with ACTH will prevent WS open label single group. (ClinicalTrials.gov Identifier: *NCT01367964*) **Comment (DS):** it may not be possible to differentiate between antiseizure and antiepileptogenesis as prevention without drug is not tested. Disease modification Use of biperiden as a disease modifying agent after traumatic brain injury: a placebo-controlled, randomised, double-blind study; phase III *Primary outcome measures*: onset of post-traumatic epilepsy (12 months after hospital discharge) *Estimated enrolment*: 132; *study start date*: May 2010 (ClinicalTrials.gov Identifier: *NCT01048138*)

developed to facilitate the identification of syndrome-related antiepileptogenic therapies (Galanopoulou *et al*., 2012).

Although a detailed discussion of preclinical models to identify antiepileptogenic treatments is beyond the scope of this brief review (see Löscher and Brandt, 2010), three concerns of current preclinical models will be briefly discussed from a clinical perspective.

The first concern is that animal models do not reflect common causes of brain jury that lead to symptomatic epilepsy in humans. Status epilepticus is clearly an uncommon cause of epilepsy in humans (Sillanpää and Schmidt, 2006a) and there is longstanding controversy as to whether kindling is a direct cause of human epilepsy (Walker *et al*., 2002). This does not negate the usefulness of these models as experimental paradigms to test antiepileptogenic properties of test compounds. However, we need to consider the possibility (although we have no evidence as yet) that the epileptogenic process in humans may differ according to aetiology of the epilepsy and between individuals even with the same type of epilepsy. If this is the case, these two models may not be predictive of common causes of human focal epileptogenesis. We may need a whole range of models of epileptogenesis to fully explore the antiepileptogenic activity of a compound.

The second concern is that, as shown by Langer *et al*. (2011), false-negative results of preclinical testing may be seen if one misses the therapeutic window for antiepileptogenic agents. Missing the therapeutic window has been recognised as one possible reason why anti-stroke agents may have failed (Fisher *et al*., 2009). This is also of concern for clinical trials in order to prevent epilepsy, as will be discussed below.

The third concern is that validation of preclinical models is currently not possible, because clinical trials of AEDs have largely failed to show evidence of antiepileptogenesis in humans.

Table 2. Antiseizure drugs for epilepsy prevention.

Old antiseizure drugs	*Phenytoin, and carbamazepine* have been unsuccessful, likely because of no effect in animal models (Löscher and Brandt, 2010) *Phenobarbital* and *valproate* had effects in doses that were too high and possibly toxic for use in humans (Temkin, 2009)
New antiseizure drugs	*Topiramate* has effects in animal models and may have neuroprotective properties (Löscher and Brandt, 2010) *Levetiracetam* has effects in animal models in clinically applicable doses, with favourable side effects and pharmacokinetic profiles (Löscher *et al*., 1998; Yan *et al*., 2005; Löscher and Brandt, 2010)

Is it the trial design?

Any clinical trial designed to evaluate treatments that could prevent epileptogenesis has to meet two essential requirements. First, the design should include a randomised treatment phase *versus* a control, usually placebo, to assess antiseizure effects, if any, and second, very importantly, a study of antiepileptogenic effects after drug washout. It is not possible to differentiate between treatment effects (seizure reduction with drug) and prevention effects (seizure reduction without drug) in trials without washout. In addition, epilepsy prevention trials are more complex, lengthy, and costly than standard antiseizure treatment trials for many reasons. Issues revolve around selection of subjects, consent for participation, length of follow-up, and selection of an appropriate endpoint (Herman, 2006).

Most antiepileptogenesis trials have been designed with the aim of preventing epilepsy following traumatic brain injury or stroke. Mani *et al*. (2011) elegantly summarised their experience of previous antiepileptogenesis trials and suggested elements of optimal trial design for successful antiepileptogenic treatment (*table 3*).

A further concern is that a therapeutic time window may exist for optimal antiepileptogenic effects of antiseizure drugs (Langer *et al*., 2011; Sloviter, 2011). Since, in many clinical situations, treatment can only be initiated after variable intervals of the initiating epileptogenic insult (*e.g*. after a stroke or head injury) or after the occurrence of spontaneous recurrent seizures, it is important to demonstrate preclinical efficacy under similar conditions (Langer *et al*., 2011). Application of therapies prior to an epileptogenic insult or after a delay may provide limited relevant information. If treatments are effective only when given at the presymptomatic stage, bio- or surrogate markers may need to be identified in order to guide the timing and duration of antiepileptogenic therapy, prior to onset of clinical symptoms. The STAIR experience with tissue-type plasminogen activator (tPA) is encouraging, because the therapeutic window has been found to be about the same in animals and humans (Fisher *et al*., 2009). A caveat, however, is that we need better insight into the actual duration of the epileptogenic period for epilepsy after stroke.

It is difficult to be sure whether therapeutic windows are missed in clinical trials. Our understanding about the time course of epileptogenesis in acquired human epilepsy is limited. We may need such data before we can make a prediction about the duration of therapeutic windows in order to prevent stroke-related epilepsy or other types of acquired focal epilepsy.

Clinical antiepileptogenic trials in patients with traumatic brain injury: concerns and hope

A Cochrane systematic review identified 10 eligible randomised controlled trials, including 2,036 participants (Schierhout and Roberts, 2001). After excluding four trials, the remaining six trials showed a pooled relative risk (RR) for early seizure prevention of 0.34 (95% CI: 0.21, 0.54). However, seizure control in the acute phase with carbamazepine or phenytoin was not accompanied by a reduction in late seizures (pooled RR=1.28; 95% CI: 0.90, 1.81). The authors concluded that antiseizure drugs are effective in reducing early seizures, but there is no evidence that treatment with prophylactic antiseizure drugs (in patients who have no seizures) reduces the occurrence of late seizures, or has any effect on death and neurological disability. The failure to influence the risk of late seizures of post-traumatic epilepsy in studies of patients with traumatic brain injury are similar to findings of meta-analysis of randomised clinical trials on seizure prevention in other conditions, such as febrile seizures, cerebral malaria, craniotomy, and excessive alcohol intake (Beghi, 2003). For these reasons, it is suggested that the use of antiseizure drugs should be short-lasting and limited to the treatment of immediate and early

Table 3. Is trial design contributing to the failure of antiepileptogenic trials? Trial methodology key points and suggestions (modified from Mani *et al*. [2011]).

Methodology key points	Suggestions
Population selection	Relatively common problem; preferably adult population Relatively high epilepsy risk Relatively short latency to epilepsy Homogenous aetiology Lack of other neurological confounding issues or progressive disease
Objective epilepsy risk factor definition and examination for all risk factors	Neurological and physical history (including thorough family history for epilepsy susceptibility; neurological and psychiatric comorbidities) Examination for severity of insult and possible acute symptomatic seizure history and status epilepticus Imaging with attention to region of interest (MRI, DTI, PET) Prolonged EEG (awake and asleep); objective assessment of epileptiform activity Consider MEG Consider chronic intracranial electrodes when they become available
Consent: allow for rapid consent, surrogate consent, waiver of informed consent	
Therapeutic agent	Easy to administer Low side effect profile: safe Can be maintained for sufficient duration as determined by preclinical data
Treatment initiation timing	Depends on cause (suggestion is within 1-3 days from most acute insult types)
Multiple arms with placebo and varying duration of prophylactic administration	
Periodic AED levels and confirmation of adherence necessary	
Long observation period after epileptogenesis intervention phase has ended	Follow-up of at least 2 years; 5 years would be better
Track other epileptogenic aspects that may be acquired during follow-up period (history, imaging, EEG)	
Sample size and powering	Target effect size should depend on expected prevalence of epilepsy, given underlying brain insult; consider powering to detect difference of at least 20-50% reduction in patients with new-onset, unprovoked seizures Trial should be multicentre, given high sample size requirements
Outcome assessment	Seizures: time to first seizure, seizure frequency, refractory epilepsy, provoked or unprovoked seizure, seizure type Blinded neurologist assessment of first seizure description report and ambiguous subsequent seizures Reassessment of biomarkers as stated above Neuropsychological test scores Functional recovery Traditional trial adverse events

seizures (Beghi, 2003). Finally, many people who experience traumatic brain injury have other issues, such as drug and alcohol abuse, prior history of loss of consciousness, and sometimes ambiguous causes of the traumatic brain injury that might be related to antecedent seizures. The comorbidity of patients with traumatic brain injury, which may include alcohol and drug abuse, and memory problems, may render recruitment and retention in clinical trials much more difficult (Mani *et al*., 2011) and, in the end, may make long-term trials unfeasible.

Two recent findings may offer new and better therapeutic options to prevent post-traumatic epilepsy. Epidemiological data suggest that the epileptogenic period after traumatic brain injury in humans may last longer than previously thought (Christensen *et al*., 2009). This surprising finding suggests that the time from brain insult to the first seizure may be much longer than previously considered, at least in some patients. However, the therapeutic window for intervention with antiepileptogenic agents may be shorter than the time to first seizure. In addition, the therapeutic window may differ from one antiepileptogenic agent to another and even from one patient to another, possibly depending on genetic factors or the severity and the region of the brain injury. Nevertheless, the data of Christensen *et al*. (2009) suggest a wide variability of time to first seizure and, possibly, of the therapeutic window. More work is needed to find out when and for how long the therapeutic window appears, for the purpose of intervention. Finally, depression was found to be an important risk factor of post-traumatic epilepsy, which may indicate a role for antidepressant treatment in the prevention of post-traumatic epilepsy (Kharatishvili and Pitkänen, 2010).

Antiepileptogenic clinical trials in stroke patients. What can go wrong?

As epileptic seizures in stroke patients are a common complication and adversely affect neurological outcome, van Tuijl *et al*. (2011) performed a trial aimed at preventing the development of late post-stroke seizures using levetiracetam (LEV). Stroke patients with a cortical syndrome and a modified Rankin score of $\geq$3 or NIHSS $\geq$6 were treated with either LEV, 1,500 mg daily as two doses, or placebo during the 12 weeks following stroke. Treatment was started within seven days following stroke onset. Only 16 patients were included in this trial. Problems of this prophylactic trial involved the monitoring of seizures, a very slow inclusion rate, the use of antiseizure co-medication, continuation of the trial medication after discharge, and the evaluation of possible side effects of the trial medication. Due to too few participants, no conclusions could be drawn regarding the ability of LEV to prevent post-stroke seizures. The study authors suggested that problems encountered during execution of this trial seem to be inherent in performing a trial aimed at preventing the development of epileptic seizures in stroke patients. Their sobering conclusion was that a trial in stroke patients aimed at preventing post-stroke seizures and epilepsy does not seem to be feasible (van Tuijl *et al*., 2011). According to *clinicaltrials.gov*, prevention of post-stroke epilepsy following a short *vs* long exposure to LEV prior to washout is being investigated in an interesting ongoing trial (*table 1*).

Antiepileptogenic trials in patients with brain tumours

A meta-analysis of randomised controlled trials (1966-2004) was designed to evaluate the efficacy of antiseizure drugs *vs* no treatment or placebo, in order to prevent seizures in patients with brain tumours who had no history of epilepsy (Sirven *et al*., 2004). There was no evidence supporting AED prophylaxis with phenobarbital, phenytoin, or valproic acid in patients with brain tumours and no history of seizures, regardless of neoplastic type. Subspecialists who treat patients with brain tumours should receive more training regarding this issue. Future randomised controlled trials should address whether any of the more recent AEDs are useful for seizure prophylaxis (Sirven *et al*., 2004).

Resolving the dilemma

Specific antiepileptogenic drugs are needed

The disappointing results of clinical trials in acquired focal epilepsy may also be due to lack of suitable antiepileptogenesis drugs or treatments. A new approach has highlighted neurodegeneration, inflammation and up-regulation of immune responses, and neuronal hyperexcitability as potential targets for antiepileptogenesis or disease modification (*table 4*).

Mounting evidence supports the hypothesis that inflammation may contribute to epileptogenesis (Choi and Koh, 2008; Vezzani *et al*., 2011; for review, see Löscher and Brandt, 2010). However, epilepsies following stroke, brain tumours or encephalitis may differ in their epileptogenic processes and it may be naïve to think that all epilepsies share the same epileptogenic process and will respond identically to a given antiepileptogenesis drug. We may need different antiepileptogenesis drugs to prevent different epilepsy syndromes.

Table 4. New horizons: potential new antiepileptogenic drugs.

Immunosuppressants (rapamycin: controversial [Buckmaster and Lew, 2011; Wong, 2011], FK506).
Anti-inflammatory agents (non-steroidal anti-inflammatory drugs celecoxib, parecoxib; SC58236, specific monoclonal antibody)
Cell proliferation and plasticity (erythropoietin, FGF-2 and BDNF gene duotherapy, FGF-2 and BDNF gene duotherapy)
New use of old AEDs (levetiracetam and ethosuximide are antiepileptogenic in genetic absence epilepsy model; see text)
Proconvulsants (atipamezole, rimonabant)

Table modified from Pitkänen (2010) and from Pitkänen and Lukasiuk (2010).

Biomarkers?

Given the long duration from brain injury to clinical detection of epileptogenesis and the lack of promising results from human antiepileptogenesis trials, development and validation of biomarkers for human epileptogenesis will be important to better detect beneficial effects of interventions (Mani *et al*., 2011; Blumenfeld *et al*., 2011). Surface EEG spikes, specific intracranial EEG spike patterns, and intracranial EEG seizures may be present before development of clinical seizures and serve as biomarkers. High frequency oscillations (HFOs) have been suggested to accompany the process of epileptogenesis based on animal data and may be present before seizures; microseizures are being investigated as an epilepsy biomarker (Mani *et al*., 2011). Changes in hippocampal structures and hypometabolism on PET have been associated with worsening of seizures in human case series and could become useful as biomarkers for epileptogenesis. MRI diffusion tensor imaging is also being investigated as a marker of epilepsy (Luat and Chugani, 2008). Each of these promising techniques could be examined during antiepileptogenesis clinical trials to validate whether they would be useful as independent biomarkers.

Old antiseizure drugs with novel antiepileptogenic activity

Although efforts to abort the focal epileptogenic process using chronic AED therapy during the extended post-injury period of patients with overt brain injury seem to have had minimal success (Temkin, 2009; Pitkänen, 2010; Löscher and Brandt, 2010), there is hope on the horizon. Surprisingly, ethosuximide has been shown to have antiepileptogenic properties in Wistar albino Glaxo/Rijswijk (WAG/Rij) rats, an established model of human absence epilepsy (Blumenfeld *et al*., 2008). Ethosuximide was given from age p21 to 5 months, covering the usual period in which seizures develop in this model (age of approximately three months). Electroencephalogram (EEG) recordings were used to measure seizure severity at serial time points in the adult rats after stopping the treatment. In addition, the treatment led to a persistent suppression of seizures, even after therapy was discontinued. Thus, animals treated with ethosuximide from age p21 to 5 months still had a marked suppression of seizures at age eight months. These findings suggest that early treatment during development may provide a new strategy for preventing epilepsy in susceptible individuals (Blumenfeld *et al*., 2008). In another series of experiments, Russo *et al*. (2010) treated WAG/Rij rats for 3.5 months (starting at 1.5 months of age, before seizure onset) with either ethosuximide or LEV. The authors demonstrated that both drugs were able to reduce the development of absence seizures, exhibiting antiepileptogenic effects in this specific animal model (Russo *et al*., 2010). These findings suggest that absence epilepsy in this strain of rats very likely follows an epileptogenic process during life and that early therapeutic intervention is possible, thereby opening a new area of research for absence epilepsy and AED treatment strategies. Furthermore, LEV was shown to have both antiseizure and antiepileptogenic effects in the spontaneously epileptic rat (SER). The SER is a double mutant (*tm/tm*, *zi/zi*) showing both tonic convulsions and absence-like seizures. Interestingly, in the five-day administration study, it was found that the effects of LEV were observed both during the drug administration and eight days after the final administration of LEV. The authors suggested that the effect of LEV indicates that it may possess an antiepileptogenic effect which it does not share with PHT, PB, VPA, or CBZ (Ji-qun *et al*., 2005). These three reports of experimental findings in models of absence epilepsy suggest that both ethosuximide and LEV may be potential antiepileptogenic agents for prevention of absence epilepsy in human patients. Further work is needed to confirm this finding in clinical trials of patients with absence epilepsy.

Disease modification in epilepsy with drugs not used for epilepsy

Prospective long-term observations, starting after the first seizure, of people with epilepsy have shown a much varied course of remission and relapse than previously thought. After a follow-up of 37 years, 19% of

patients entered late remission after many years of having seizures. Although a further 19% had refractory epilepsy and never became seizure-free for a year, 14% developed refractory epilepsy after being seizure-free for many years (Sillanpää and Schmidt, 2006b). Since we have no antiseizure drugs with known effects on improving the natural history of epilepsy by fostering late remission or preventing refractory epilepsy, other drugs that are not previously used in epilepsy may prove to be useful. An interesting example of such a drug is biperiden, used for the prevention of post-traumatic epilepsy (see *table 1*). A search for drugs used outside of epilepsy for prevention of epilepsy may be an option for the future.

Finally, early intervention to minimise comorbidities has been advocated in epilepsy (Lux *et al*., 2005; Jozwiak *et al*., 2011). Identifying the therapeutic time window, if it exists, and clinically relevant biomarkers may be needed to optimise the design of future clinical trials. One major challenge in the design of these studies, however, appears to be the delineation of appropriate and easily quantifiable outcomes, including cognitive, behavioural, cardiorespiratory, and neurological outcomes that are relevant to the respective comorbidities in people with epilepsy.

Disease modification in patients with less severe epilepsy

We may need to readjust our expectations from the currently unrealistic goal of completely preventing severe symptomatic epilepsy in those at risk, to a more feasible goal of delaying or preventing the progression of ongoing epilepsy. We have never adequately tested, in preclinical or clinical trials, whether we can delay or prevent worsening of seizure frequency in pre-existing epilepsy following washout of currently available antiseizure drugs or potential antiepileptogenic agents. In addition, it may be useful to consider such trials in animals or humans with less severe symptomatic or cryptogenic epilepsies, or genetic epilepsies. Finally, reducing seizure frequency after washout of antiseizure agents (or antiepileptogenic agents), even for a limited time, would be a clinically very important improvement.

Conclusions

Epilepsy is characterised by recurrent, spontaneous seizures; continuous medication is therefore necessary in many patients even after seizures have long been suppressed by antiseizure drug treatment (Schmidt and Löscher, 2005; Sillanpää and Schmidt, 2006a). The most disturbing issue is the apparent inability of antiseizure drugs to provide a persistent cure, because these compounds generally suppress the occurrence of epileptic seizures without having known antiepileptogenic properties. However, to be fair, antiseizure drugs (despite traditionally being called "antiepileptic" drugs which they are not known to be) were not developed preclinically or clinically to be antiepileptogenic. We therefore need the preclinical and clinical development of proper antiepileptogenic agents. In addition, previous clinical trials of antiseizure drugs aimed at halting epileptogenesis have been hampered by poor enrolment, multimorbidity and, possibly, by missing the critical therapeutic window, if it exists. Hope is on the horizon now that we have concepts to develop specific antiepileptogenic agents, however, much basic and clinical work is needed to make antiepileptogenesis a realistic goal for clinical trials. □

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