The Intrinsic Severity Hypothesis of Pharmacoresistance to Antiepileptic Drugs

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SUMMARY

Pharmacoresistance to antiepileptic drugs (AEDs) is a barrier to seizure freedom for many persons with epilepsy. For nearly two decades, pharmacoresistance has been framed in terms of factors affecting the access of AEDs to their molecular targets in the brain or the actions of the drugs on these targets. Shortcomings in this prevailing view led to the formulation of the intrinsic severity hypothesis of pharmacoresistance to AEDs, which is based on the recognition that there are neurobiologic factors that confer phenotypic variation among individuals with etiologically similar forms of epilepsy and postulates that more severe epilepsy is more difficult to treat with AEDs. In recent years, progress has been made identifying potential genetic mechanisms of variation in epilepsy severity, including subclinical mutations in ion channels that increase or reduce epilepsy severity in mice. Efforts are underway to identify clinically important genetic modifiers. If it can be demonstrated that such severity factors play a role in pharmacoresistance, treatments could be devised to reverse severity mechanisms. By overcoming pharmacoresistance, this new approach to epilepsy therapy may allow drug refractory patients to achieve seizure freedom without side effects.

KEY WORDS: Seizure, Genetic modifier, Refractory epilepsy, Multidrug resistance transporter, Voltage-activated sodium channel.

Refractory epilepsy is associated with diminished health-related quality of life. Uncontrolled seizures may cause physical injuries, psychological morbidities, progressive cognitive and memory impairment, and can impose social and financial burdens (Devinsky, 1999; Kwan & Brodie, 2002; Hermann et al., 2006; Jacoby & Baker, 2008). In addition, uncontrolled seizures may lead to reduced life span because of an increased risk of sudden unexpected death (Forsgren et al., 2005; Ryvlin et al., 2011). In contrast, persons with epilepsy who achieve seizure freedom with antiepileptic drug (AED) therapy often experience health-related quality of life similar to that of the general population (Leidy et al., 1999; Stavem et al., 2000; Aldenkamp et al., 2003). Therefore, there is an urgent need to understand pharmacoresistance in epilepsy and to develop approaches to counteract it.

It has been proposed that patients who exhibit AED pharmacoresistance are in a separate category from those that achieve seizure freedom with drug treatment (Kwan et al., 2011) and that specific neurobiologic characteristics are responsible for the failure to achieve seizure freedom (Gorter & Potschka, 2012; Potschka & Brodie, 2012). This view implies that approaches that reverse the resistance mechanisms could lead to treatment responsiveness. However, an alternative “intrinsic severity hypothesis” is that pharmacoresistance is due not to specific pharmacoresistance factors but rather that epilepsy severity exists on a continuum and that more severe epilepsies are more difficult to treat (Rogawski & Johnson, 2008). Therefore, the scientific challenge may not be to identify neurobiologic mechanisms of pharmacoresistance but rather to develop an understanding of the brain mechanisms that cause variations in epilepsy severity. It might be possible to develop treatments that target the factors conferring increased severity, which may be distinct from the causes of the underlying epilepsy. For example, although epilepsy may be the result of head trauma, tumor, stroke, cortical dysgenesis, or epilepsy-inducing ion channel mutations, the severity may be determined by independent
Defining Pharmacoresistance

From a clinical perspective, refractory epilepsy is defined as seizures so frequent or severe that they limit the patient’s ability to live fully or necessitate the use of medications that produce adverse effects (Devinsky, 1999). Defining pharmacoresistance in terms that can be addressed scientifically is more difficult (French, 2006). Even a single seizure can have dramatic negative physical and psychosocial consequences. Therefore, the clinical goal of epilepsy therapy is the elimination of seizures and often this is taken as a research criterion. However, pharmacoresistance is not absolute (French, 2006). Patients who do not achieve seizure freedom often experience a reduction in seizure frequency or severity when treated with AEDs. This is apparent in clinical trials that evaluate new AEDs, which because of ethical concerns are always conducted with subjects who continue to experience seizures on an optimized baseline AED regimen. Addition of the investigational drug to the baseline medications often leads to a substantial reduction in seizure frequency. In addition, in withdrawal to monotherapy trials, patients often exhibit an increase in seizure frequency and a worsening in seizure severity when the baseline drugs are stopped. Therefore, patients designated as pharmacoresistant do experience a response to medications, although the response is inadequate. Pharmacoresistance is a relative phenomenon. This understanding is compatible with the existence of specific neurobiologic pharmacoresistance mechanisms and also with the view that pharmacoresistance is dependent on epilepsy severity.

Factors Related to Pharmacoresistance

Various studies have sought to determine patient characteristics that are associated with AED refractoriness. The most consistent factor among a broad range of studies is a high frequency of seizures prior to treatment (Elwes et al., 1984; Collaborative Group for the Study of Epilepsy, 1992; Sillanpää, 1993; Casetta et al., 1999; Kwan & Brodie, 2000; Berg et al., 2001; Chawla et al., 2002; Kwong et al., 2003; Gururaj et al., 2006; Leschziner et al., 2006; Hitiris et al., 2007; Malik et al., 2008; Sillanpää & Schmidt, 2009). In addition, family history of epilepsy is a relevant factor (Hitiris et al., 2007). Certain factors that may relate to the nature of the epilepsy have also been associated with intractability, such as remote symptomatic seizures, history of traumatic brain injury, neurologic impairment, infantile spasms, and a history of neonatal or febrile seizures or status epilepticus (Berg et al., 1996, 2001; Oskoui et al., 2005). In general, the epileptic encephalopathy and secondary generalized syndromes have a higher risk of pharmacoresistance than other forms of epilepsy (Berg, 2009). In addition, epilepsies associated with structural lesions identified on neuroimaging are more likely to be intractable (Spooner et al., 2006). In contrast, idiopathic epilepsies not associated with structural brain damage or a known antecedent (remote) brain disorder are far less likely to be drug resistant.

Patterns of Pharmacoresistance

The landmark study of Kwan and Brodie (2000) demonstrated that many newly diagnosed patients with epilepsy can be categorized from time of onset as drug responsive or drug resistant. Other more recent studies have concluded that pharmacoresistance may not necessarily be present from the outset but that it can evolve over time, at least in focal epilepsies (Berg, 2009). There is also evidence that in some patients, pharmacoresistance has a waxing and waning course, alternating between drug responsiveness and resistance (Pati & Alexopoulos, 2010). Therefore, neurobiologic determinants of pharmacoresistance—whether they are specific pharmacoresistance factors or are related to the severity of the epilepsy—are often invariant but in some cases may fluctuate and progress during a patient’s lifetime.

Pan-Pharmacoresistance

Pharmacoresistance does not imply that there is an inadequate response to one or another specific AED or even to a specific class of agents, such as sodium channel blocking AEDs. Currently there are >25 distinct molecular entities registered worldwide for the chronic treatment of epilepsy. True pharmacoresistant epilepsy implies that there is an inadequate response to all available agents singly and in combination. Practically, it is not feasible to test all of the marketed drugs and their combinations. However, this is not believed to be necessary. Most definitions of pharmacoresistant or intractable epilepsy require only two or three drug failures (Berg, 2009; Pati & Alexopoulos, 2010). Such definitions imply that there is a high likelihood that the failure of two or three AED regimens predicts failure of other agents and combinations. Because there is little evidence that any specific appropriately chosen AED is more prone to failure than others, it can be
assumed that clinical pharmacoresistance implies pan-pharmacoresistance. Any neurobiologic hypothesis of pharmacoresistance must be able to explain the reduced efficacy of all appropriately chosen AEDs and not just one AED or a mechanistic class of AEDs.

**Mechanisms of Pharmacoresistance**

There has been considerable interest in the mechanisms responsible for pharmacoresistance to AEDs, with particular attention on the specific cellular and molecular factors that lead to reduced drug sensitivity (Löschler and Potshcka, 2002, 2005; Remy & Beck, 2006; Gorter & Potshcka, 2012). Two major hypotheses have been the focus of research: the multidrug transporter hypothesis and the target hypothesis.

The multidrug transporter hypothesis posits that increased expression or function of drug efflux transporters, such as P-glycoprotein (P-gp) and multidrug resistance–associated proteins (MRPs), reduces the local concentration of AEDs in epileptic brain regions to subtherapeutic levels (Löschler & Potschka, 2002). These transporters are localized to the blood–brain barrier where their primary physiologic role is to extrude potentially harmful xenobiotic molecules from the brain. Most of the attention has been focused on P-gp (MDR1), an ATP-binding cassette (ABC) transporter, which has the remarkable ability to translocate a wide variety of structurally diverse nonpolar, weakly amphipathic compounds. P-gp expression is increased markedly in epileptic brain tissue resected from patients with pharmacoresistant partial epilepsy and is also up-regulated following seizures in rodent models of partial epilepsy (Tishler et al., 1998; Sisodiya et al., 2002). Increased P-gp expression has been associated with reduced brain AED levels in animals. It is notable that in some animal models, administration of P-gp inhibitors has been found to reverse AED resistance (Brandt et al., 2006; Van Vliet et al., 2006). However, there has been controversy as to which AEDs are transported by human P-gp (Sills et al., 2002; Gorter & Potschka, 2012; Zhang et al., 2012). The current view is that several AEDs, including phenytoin, phenobarbital, lamotrigine, and oxcarbazepine, are likely to be substrates, whereas there is uncertainty regarding many other AEDs, and for most AEDs clinical evidence in humans that the drugs are transported by P-gp is lacking (Sills, 2008; Zhang et al., 2012). A key element in the proof that transporter induction is related to AED pharmacoresistance in humans is the demonstration that pharmacoresistance can be reversed by transporter inhibition. Although the transporter hypothesis has been under evaluation for nearly two decades, such evidence has not been forthcoming (Löschler et al., 2011; Gorter & Potschka, 2012) and, from a practical point of view, this line of research has not yet advanced epilepsy treatment. Therefore, alternative hypotheses must be considered.

The second major hypothesis of AED pharmacoresistance is the target hypothesis, which posits alterations in the structure, function, or localization of the molecular sites of action of AEDs in epileptic networks (Remy & Beck, 2006). Two forms of the target hypothesis can be discerned. In the acquired form, the change in the target occurs in conjunction with epileptogenesis, as a result of seizures, or is a consequence of drug treatment. In the genetic form there is an inherited, inborn difference in the target that confers resistance. There is considerable evidence that acquired target-based pharmacoresistance does occur and is relevant clinically in some specific situations. For example, during prolonged status epilepticus, resistance develops to benzodiazepines as a result of internalization of synaptic γ-aminobutyric acid (GABA)A receptors (Wasterlain & Chen, 2008; Fritsch et al., 2010; Joshi & Kapur, 2012). Target-based resistance to AEDs may also be a factor in catamenial epilepsy, in which breakthrough seizures occur at times during the menstrual cycle. In the perimenstrual form of catamenial epilepsy, such loss of seizure control occurs as a result of the withdrawal of endogenous anticonvulsant neurosteroids as a result of hormonal fluctuations (Reddy & Rogawski, 2009).

In addition, however, target-based pharmacoresistance mechanisms may come into play (Reddy et al., 2001).

Alterations in voltage-activated sodium channels have also been proposed as a basis for acquired AED pharmacoresistance. In kindled rats, sodium channels have been found to exhibit reduced sensitivity to carbamazepine but not valproate (Vreugdenhil et al., 1998; Vreugdenhil & Wadman, 1999). Carbamazepine sensitivity returned to normal 5 weeks after kindling, indicating that the changes were related to kindled seizures and not the epileptic state per se, which is persistent. Reduced sensitivity to carbamazepine was also observed in CA1 neurons from patients with intractable temporal lobe epilepsy (Vreugdenhil et al., 1998). A series of later studies confirmed changes in the sensitivity to carbamazepine and also found reduced sensitivity to phenytoin and lamotrigine in epileptic rats that had experienced pilocarpine status epilepticus and also in hippocampal neurons in tissue surgically resected from patients with temporal lobe epilepsy (Reckziegel et al., 1999; Remy et al., 2003a,b; Schaub et al., 2007).

Voltage-activated sodium channels have also been implicated in the genetic form of the target hypothesis. In 2005, Tate et al. reported that a common functional polymorphism in the SCN1A gene, which encodes an isoform of voltage-activated sodium channels, was associated with the maximum doses of phenytoin and carbamazepine used clinically. Although follow-on studies have raised doubt about the association (Tate et al., 2006; Zimprich et al., 2008), the authors concluded that the new results did not rule out the possibility that SCN1A polymorphisms could
be a mechanism of AED pharmacoresistance. NaV1.1 sodium channels encoded by the SCN1A gene are now known to be largely expressed in interneurons and since AEDs generally reduce hyperexcitability are not likely to be an AED target that is relevant to therapeutic activity (Martin et al., 2010). In addition, however, a polymorphism in a single molecular target such as NaV1.1 sodium channels is unlikely to account for pan-pharmacoresistance.

AEDs are believed to protect against seizures by virtue of their interaction with a wide variety of molecular targets in the brain, including the principal subunits of voltage-gated sodium and calcium channels as well as 2,6 proteins that are associated with calcium channels, GABA_A receptors, the GAT-1 GABA transporter, the GABA catabolic enzyme GABA transaminase, K_V7/KCNQ/M potassium channels, the synaptic vesicle protein SV2A, and AMPA receptors (Meldrum & Rogawski, 2007). Given the diversity of molecular targets it seems improbable that all of the targets would be modified in such a way as to produce pharmacoresistance to all available AEDs. Remy and Beck (2006) have proposed that different resistance mechanisms may apply to different AEDs. For example, target mechanisms may be relevant to carbamazepine, which is not a substrate for many multidrug transporters, whereas target mechanisms may be less important for phenytoin, which is a P-gp substrate. Still, as new AEDs have been introduced into clinical practice this idea seems less and less relevant. Many of the newer drugs act at novel molecular targets that are entirely distinct from the targets of the older agents. If target-specific mechanisms were a factor in pan-pharmacoresistance, as new, mechanistically novel AEDs were discovered and introduced into clinical practice there should have been a substantial reduction in the incidence of pharmacoresistance, but this has occurred.

Studies with the phenytoin-resistant kindled rat, an animal model of pharmacoresistance, also raise doubts about the relevance of the target hypothesis. Groups of amygdala-kindled rats can be subdivided into those that respond consistently to phenytoin and others that do not respond and are therefore pharmacoresistant (Ebert & Löscher, 1999). In confirmation of the studies cited above, the phenytoin sensitivity of voltage-activated sodium channels in the kindled rats was found to be reduced compared to controls (Jeub et al., 2002). However, there was no difference in the inhibitory effect of phenytoin on sodium channels in acutely isolated hippocampal neurons from phenytoin responders and nonresponders, providing evidence against the target hypothesis.

**The Intrinsic Severity Hypothesis**

Shortcomings in the prevailing view framing pharmacoresistance in terms of cellular and molecular factors distinct from the underlying epilepsy led to the formulation of the *intrinsic severity hypothesis* of pharmacoresistance to AEDs, which postulates that pharmacoresistance is an inherent property of the epilepsy related to disease severity (Rogawski & Johnson, 2008). For most medical symptoms and conditions, severity is a key descriptive characteristic. Severity can occur on a continuum ranging from mild to moderate to severe. Many conditions leading to epilepsy are characterized by severity, such as head injuries or cortical dysplasias, which can be mild, moderate, or severe. Epilepsy, however, is generally described in binary terms as either present or not present, depending upon whether an individual does or does not exhibit spontaneous recurrent seizures. Although attempts have been made to develop seizure severity scales based on objective (O’Donoghue et al., 1996; Baker et al., 1998) and subjective (Cramer et al., 2003) factors, they have not been widely adopted. In any case, seizure severity per se does not necessarily provide an assessment of epilepsy severity.

Epilepsy severity could be assessed practically in many different forms, including types of seizures exhibited, impact on quality of life, disability, presence of comorbidities, lethality, or by various biomarkers, including measures of neural injury or pathology or electroencephalography (EEG). At present, there is no consensus as to the most appropriate clinical measures of epilepsy severity. For the purposes of this discussion, severity is intended to relate to the neurobiologic factors that confer phenotypic variation among individuals with etiologically similar forms of epilepsy, such as a specific epilepsy-causing mutation or a similar brain injury. A challenge for researchers will be to discern practical clinical measures of severity with relevance to pharmacoresistance.

From a neurobiologic perspective, seizure frequency seems a particularly appropriate marker of severity. All vertebrate brains can express seizures; epilepsy represents a condition of reduced seizure threshold such that seizures occur spontaneously in response to as yet poorly defined endogenous physiologic fluctuations. Assuming that the physiologic fluctuations occur similarly in persons irrespective of epilepsy severity, then the frequency of seizures is related to the magnitude of the physiologic fluctuation required to trigger a seizure. Individuals who have infrequent seizures require a large magnitude physiologic stimulus to trigger a seizure. Conversely, those who have more frequent seizures require a smaller stimulus. The magnitude of the endogenous trigger can therefore be viewed as an inverse measure of epilepsy severity, and seizure frequency is an easily quantifiable clinical characteristic that reflects this view of epilepsy severity. Although seizure frequency has virtues as a marker of severity, it is by no means the only marker. Moreover, no specific symptom defines severity. Rather, severity is a neurobiologic property of the epilepsy.
Neurobiologically, severity may simply reflect the magnitude of the epileptic process. In addition, separate factors, including genetic factors, likely regulate severity. Theoretically, severity factors could be acquired as stochastic events during development or by environmental insults (possibly through epigenetic mechanisms; Kobow et al., 2013), or they could be genetically encoded. Although there is little information on acquired epilepsy severity factors, studies of monogenic epilepsies have demonstrated that disease severity is often highly variable among individuals with the same mutation, likely as a result of variation in genetic modifiers (Fujiwara, 2006). Moreover, several recent reports have identified specific genetic modifiers conferring altered epilepsy severity in transgenic mouse models. The markers of severity in these studies have included the earlier developmental onset of seizures, increased seizure frequency, the predominance of generalized tonic–clonic seizures and myoclonic jerks instead of partial seizures, and lethality. For example, a subclinical mutation in Scn9a was found to dramatically increase epilepsy severity in mice bearing an epilepsy-inducing mutation in Scn2a (Kearney et al., 2006), and, similarly, mutations in Scn2a and Kcnq2 were found to increase epilepsies conferring an Scn1a epilepsy mutant (Hawkins et al., 2011). Enhanced expression of Kcv2 was also found to increase epilepsy severity in the Scn2a mutants (Jorge et al., 2011). Of interest, unique coding variants in KCNV2, the human ortholog of Kcv2, were found in two children with epilepsy, one of which was highly refractory to AEDs. Genetic severity reducing factors have also been identified, including a null mutation in Scn8a that compensates for the epilepsy mutation in Scn1a (Martin et al., 2007, 2010; Hawkins et al., 2011).

**Experimental Studies Evaluating the Intrinsic Severity Hypothesis**

An important contribution to the understanding of AED pharmacoresistance is the discovery by Lösch et al. that there are variations in AED sensitivity within groups of outbred rats subjected to various epileptogenic treatments (Lösch & Rundfeldt, 1991; Lösch, 2006, 2011). Analyses of the response to the inciting stimulus demonstrated no differences in the severity of the seizure triggering epileptogenesis (Volk et al., 2006). Nevertheless, epileptic animals exhibited dramatic individual variability in drug responsiveness strongly suggesting that genetic factors play a key role in determining whether pharmacoresistance does or does not occur.

These models have been used to assess whether seizure frequency predicts drug responsiveness. In one study, the epileptogenic stimulus was status epilepticus induced by prolonged electrical stimulation of the basolateral amygdala (Lösch & Brandt, 2010). Animals were assessed for responsiveness to phenobarbital, which also generalizes to phenytoin. Responsive rats exhibited a relatively low, uniform seizure frequency; none of the responders had a high seizure frequency. In contrast, many nonresponders exhibited very high seizure frequencies. However, there were nonresponders who also exhibited low seizure frequencies comparable to those of phenobarbital-responsive animals. As in the clinical situation, high seizure frequency was a reliable predictor of pharmacoresistance. However, seizure frequency is clearly not the only determinant of pharmacoresistance. In fact, the same research group reported previously that hippocampal neurodegeneration, which interestingly is not required for epileptogenesis and is not present in pharmacosensitive animals, is always present in pharmacoresistant rats (Volk et al., 2006). Therefore, in this situation, structural brain damage was a marker of pharmacoresistance. Clearly, it would be well advised not to consider seizure frequency the only marker of epilepsy severity.

In a more recent study with the post–pilocarpine-induced status epilepticus model, there was no difference in seizure frequency between phenobarbital responders and nonresponders (Bankstahl et al., 2012). Of interest, however, nonresponders exhibited hyperactive locomotor behavior compared with nonresponders, indicating that behavioral phenotype could be an indicator of epilepsy severity relevant to pharmacoresistance.

**Criticism of the Intrinsic Severity Hypothesis**

Several authors have noted appropriately that there is a lack of knowledge regarding the neurobiologic bases of epilepsy severity (Schmidt & Lösch, 2009; Gorter & Potischka, 2012). These comments serve as a call to action for researchers to identify clinically relevant severity factors and for clinicians to define pertinent clinical markers of severity. It has also been noted that new evidence indicates that some previously intractable patients do achieve seizure freedom with new AEDs (Callaghan et al., 2007; Luciano & Shorvon, 2007; Brodie, 2010). This hopeful observation provides an impetus for continued research to discover and develop new AEDs. However, it does not affect the potential validity of the intrinsic severity hypothesis, since a new AED that acts by a novel mechanism may be more effective in a specific patient, even if the epilepsy is severe, because the new drug is especially suited to the neurobiologic form of epilepsy affecting that patient. Another critique of the intrinsic severity hypothesis is that some patients with infrequent seizures are drug refractory. As noted, seizure frequency should not be taken as the only measure of severity. Moreover, epilepsy is a highly heterogeneous diagnosis; it is well recognized that phenotypically similar epilepsies may have diverse neurobiologic underpinnings. There is no absolute scale for responsiveness to phenobarbital, which also generalizes to phenytoin. Responsive rats exhibited a relatively low, uniform seizure frequency; none of the responders had a high seizure frequency. In contrast, many nonresponders exhibited very high seizure frequencies. However, there were nonresponders who also exhibited low seizure frequencies comparable to those of phenobarbital-responsive animals. As in the clinical situation, high seizure frequency was a reliable predictor of pharmacoresistance. However, seizure frequency is clearly not the only determinant of pharmacoresistance. In fact, the same research group reported previously that hippocampal neurodegeneration, which interestingly is not required for epileptogenesis and is not present in pharmacosensitive animals, is always present in pharmacoresistant rats (Volk et al., 2006). Therefore, in this situation, structural brain damage was a marker of pharmacoresistance. Clearly, it would be well advised not to consider seizure frequency the only marker of epilepsy severity.
on which to consider seizures “frequent” or “infrequent.” Such a designation makes sense only in relation to a specific neurobiologically defined epilepsy. At present it is not possible to make such a designation. Therefore, a patient who has relatively infrequent seizures may actually have a severe form of the disease in the context of the underlying neurobiologic epilepsy type.

**Severity Reduction—A New Therapeutic Strategy**

A treatment targeted at epilepsy severity mechanisms would represent an entirely new therapeutic strategy for epilepsy that is distinct from currently available treatment approaches. Such a treatment would not be intended to target brain excitability mechanisms involved in seizure generation or propagation, as do currently available AEDs. The treatment would also not be intended to eradicate the underlying epilepsy and be curative as is the goal of resective epilepsy surgery. Rather such an approach would specifically target those brain mechanisms that confer increased epilepsy severity. It is noteworthy that a severity-reducing treatment may not be detected with currently available methods that are used for identifying potential AEDs. Commonly, drug screening is conducted with nonepileptic animals in which seizures are provoked chemically or electrically. The specific severity-enhancing factor being targeted may not be present in the animal used for screening. New models will need to be devised in which relevant severity factors interact with epilepsy mechanisms.

**Conclusions**

Multidrug transporters and alterations in AED targets may play a role in drug refractoriness in some circumstances, supporting an integrative view of pharmacoresistance (Schmidt & Löscher, 2009). However, it seems increasingly likely that other factors play a more important role, particularly in the clinically important situation where there is pan-pharmacoresistance and seizure freedom is unattainable with all available AEDs. The evidence reviewed here raises the possibility that drug refractoriness in this situation often results from factors related to the underlying epilepsy and that the failure to achieve seizure control does not depend upon specific pharmacoresistance mechanisms. Clinicians generally do not assess epilepsy severity, but there is certainly dramatic variation in disease severity among patients with neurobiologically similar epilepsies. In recent years, considerable progress has been made in identifying genetic mechanisms that could account for such variations in severity. This emerging knowledge could enable a new generation of epilepsy treatments that target severity mechanisms. By overcoming pharmacoresistance, this new strategy for epilepsy therapy could be the key to reducing the high fraction of people with epilepsy who fail to achieve seizure freedom despite the availability of a panoply of mechanistically distinct AEDs.

**Disclosure**

The author has no conflict of interest to disclose. I confirm that I have read the Journal’s position on issues involved in ethical publication and affirm that this review is consistent with those guidelines.

**References**


