What Clinical Observations on the Epidemiology of Antiepileptic Drug Intractability Tell Us About the Mechanisms of Pharmacoresistance

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The patient is a 35-year-old Caucasian man who initially presented at age 20 with a generalized tonic–clonic seizure at a restaurant, which was witnessed by his girlfriend. She did not see the onset of the seizure, or had recollection. The emergency physician initiated phenytoin 300 mg qhs and referred him to a neurologist. He had a routine outpatient EEG, which was normal. No further seizures were reported for 3 months, and there was consideration that this may have been an isolated event. A second seizure occurred while he was in a college classroom, and a variety of observers agreed that he had been mumbled and turned his head prior to convulsing. He had scrupulously compliant, as he was anxious to resume driving, and his phenytoin level at the time of the seizure was 18 mg/l with no drug-related complaints.

His neurologist concluded that phenytoin was simply not an effective agent for him, and referred him to an epileptologist. A repeat prolonged EEG showed multiple spike and sharp waves in the left temporal region, and an MRI failed to demonstrate any pathology. Although his initial dose of phenytoin had been increased to 400 mg daily, and his level rose to 25, he only had minimal increased sedation. He had several other mumbling episodes, and his epileptologist added lamotrigine with an appropriately slow titration to 200 mg bid. No further events ensued for 3 months, and he agreed to taper his phenytoin by 50 mg per week to attain monotherapy with lamotrigine.

He had one complex partial seizure without secondary generalization in the sixth week of downward titration of phenytoin. This event was felt to represent possible withdrawal effect as his level had precipitously dropped in the previous week. He continued on with no further seizures for 2 months after complete elimination of phenytoin.

He then had a day with two complex partial seizures, the second of which secondarily generalized and resulted in a fractured finger. The emergency physician resumed his phenytoin at 400 mg daily and his epileptologist saw him urgently the next morning. Because he complained of sedation on phenytoin–lamotrigine duotherapy, he was then started on levitiracetam and titrated over 2 weeks up to 1500 mg bid. The phenytoin was not continued.
He did well for 5 months, and then had a complex partial seizure. His lamotrigine was increased gradually to his maximal tolerance at 400 mg bid. Fortunately, his epileptologist had become concerned that he should refrain from driving until he was a full year seizure-free. This time his seizures recurred after 7 months.

Subsequently, he underwent a phase I pre-surgical evaluation at a comprehensive epilepsy center, and he was found to have a positive ictal SPECT in the left posterior temporal lobe and a possible area of polymicrogyria on 3T MRI. At this point he was 4 years after presentation. Wada testing indicated that his language and memory had inadequate bilateral representation and the lesion was likely quite close to eloquent cortex. He declined surgery and returned to his epileptologist.

He then pursued a sequence of 3- to 6- month trials of various duo- and triotherapies, including the following:

- Oxcarbazepine and lamotrigine
- Oxcarbazepine and levetiracetam
- Levitiracetam and divalproex
- Topiramate and divalproex
- Topiramate, divalproex and levitiracetam

None of these combinations resulted in any change in his usual frequency of 1–2 complex partial seizures every 3–5 months. He did, however, stop having convulsive events whenever on levetiracetam. Otherwise, no meaningful conclusions could be made about his response to therapies. At his request, he tried LEV monotherapy up to 2000 mg bid but still had complex partial seizures every 3 months. He remained on LEV 1500 mg bid and oxcarbazepine 900 mg bid as his “optimal” therapy to minimize seizures and side effects. He has not driven for 8 years and moved to an area with good public transportation to maintain his employment in an engineering firm.

COMMENTARY

Pharmacoresistant epilepsy is more prevalent, but not restricted to localization-related cases. What determines pharmacoresistance, and when, in a particular case, further treatment adjustments become moot, is an elusive question. Considered another way, there is no evidence that explains why a particular patient has a ceiling for overall seizure control, or when the treating epileptologists ‘hit the wall’ in finding useful therapeutic options.

Outcome studies in adults have indicated that 59.2% of patients ultimately achieve long-term remission of seizures. This outcome does not appear to be markedly influenced by epilepsy syndrome or choice of drugs (as long as not inappropriate for the seizure type). Over half of these good responses were achieved by the first drug selected.

The SANAD study indicated that there was little difference in success in localization-related epilepsy seizure freedom for the initial 12 months of therapy with carbamazepine (29% with 95% CI 24–34%), lamotrigine (25% with 95% CI 18–32%), oxcarbazepine (27% with 95% CI 17–36%), or topiramate (25% with 95% CI 18–33%). Although immediate response was greatest for sodium valproate (36% with 95% CI 29–42%) in the idiopathic generalized epilepsy subjects, topiramate (32% with 95% CI 23–42%) and lamotrigine (26% with 95% CI 17–35%) were comparable, especially when the overlap of confidence intervals was considered. Levetiracetam (LEV) was not utilized in SANAD, but a comparative study between levetiracetam and controlled release CBZ-CR showed similar 1-year seizure freedom rates of about 50% in new epilepsy patients.
Thus, at least for the first year, efficacy may not be strikingly different among antiepileptic drugs (AEDs) appropriate for seizure type.

Those patients whose seizures do not remit with the first selected AED have a progressively worse chance of seizure freedom with every subsequent drug attempted. Failing the first drug portended a 27% chance of poor ultimate control, while failing the second and third options lowered the chance of remission to 10% and 3%, respectively. Considering the converse, patients who did not become seizure-free with their second AED had a 90% chance of continuing to have seizures despite any medication.

It is usually when a patient’s seizures fail to improve with two to three appropriate choices of AEDs that consideration of more complex therapies begins. Whether there is also a ceiling effect with neurostimulation and surgical options is not clear, as these therapies are more commonly performed in patients who are already felt to be refractory to AEDs. The duration of seizure freedom in the post-surgical population is particularly difficult to analyze, due to both continued use and tapering of AEDs, as well as the potential for evolution of the causative lesion.

Patients with refractory epilepsy often seek help from epileptologists and comprehensive epilepsy centers. When such patients have a singularly good response to an agent, the result is notable. Of course, the question remains whether this response is simply a transient response or one that may be longer lasting than the duration of the study. Thus, the patient with refractory epilepsy justifies study extensions to determine long-term prognosis and late adverse effects.

On a personal perspective, the patients with refractory and difficult-to-control seizures are the lifeblood, the bane and the brass ring of the epileptologist’s existence. Without them, we would be superfluous. With them, we and our patients have to endure repeated failures toward the goal of “no seizures”. Careful and successful analysis of patients who never become seizure-free will hopefully further our knowledge of pharmacodynamics as well as the emerging field of pharmacogenomics. If we can identify the genetic patterns that determine resistance to seizure freedom, then we may be able to raise the ceiling on epilepsy.

REFERENCES

Why Is There a Similar Ceiling Effect for the Efficacy of Most if Not All Antiepileptic Drugs in Adult Epilepsy?

Rajiv Mohanraj and Martin J Brodie

OUTCOMES DATA REVIEW

Data from outcome studies in adults with newly diagnosed epilepsy suggest patterns of response to AEDs that can be observed consistently across a range of epilepsy syndromes. In a series of 780 patients starting on their first AED over a 20-year period at the Western Infirmary in Glasgow, Scotland, 31.4% responded immediately to treatment, suffering no further seizures after taking the first drug dose. These immediate responders constituted more than half of the 59.2% of patients who subsequently achieved long-term remission. The prognosis for immediate response was not markedly influenced by syndrome classification or choice of drugs. Indeed, many patients were controlled on a modest or moderate AED dose. A smaller proportion (5.4% overall) showed a transiently good response, achieving seizure freedom for more than 12 months before suffering relapse of seizures and subsequently developing refractory epilepsy. The remaining 35.4% of this population never achieved seizure freedom for any consecutive 12-month period despite treatment with a range of AEDs.

Similar patterns of response to treatment were observed in the recently concluded SANAD study. In the localization-related epilepsy arm, 29% (95% CI 24–34%) of
patients starting on CBZ-CR achieved 12 months of seizure freedom by the end of the first year on treatment. This immediate responder rate was significantly different only for gabapentin [20% (95% CI 13–26%)], with lamotrigine [25% (95% CI 18–32%)], oxcarbazepine [27% (95% CI 17–36%)] and topiramate [25% (95% CI 18–32%)] producing similar seizure-free rates in the per protocol analysis. In the idiopathic generalized epilepsy arm, the immediate responder rate for sodium valproate was 36% (95% CI 29–42%). Lamotrigine [26% (95% CI 17–35%)] and topiramate [32% (95% CI 23–42%)] produced comparable immediate responder rates.

These observations have been supported by a recent double-blind, randomized trial in newly diagnosed epilepsy comparing controlled-release CBZ-CR with LEV. No difference in outcome was found between the drugs. One year seizure-free rates of around 50% were observed with both agents using the intention-to-treat analysis. These figures were almost identical to those reported from Glasgow. In addition, the vast majority of responders (89% taking CBZ-CR versus 86% on LEV) did so at low dosage, that is, CBZ-CR 200 mg or LEV 500 mg twice daily, again mirroring the modest doses that were effective in many Scottish patients.

A number of studies have demonstrated that early treatment with AEDs, while preventing seizure recurrence in the short term, did not alter long-term outcomes. On the other hand, failure to respond to the first AED does herald a poorer prognosis. In the Glasgow series, only 27% of those patients failing their first AED due to lack of efficacy subsequently demonstrated a good outcome. Those who did not become seizure-free with two or three AED schedules because of lack of efficacy had a less than 10% and 3% chance, respectively, of ever achieving remission. This last group could, therefore, be considered to have refractory epilepsy.

Given the lack of influence of timing and choice of AED, the prognosis for patients with epilepsy has been considered to be an inherent property of the epilepsy syndrome. This is certainly the case for a range of epilepsies in infancy and childhood. There is a less clear link between pathological substrates underlying some adult epilepsies and treatment outcomes. In addition, people with the same syndrome do not all respond to AEDs in a uniform manner. In our analysis of 343 patients with newly diagnosed localization-related epilepsy, no significant differences were found in remission rates between patient populations with cryptogenic and symptomatic epilepsies. Immediate responder and remission rates were also comparable with some patients with the same syndrome doing well and others doing badly despite taking similar AED therapy. This also applied to small groups of patients with newly diagnosed epilepsy thought to be secondary to mesial temporal sclerosis or cortical dysplasia. Although, overall, patients with newly diagnosed idiopathic generalized epilepsies were more likely to achieve remission than those with localization-related epilepsies, again some teenagers with, for instance, juvenile myoclonic epilepsy appeared to be refractory de novo.

Relevance to clinical practice

The vast majority of adults who respond to pharmacotherapy will do with their first AED. The more regimens required to be tried, the more likely will the epilepsy prove to be refractory with only a handful of individuals doing well after failing three drug schedules. Initial response to treatment in adult newly diagnosed epilepsy appears to be largely independent of seizure or syndrome classification and choice of AED. Thus,
the prognosis for many patients with newly diagnosed epilepsy, whether good or bad, will become apparent within a few months of starting treatment.

**What unanswered questions still remain for clinical researchers**

The majority of epilepsy syndromes encountered in adults display the complete gamut of responsiveness to AED treatment from immediate control of seizures to refractoriness from the outset. This raises an important question – does clinical classification of epilepsy syndromes reflect the pathophysiological mechanisms responsible for seizure generation and drug responsiveness? Studies of monogenic epilepsies suggest a great deal of genetic heterogeneity underlying well-defined phenotypes. The same is likely to be true of acquired epilepsies. There are likely to be differences in molecular, cellular and network alterations that underpin clinically homogenous epilepsy syndromes. Elucidating these is crucial to our understanding of drug resistance in human epilepsies.

There is no published evidence to suggest that the advent of newer AEDs with novel mechanisms of action has resulted in better treatment outcomes. It is reasonable, therefore, to postulate a common mechanism limiting the effectiveness of AEDs. This may relate to the expression throughout the brain of drug-resistance proteins, such as P-glycoprotein. Pharmacokinetic and pharmacodynamic tolerance to AEDs may also play a role in patients who show initial response to AEDs before becoming treatment resistant.

Alterations in the structure, expression levels and function of drug transporter proteins, metabolizing enzymes and drug targets caused by genetic variations have the potential to affect the response to AEDs. However, the design, execution and data analysis in pharmacogenetic studies are not straightforward. Treatment response is a complex outcome, brought about by a combination of genetic and environmental factors. This will limit the predictive power of any single genetic marker. Pharmacogenomic studies can be considered analogous to genetic association studies of complex disorders in this respect, and an approach utilizing the concept of multiple susceptibility single-nucleotide polymorphisms may be more informative. Perhaps we need to examine the complete genotype before we understand the individual basis for pharmacoresistance.

Determining phenotypes is also complicated, as a uniform definition of responders and nonresponders can be difficult to identify. A pragmatic approach might be to limit comparisons initially to immediate responders and those who remain refractory from the outset. The short answer to the question posed in the title is that the adult epilepsy population largely divides into two with most responders doing well on a modest dose of any therapeutic agent while those with refractory epilepsy usually tend to be pharmacoresistant de novo to all available AEDs used singly or in combination.

**REFERENCES**


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What Clinical Observations on the Epidemiology of Antiepileptic Drug Intractability Tell Us About the Mechanisms of Pharmacoresistance

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In the past several years, there have been important advances in the clinical epidemiology of antiepileptic drug resistance, as reviewed by Mohanraj and Brodie. It would appear that by and large, intractability is independent of the choice of AED. Many patients will become seizure-free on the first agent tried, irrespective of which one their physician decides to pick. Nonresponders to the first drug are in a different category: It is likely that they will continue to have seizures no matter which medicine or combination of medicines is tried. This simple clinical observation puts important constraints on the possible biological mechanisms for pharmacoresistance. In this essay, I consider the clinical implications of the new research on the neurobiological mechanisms of AED intractability.

AEDS HAVE MANY DISTINCT CELLULAR MECHANISMS OF ACTION

Clinicians have a wide range of AEDs to choose from. There are 23 distinct chemical entities marketed worldwide for epilepsy therapy. Some of these agents are known to be useful for a limited range of seizure types. For example, ethosuximide is largely exclusively used in childhood absence. Tiagabine, vigabatrin, phenytoin, carbamazepine, and oxcarbazepine are mainly useful for partial and primarily generalized seizures.
The other agents, including valproate, topiramate and levetiracetam have broader utility. With very few exceptions, each AED acts in a mechanistically distinct way. This is not the situation in other therapeutic areas. For example, the triptans used to abort migraine attacks all act in a similar fashion as agonists of serotonin 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors; the selective serotonin reuptake inhibitors used to treat depression all block the serotonin transporter; the many statins are all HMG-CoA reductase inhibitors; and the proton pump inhibitors all have the same molecular target. In contrast, each AED generally acts on a unique set of molecular targets. Even when they share the same molecular target, as is the case for AEDs that act on voltage-activated sodium channels, the biophysical details for each drug are sufficiently different that the mechanisms must be considered distinct. For example, there may be important differences in binding rate, binding affinity, the ability to block open channels or effects on persistent sodium current, or effects on other ion channels, as is the case for lamotrigine, where modulation of voltage-activated calcium channels may be relevant to its therapeutic activity. Another major class of AED actions relates to interactions with GABA-mediated inhibition. Some drugs, most notably benzodiazepines and phenobarbital, but also felbamate and topiramate, positively modulate GABA$_A$ receptors. The specific actions of these agents are distinct. For example, benzodiazepines and phenobarbital modulate GABA$_A$ receptors at distinct sites and in different ways. Unlike benzodiazepines, phenobarbital, felbamate and topiramate act on targets other than GABA$_A$ receptors that likely contribute to therapeutic activity. Vigabatrin inhibits GABA transaminase, whereas tiagabine blocks the GAT-1 GABA transporter; each of these agents affects the dynamics of inhibitory function in dramatically different ways. Other AEDs exert their anticonvulsant action through novel targets. For example, LEV acts through SV2A, a ubiquitous synaptic vesicle protein, whereas gabapentin and pregabalin act through $\alpha_2\delta$, a novel presynaptic protein associated with voltage-activated calcium channels.

**INADEQUACY OF THE TARGET HYPOTHESIS**

A number of hypotheses have been proposed to explain AED pharmacoresistance. One major hypothesis is that alterations in the structure or function of the molecular targets through which AEDs act lead to reduced drug activity. However, since diverse AEDs act in so many different ways and on different sets of molecular targets, this so-called target hypothesis seems incompatible with the clinical evidence that certain patients are resistant to all available drugs. It is unlikely that all of the targets would become changed in such a way to produce pan pharmacoresistance. There are two forms to the target hypothesis and this argument applies equally well to both. In the conventional form of the target hypothesis, the molecular target – most commonly voltage-activated sodium channels – loses pharmacological sensitivity to AEDs during the acquisition of pharmacoresistance. However, in the studies supporting this hypothesis, the sensitivity to drugs that act on other molecular targets, notably valproate and lamotrigine, was unaffected. The mechanism of action of valproate is poorly understood but is unlikely to relate largely to an interaction with sodium channels. Lamotrigine has a different spectrum of activity than other AEDs and, as noted, acts on calcium channels in addition to sodium channels. Clearly, this resistance mechanism could only apply to AEDs that act largely on the specific target affected. Other challenges to the target hypothesis are discussed by Schmidt and Löscher. A second form of the target hypothesis posits that there are genetically determined polymorphisms in an AED target that alter...
AED responsiveness. Indeed, Tate et al.\textsuperscript{11} identified a polymorphism in the SCN1A sodium channel gene that appeared to confer resistance to carbamazepine and phenytoin, although they subsequently did not replicate the association.\textsuperscript{12} Whether or not a sodium channel polymorphism is associated with pharmacoresistance to drugs that act on sodium channels, clinical AED intractability, in which there is a failure to adequately respond to all available agents, is not explained.

### QUESTIONS REGARDING THE TRANSPORTER HYPOTHESIS

A leading hypothesis regarding drug resistance in epilepsy is the so-called transporter hypothesis which postulates that drug efflux transporters located in the apical membrane of capillary endothelial cells that form the blood–brain barrier limit AED availability to their molecular targets in the brain.\textsuperscript{13} The best-studied transporter is P-glycoprotein (P-gp) but other transporters, including multidrug-resistance-associated proteins (MRPs), could also play a role in pharmacoresistance to AEDs. Reports that P-gp and members of the MRP family are overexpressed in experimentally induced seizure foci and brain tissue specimens removed during surgery of patients with pharmacoresistant epilepsy have raised the possibility that localized overexpression of transporter proteins accounts for the inability to overcome resistance by increasing the drug dose, since other brain regions would then be exposed to supratherapeutic (toxic) drug concentrations.\textsuperscript{14–16} In addition to the observation of increased transporter expression, which could be due to the epileptic process itself or the occurrence of seizures, it has been proposed that genetic polymorphisms in a transporter gene could account for increased functional transporter activity. However, none of the proposed associations between transporter genotype and clinical drug response have been replicated.\textsuperscript{17–19} In any case the genetic form of the transporter hypothesis seems unlikely since a generalized upregulation of transporter activity could be overcome by increasing the AED dose.

The major weakness of the multidrug transporter hypothesis is the lack of evidence that AEDs are substrates for P-gp or any other human efflux transporter.\textsuperscript{20,21} While there is evidence in experimental animals that several commonly used AEDs are transported to some extent by both P-gp and MRPs,\textsuperscript{13,22} recent experiments employing transfected cell lines expressing rodent and human efflux transporters have cast doubt that the drugs are truly substrates for the human forms of the transporters.\textsuperscript{23} Even in mice, the extent to which AEDs are transported by P-gp must be very small as genetic deletion of P-gp does not influence brain uptake of many AEDs.\textsuperscript{24} Indeed, it is apparent that AEDs are not efficiently extruded from brain since all AEDs exhibit CNS side effects, even if they fail to confer adequate seizure protection. Finally, the fact that most AEDs show linear uptake into the brain over a wide range of concentrations calls into question the existence of a saturable transport system that influences the dynamics of AED transport across the blood–brain barrier.\textsuperscript{25}

### DOES “INHERENT SEVERITY” ACCOUNT FOR PHARMACORESISTANCE?

A variety of clinical factors are known to be associated with intractability. The most important and well validated of these factors is the frequency of seizures in the period immediately after diagnosis. Several early studies demonstrated that frequent seizures are associated with bad prognosis\textsuperscript{26} and that high initial seizure frequency during the
period after presentation is an important predictor of seizure intractability.\textsuperscript{27–29} A recent study confirmed the prognostic implications of high early seizure frequency and also identified several other factors associated with intractability including family history of epilepsy, febrile seizures, traumatic brain injury, recreational drug use and a history of depression.\textsuperscript{30} These results suggest that neurobiological factors related to the occurrence of frequent seizures are associated with intractability. This observation seems logical: If the epilepsy is of a nature that seizures are easy to trigger, the seizures may be more difficult to prevent. AEDs probably do not act as a switch to turn off the possibility of seizure occurrence; rather, they make it more difficult to trigger a seizure. That is, they raise the threshold for a seizure-inducing stimulus. In most (but not all) animal models in which seizures are induced by a pharmacological or electrical stimulus, raising the intensity of the trigger can overcome the seizure protection conferred by a given dose of an AED. As is the case with a triggered seizure, if seizure susceptibility is inherently high, it may not be possible to prevent seizure occurrence with any nontoxic drug dose. This leads to the concept that there is a degree of inherent severity in any individual epilepsy patient that does not necessarily depend upon the underlying etiology. Rather, for syndromes of similar etiology, the severity can range from mild to severe, just as diabetes or cystic fibrosis can range in disease severity. Indeed, it appears that disease severity can depend upon specific modifier genes, as in the case of a movement disorder in mice linked to a mutation in the Na\textsubscript{V}1.6 voltage-activated sodium channel.\textsuperscript{31} Mice homozygous for the Na\textsubscript{V}1.6 mutation (\textit{med}+/\textit{med}+) exhibit a highly variable phenotype ranging from slowly progressive tremor and dystonia and lifespan >1.5 years to paralysis and death at 1 month of life. Disease severity has been found to depend upon the genetic background, specifically to an unlinked gene (\textit{Scnm1}) that influences the splicing of the mRNA that encodes Na\textsubscript{V}1.6. This modifier gene dramatically alters the severity of the neurological syndrome. It seems likely that there are similar modifier effects that alter the severity of epilepsy and overall drug responsiveness.

The concept of genetically determined epilepsy severity implies that seizures in severely affected patients are difficult to control from the time of their first seizure and that the occurrence of uncontrolled seizures over time is not the cause of the intractability. Indeed, the wealth of evidence suggests that most cases of epilepsy are not progressive and do not worsen over time as a result of uncontrolled seizures.\textsuperscript{32,33} Finally, I note that disease severity need not necessarily be static, but may fluctuate in response to internal factors and environmental influences. For example, in perimenstrual catamennial epilepsy, severity (and drug intractability) is dependent on hormonal fluctuations occurring at the time of menstruation.\textsuperscript{34}

\textbf{CONCLUSIONS}

What implications does the “inherent severity” hypothesis have for the development of strategies to overcome pharmacoresistance? While it will always be challenging to treat more severely affected patients, it should not be assumed that seizure freedom is unattainable in such patients. The inherent severity model proposes that there is a continuum in severity so that new AEDs acting on novel molecular targets may offer protection for such patients. Recent data is compatible with this optimistic view. Thus, Callaghan \textit{et al}.\textsuperscript{35} found that drug refractory patients who have not responded to at least two AEDs do achieve remission at a rate of about 5% per year. In the majority of cases, the remission was associated with the addition or increase in dose of an
AED, most commonly lamotrigine or levetiracetam. While insufficient data was available for these authors to conclude that these drugs are more likely to induce remission than other AEDs, it seems plausible that the availability of a broader range of AEDs accounts for the fact that these authors obtained better rates of seizure remission in their patients with previously refractory seizures than has previously been observed. A variety of new AEDs are currently in development, some of which act in new ways on old targets and others that act on entirely new targets. We can expect that these new drugs will further benefit patients by having improved side effect profiles, improved pharmacokinetic properties, reduced propensity for drug interactions, less teratogenic potential, an improved spectrum of activity and, most importantly, by their ability to induce seizure remission in some patients previously considered to have intractable seizures. In the future, if modifier genes can be identified that influence severity in human epilepsies, it may be possible to specifically target the biological mechanisms accounting for greater severity, making seizure control feasible patients with difficult-to-control seizures.

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