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Identification of Pharmacoresistant Epilepsy

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Summary

There is no single definition of pharmacoresistant (intractable, refractory) epilepsy. Prospective identification of pharmacoresistance is complicated by the variability of its appearance across different types of epilepsy as well as the variability of seizure control within a given patient over time. Failure of informative trials of two appropriate antiepileptic drugs has been recommended as a threshold that should trigger referral for evaluation at a comprehensive epilepsy center. Maximizing seizure control is imperative for reducing the risks and consequences of epilepsy including the cognitive and psychiatric co-morbidities and even sudden death.

Until relatively recently, the epilepsy literature regarding seizure prognosis has been divided between epidemiological studies of remission and studies focused upon experimental pharmacological therapies and surgical treatment of refractory epilepsy. In the first case, the epidemiological studies were not specifically interested in pharmacoresistance. At best, there was a tacit assumption that not being in remission was the complement of pharmacoresistance. Hence, by studying remission, one was, for all intents and purposes, studying pharmacoresistance. In the second case, experimental and surgical therapies were targeted to patients who were clearly refractory to standard pharmacologic treatments. The fact of pharmacoresistance was established well before patients entered such treatment studies. The pertinent questions regarded whether a new approach could offer any hope where the standard ones had already clearly failed.

These studies offer no clear definition of intractability. In the case of epidemiological studies, defining pharmacoresistance is irrelevant to the outcome. Remission is defined as the absence of seizures [1,21,22,34,47], and the reason for not being in remission is immaterial. For studies of surgical therapy and randomized trials of new drugs, the definition is also not especially relevant as patients treated in these settings are selected to be some of the most extreme cases in whom no doubt remains regarding their seizures' resistance to therapy. For example, in one surgical study, the median number of different AEDs tried prior to referral for surgery was five [7].

In very broad and general terms, pharmacoresistance is the failure of seizures to come under complete control or acceptable control in response to AED therapy. Different specific conceptual definitions have been summarized previously [2]. In theory, one could require that all possible drugs in all possible combinations be used in order to determine this [29]. Practically, this is an impossible standard to meet and likely dangerous for patients as well. This leaves

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important questions regarding how best to define pharmacoresistance in a way that it can be meaningfully studied.

To date, only a few studies have defined pharmacoresistance separately from lack of remission [1,9,14,17,18,27,37,57]. In these definitions, common elements are a) the number of drugs that need to be failed, b) the seizure frequency, and c) factors related to time (Table 1). The consensus regarding number of drug failures appears to be two or three. For other aspects there is somewhat greater variability. Some require a specified period during which a minimum seizure frequency is observed. Others require that a seizure have occurred within a specified period of time (e.g. the last six months). The absolute agreement among these various definitions tended to be high (83–96%), although agreement corrected for chance (Kappa) ranged from a low of 0.35 (poor) to a high of 0.79 (excellent)[6].

Many of the definitions are designed for identifying the prevalence of pharmacoresistance at a given point in time (e.g. two years after diagnosis 27, five years after diagnosis 1 or as of last contact 17). Prevalence is a useful concept in epidemiology and public health. It provides an estimate of the number of individuals at a specified point in time who have a specific condition. The prevalence of intractable epilepsy in a geographically defined population in France was recently estimated using two slightly different definitions to determine the number of people in the population who met each definition and the proportion of people with epilepsy who were pharmacoresistant 53. Both definitions required the failure of two AEDs. Defining intractability as any seizure in the past year yielded a population prevalence of 1.4/1000 and accounted for 26% of people with epilepsy. The second definition required an average of 1 seizure/month during the past year and yielded a population prevalence of 0.9/1000 accounting for 17% of people with epilepsy. For understanding what types of medical and other services might be required to care for epilepsy in the population, this information is quite valuable. This was the first and, to be noted, quite successful, effort to quantify the population burden of refractory epilepsy with a definition that included drug failure.

Recognizing pharmacoresistance as it occurs

Although important for public health and needs assessments, the prevalence of pharmacoresistance at a given point in time is not necessarily the question of greatest clinical relevance when considering treatment and management of individual patients. Identifying which patients are at high risk of pharmacoresistance and prospectively identifying drug resistance as soon as it becomes evident is arguably more important. This corresponds to the clinical situation in which a patient is followed from day to day, reports his seizures to his physician, the physician adjusts the doses upwards, monitors for side effects, the physician and patient decide to try a new AED, and so forth. On what day and based on what criteria can a patient's seizures be deemed pharmacoresistant? Implicit in this notion is that once someone has met criteria for pharmacoresistance, it is time to consider a new approach or pursue other options.

The substitution of prevalent pharmacoresistance for incident pharmacoresistance in many of the cohort studies that have examined this issue is, in part, based on two common assumptions. First, there appears to be an implicit assumption that pharmacoresistance, when it occurs, will be evident from the onset of epilepsy. Second, there is another implicit assumption that the course of epilepsy is a relatively static or stable phenomenon: patients who are controlled remain so; patients who are pharmacoresistant have seizures at a relatively constant rate. Neither of these assumptions turns out to be the case, at least not for all patients, and this has important implications for how we define pharmacoresistance and study it. In addition, prevalence measures ignore the role of increased mortality among patients with uncontrolled

seizures [13,16,46,54]. People with pharmacoresistant epilepsy who die tend to be undercounted in prevalence estimates.

To date, only two studies have examined the development of pharmacoresistance prospectively from the time of initial diagnosis of epilepsy. Information about drug use and failure as well as seizure occurrence was evaluated on an on-going basis (every 3–4 months) in one study from the US 14 and at 7 and 14 years after initial diagnosis in the other study from Australia 57. Study subjects were considered pharmacoresistant once they met the criteria of the definitions used in the study. In both instances, the investigators observed that pharmacoresistance did not necessarily occur immediately and could first be preceded by a period of seizure remission. The Australian study only enrolled children with temporal lobe epilepsy. In the American study, children with all forms of epilepsy were enrolled. The finding of delayed expression of pharmacoresistance was largely a phenomenon observed in the focal epilepsies. Retrospective accounts from surgical series have also documented that a proportion of patients undergoing evaluations for resective surgery have histories of significant remission periods prior to referral for surgery (either before or after the initial appearance of pharmacoresistance) 7,31.

Children with epileptic encephalopathies and other secondary generalized epilepsies tended to express their pharmacoresistance very early in the course of their epilepsy. These disorders tend to start explosively with multiple daily seizures which are quickly demonstrated to be refractory to standard treatments. In focal epilepsies, high initial seizure frequency is also associated with an increased risk of early expression of pharmacoresistance [11]. This tendency may reinforce the perception that intractability is necessarily apparent from the outset.

Seizure frequency and duration of treatment

Patient characteristics, in particular seizure frequency, may play a role in how quickly drug efficacy or inefficacy can be determined. In patients who typically have multiple daily seizures, determination of a drug's efficacy or lack thereof may be made in a matter of a week in many cases although for complete control of seizures (success) there is no specific criterion. In one study, a year of seizure freedom was required before considering a drug trial successful [14]. Trials of drugs stopped after less than a year, even if the patient was seizure-free were considered noninformative. For patients with seizures occurring on a weekly or monthly basis, more time will be required to determine failure. For those with truly infrequent seizures, for example a few per year, there is no clear way to determine efficacy versus failure, at least not quickly.

Several studies, including the Australian[57] and American[14] studies discussed above, have documented the occurrence of brief remissions after having met various criteria for pharmacoresistance [1,37,58]. For the most part, the remissions were not long-lasting, and patients frequently relapsed. In the end, at least for the majority of patients with otherwise poorly differentiated focal epilepsy, it appears that pharmacoresistance may not always be evident from the outset. Furthermore, once criteria for pharmacoresistance are met, the course of seizures may not necessarily be inexorably refractory but may be punctuated by periods of relative seizures quiescence. In an extension of the US study [10], 57% of patients who had failed trials of two different AEDs subsequently had at least a 1-year period of remission. Repeated remissions and relapses were common. After a median period of 10 years follow-up since second AED failure, 37% were at least 1 year seizure-free and 23% were at least three years seizure-free. Among those seizure-free at last contact was a disproportionate number with traditional idiopathic syndromes. Overall, 50% of the idiopathic group compared with only 20% of the focal and 18% of the epileptic encephalopathy group were in remission at last contact.

Predictors of pharmacoresitance

Prognostic information about who will develop pharmcoresistance is quite limited. In adult-onset epilepsy, there are no adequate studies based on well-defined and characterized cohorts and utilizing a meaningful definition of pharmacoresistance. In childhood-onset epilepsy, three large prospective and representative cohort studies provide a mixed message on this matter. All three found that the epileptic encephalopathy/secondary generalized syndromes had higher risks than other forms of epilepsy; however, the levels of risks varied considerably. Two studies found that about half of children in this group developed pharmacoresistance [14,17]. The third reported that only about 10% were pharmacoresistant [1]. Further, in the US study, traditional idiopathic syndromes had the lowest risk of pharmacoresistance and other focal epilepsy an intermediate risk. This was not the case in the other two studies.

The Australian study, limited to temporal lobe epilepsy, found that the strongest discriminator between pharmacoresistant and controlled patients was an abnormal MRI finding[57]. An earlier study based on a 2-year follow-up period but also focused on pediatric temporal lobe epilepsy, reported highly comparable results [27]. These observations highlight an important concern with epidemiological studies and with trying to study pharmacoresistance in a population-based setting. While the population-based model provides good representation, it rarely has adequate clinical detail to provide information useful to studies regarding tertiary epilepsy care. The absence of neuroimaging, particularly MRI, in most epidemiological studies is a limitation of this type of model for studying epilepsy. Studies of pharmacoresistance in the future should incorporate routine MRI exams to the greatest extent practical and ethically possible.

Current Referral Recommendations

The ILAE's subcommission on pediatric epilepsy surgery recommends that children who have failed trials of two or three AEDs be evaluated at a comprehensive epilepsy center [26]. The NAEC recommends that patients whose seizures are not fully controlled after one year be evaluated at a specialized center [50]. This issue was also highlighted in a recent practice parameter which recognized that failure of two drugs was becoming a common criterion for pharmacoresistance and recommended that adults who had failed trials of appropriate AEDs be referred for evaluation to an epilepsy surgery center [29]. Part of the reason to recommend a comprehensive center is so that patients who might benefit from surgical procedures can be identified and properly evaluated. Other considerations however are accuracy in diagnosis starting with whether the patient in fact has epilepsy or some other disorder whose symptoms are mistaken for seizures [32,42,52,56]. In addition especially in the case of childhood epilepsy, accurate diagnosis of the specific type of epilepsy is key, to the extent that may influence treatment and management decisions and provide information about likely prognosis.

In children, there is a large array of highly distinctive forms of epilepsy, "syndromes," which tend to have very specific implications for treatment and prognosis. Recognition of these particular forms of epilepsy, including specific causes of epilepsy, has been helpful in improving their pharmacological management. This is seen in expert opinion of preferred first and second choices of therapy in various clinical scenarios[62,63] and addressed in recent practice guidelines[33]. Fairly recently, we have also seen a few examples of moderate success in the treatment of highly refractory forms and causes of epilepsy. In particular, vigabatrin for infantile spasms secondary to tuberous sclerosis[49]; stiripentol for Dravet syndrome[19,20]; and possibly the ketogenic diet for epilepsy associated with GLUT1 deficiency[43].

Approximately 50% of epilepsy of childhood onset and closer to 90% of epilepsy of adult-onset is of a focal nature and does not conform to any of the well-described genetic and developmental epilepsy syndromes (including the epileptic encephalopathies as well as the more typically tractable "idiopathic" syndromes) [12,15,38]. These were recently dubbed the

"garden variety focal epilepsy." 25 It is from this group with focal epilepsies, that the majority of resective surgical patients arise.

These focal epilepsies are poorly characterized and generally described solely with respect to the presence or absence of a demonstrable lesion or other condition (symptomatic versus cryptogenic) and the region of the brain from which the seizures appear to arise (e.g. frontal or occipital lobe) based on varying degrees of clinical investigations. As previously proposed [5], concerted efforts might profitably be applied to better "phenotyping" these garden variety focal epilepsies in an effort to identify specific forms. Factors such as specific EEG patterns and findings, age at onset, patterns of seizure occurrence, seizure duration (e.g. status epilepticus), diurnal patterns, provoking or triggering factors, and other features might, if rigorously examined, provide some keys into subtypes of focal epilepsy that are currently not recognized. To the extent this may be relevant to choice of AED, this may serve to improve treatment and potentially decrease the number viewed as pharmacoresistant. A recent study examined the response to successive treatments (AEDs) in patients who had failed previous AEDs. Although the chance of success of the next AED decreased with increasingly number of previous failures, a proportion did achieve seizure-freedom. Whether this reflects true response to the drugs or some aspect of the natural history cannot be addressed by this study. To the extent it reflects true drug response, it appears as though there is a certain random element in who responds to which drug. Ideally we should be able to identify who will be most likely to respond to which drug so that agents do not have to be tried at random.

Why is it necessary to identify pharmacoresistance as soon as possible?

Uncontrolled seizures can have a devastating impact on the individual and family. School employment, driving, and all aspects of social functioning and activities can be adversely affected. Psychiatric complications, particularly depression and anxiety, may, in part, be consequences of uncontrolled seizures [41] although there is clearly a complex and bidirectional association between epilepsy and depression [40]. Mortality is considerably increased in people with epilepsy [45]. This is particularly of concern for mortality secondary to seizure-related accidents[3,55] and for sudden unexpected death associated with epilepsy or SUDEP [44,60].

There is also the growing recognition of the toll uncontrolled seizures take on cognition and developmental function. This is a concern for the intractable focal epilepsies in adults [29]. Hermann et al demonstrated declines in confrontational naming, memory function, and fine motor control over time in adults with refractory TLE compared to healthy controls without epilepsy [36]. The phenomenon is perhaps most dramatic in a group of disorders with onset primarily during infancy and early childhood, the epileptic encephalopathies. The concept of epileptic encephalopathy is still in development [4,23,28,51] The observation of developmental plateauing or even losses in children who, prior to the onset of seizures appeared relatively if not entirely normal, has lead to the hypothesis that it is the epileptic activity in the developing brain that may interfere with and possibly permanently derail the acquisition of normal brain function. The concern is greatest for those syndromes traditionally labeled as epileptic encephalopathies, however, some evidence raises the possibility that there may be a spectrum of dysfunction and that adverse impact may occur in association with other forms of epilepsy that are not necessarily counted among the epileptic encephalopathies. For example, Hermann et al. 35 found that younger versus older (<8 versus ≥8 years) age at onset of temporal lobe epilepsy was associated with reduction in white matter volume and significantly decreased performance on an array of neurocognitive measures. Cormack et al. studied a group of children undergoing resection for intractable temporal lobe epilepsy [24]. They found that the younger the age at onset, the greater the risk of intellectual disability. In fact, of those with onset less than 1 year 82% were considered intellectually disabled (IQ<70) compared to 12% of those with onset at age five years or greater. Even taking into account underlying lesions, seizure

control and treatment, one study reported evidence that younger age at onset (<5) was associated with evidence of lower level of intellectual ability compared to older age at onset (>5 years) 8. This was found even within groups of patients who had "cryptogenic" focal and idiopathic generalized epilepsy.

Cognition as a facet of intractable epilepsy

The concerns with the adverse impact on cognition, especially in the developing brain raise another issue: is control of seizures the full measure of whether a patient's epilepsy is drug responsive or pharmacoresistant? On the one hand, there is reason to suspect that mechanisms underlying the developmental syndromes known as the epileptic encephalopathies may differ from those of "garden variety focal epilepsy." It would be reasonable to investigate the mechanisms of intractability and treatment separately within each of these broad groups and more realistically, within specific subtypes and syndromes. On the other hand, we are faced with the possibility that the impact of epileptic activity, especially in the developing brain, may occur along a continuum of severity that spans all forms of epilepsy from the most intractable to the seemingly "benign." There may well be effects at all ages including in adulthood; however, the effects may be more severe and less reversible when the epileptic activity disrupts neurodevelopmental processes during critical times in development. These complexities represent another facet in considering how best to define and understand intractability and how to treat epilepsy most effectively both in the short and in the long-term.

Limited but compelling data from surgical studies support the notion that early intervention, when feasible, may ultimately spare developmental function and improve long-term behavioral and cognitive outcomes [30,39,59,61]. Preliminary data on the treatment of cryptogenic infantile spasms also suggests there may be some hope for rescued development [48]. Thus accurate recognition of pharmacoresistance as soon as possible is not simply a methodological nicety but a clinical necessity.

Early intervention, however, requires early recognition. This in turn requires clear guidelines for drug use and definitions of treatment failure. It always requires that these guidelines and recommendations be effectively disseminated to care providers of people who have epilepsy.

Future challenges

There remains much to do at this point. First and foremost, the field needs a valid and robust operational definition of pharmacoresistance, one that can be meaningfully used in most if not all clinical research settings and which is relevant to clinical patient care. This definition must include explicit guidelines for what constitutes drugs failure and how many different drugs should be failed for a patient's epilepsy to be deemed pharmacoresistant. At this point, consensus seems to be converging on two AEDs. Systematic, prospective application of the definition in appropriately designed clinical investigations should replace retrospective chart review studies and secondary analyses of data sets that are not suited to address key questions surrounding pharmacoresistance. Although population-based studies are often touted as the gold standard approach for studying prognosis, in fact, such studies are often deficient in the areas most required for the study of pharmacoresistance and other clinically relevant issues. A hybrid design in which we allow some compromise in the recruitment and representativeness of patients in exchange for high quality clinical information is necessary. In fact, some of the studies are already like this but are criticized for not being population-based [1,14]. The emphasis also must shift to how best to identify pharmacoresistance at its earliest possible presentation, who is at greatest risk, and then how best to treat and manage those who appear pharmacoresistant. This is a serious problem which deserves concerted, methodologically sound and clinically sophisticated efforts to resolve.

Teaching nonepilepsy specialist clinicians who manage care for patients with epilepsy the importance of assessing treatment failure in a timely systematic manner would be an important component for both clinical management and research endeavors. Emphasizing the risks and consequences of uncontrolled seizures from relatively minor cognitive effects to mental retardation, autism and sudden death should be an important part of education for care providers, patients, and their families. Although not all patients who meet criteria for pharmacoresistance are surgical candidates, such a determination can often only be made after comprehensive evaluation by epilepsy specialists. Because the diagnosis of epilepsy is not always simple, a comprehensive assessment should also address the accuracy of the diagnosis of epilepsy and of the specific form of epilepsy when it can be identified.

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Table 1

Components of selected definitions of pharmacoresistant or intractable epilepsy.

Author	Study methods*	Drug failures	Seizure frequency	Other criteria
Huttenlocher [37]	Retrospective cohort, chart review	2	1 seizure/month	for ≥2 years
Berg [9]	Retrospective case-control, chart review	3	1 seizure/month	for ≥2 years
Casetta [18]	Nested case-control study in prospective cohort	3	1 seizure/month	for ≥2 years
Arts [1]	Prospective, chart review	2	any	<3 months seizure-free during 5th year of follow-up
Dlugos [27]	Retrospective, chart review	2	any	<6 months seizure-free 19–24 after initial diagnosis and treatment
Camfield[17]	Prospective, chart review	3	1 seizure every 2 months in	During last most recent year
Berg [14] (2 definitions)	Prospective, direct patient contact&chart review	2	Average ≥1 sz/month	for 18 months, no more than 3 months seizure-free
		2	No mininimal frequency requirement	Explicitly excluded non-informative trials as “failures”
Spooner [57]	Prospective, chart review.	2	No minimal frequency requirement	