

DRUG-RESISTANT EPILEPSY: *WHAT IS IT, WHO HAS IT, AND HOW TO TREAT IT?*

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I. What is drug-resistant epilepsy

Epilepsy is a common neurologic disorder typically treated with antiepileptic drugs (AEDs). Approximately 2.4 million people in the US have epilepsy (65 million worldwide). About two-thirds of patients with epilepsy respond well to medication, meaning they achieve seizure freedom for a prolonged period of time. Approximately a third of adult patients with epilepsy still have seizures, however, despite anticonvulsant treatment. Many terms (“refractory,” “intractable,” “pharmacoresistant”) and ways of categorizing these patients have been used over time, resulting in some confusion clinically and lack of a structured definition with which to think about and study such patients until recent years. In 2010, the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies published a consensus paper including a formal definition, using the term *drug-resistant epilepsy*. The definition is as follows:

“Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.” (1)

This is a clinical diagnosis, one does not need continuous videoEEG monitoring to confirm drug-resistance. Kwan and Brodie published a prospective look at outcomes with AED use in 2000 (2). The first AED used successfully treated seizures in 47% of patients. Of those who failed the first AED, a second AED was successful in achieving seizure freedom in 13% of patients. Use of a third AED in those who failed the first two resulted in seizure freedom in only 1% of patients.

Of the 2.4 million people, or 6/1000, in the US that have epilepsy, about one-third (2/1000) have generalized epilepsy, while two-thirds (4/1000) have focal epilepsy. Of these 4/1000 with focal epilepsy, about two-thirds, or 2.5/1000 have seizures that are well-controlled, leaving about a third, or **1.5/1000 with drug-resistant epilepsy**. A significant number of these patients with focal epilepsy may be candidates for epilepsy surgery or other forms of treatment.

II. Why is it important?

Ongoing seizures can be very debilitating, and are often associated with significant morbidity and even mortality. There are high rates of seizure-related injuries (burns, falls), accidental deaths and an elevated suicide rate seen in this population. There also higher rates of sudden unexpected death in epilepsy (SUDEP) in this population. The SUDEP risk is estimated at 1:100 in surgical candidates.

It is very important to identify if a patient is drug-resistant as early as possible-- surgery can be *curative* in a significant number of cases (3). The idea that we can cure epilepsy is relatively new. In the past, the teaching was to move from one AED to the next, or add more agents on if seizures persisted. This would go on for years, resulting often in more side effects and toxicities, but in the drug-resistant group, very little improvement in seizure frequency. There is increasing evidence suggesting referral for surgery earlier in the disease course. Patients with ongoing seizures have been shown to have increasing cognitive dysfunction over time (4). Becoming seizure-free at a younger age can lessen the cognitive, behavioral and psychosocial problems experienced by epilepsy patients, potentially improving social integration. Unfortunately, despite this being a common disorder and increasing number of epilepsy centers, epilepsy surgery is largely underutilized.

Despite the large number of patients living with drug-resistant epilepsy in the US, according to the National Association of Epilepsy Centers, only 2000 patients undergo epilepsy surgery annually (5). In general, about a quarter to a third of patients referred to epilepsy centers have surgery, so really <1% of patients with drug-resistant epilepsy are even referred to epilepsy centers (5). The Multicenter Study for Epilepsy Surgery reported

in Neurology in 2003 that the time to referral for surgery was >20 years in patients who had epilepsy since childhood (6). Much of this delay is due to practitioners who care for patients with epilepsy not identifying patients as drug-resistant, falsely thinking their patient is likely not a surgical candidate, and/or being fearful or concerned about epilepsy surgery (7). There are many misconceptions regarding epilepsy surgery, outlined in a recent piece by Engel in Neurology 2016. These include the notion that all AEDs need to be tried, the presence of bilateral EEG spikes are a contraindication to surgery, the lack of MRI lesion (or presence of multiple lesions) excludes a patient from surgical consideration, presence of poor memory puts patients at higher risk, and the idea that a patient with focal epilepsy and a focal lesion on MRI can have surgery without a thoughtful pre-surgical evaluation. These misunderstandings are largely erroneous, but unfortunately have been potentiated over time. As Dr. Engel wrote at the end of that piece, "Early referral provides the best opportunity to avoid irreversible psychological and social problems, a lifetime of disability, and premature death."(5)

III. What can be done for this population?

Though it is good to consider surgery early in a patient's course, there are several important things to consider for those who either are not interested in surgery or are not good candidates. Perhaps the most important consideration is to optimize medical therapy. One must be sure to use the appropriate medication choice for the specific seizure type or epilepsy syndrome. Adherence must be confirmed before considering a patient drug-resistant. Many of the AEDs have therapeutic windows that should be assessed by periodically checking blood levels to be sure the dose is sufficient, thus excluding pseudopharmacoresistance. Dual therapy should be attempted, which may require reducing the dose of the first AED in order to better tolerate the polytherapy. Seizure-provoking medications should be removed. Optimizing other aspects of the patient's health can also help with seizure control including treatment of co-morbidities including sleep apnea, which is common in this population. Psychiatric or substance use disorders also need to be optimally treated. And of course, confirm the diagnosis of epilepsy is correct, and not a syndrome mimicking seizures, such as a movement disorder or psychogenic non-epileptic seizures.

There are now several types of surgical options including resection, laser ablation or a combination of these. Surgery is not for everyone, and not all patients are good candidates for surgery. Other options for such patients include neurostimulation with devices such as vagal nerve stimulation, responsive nerve stimulation, or diet therapies. The ketogenic diet, based on very low carbohydrate, high fat and adequate protein, has long-been known to be effective for treatment of seizures in children, and recent studies in adults have shown effectiveness as well. The exact mechanism for its effectiveness is not well understood, but seems to be related to the effect of ketones in the body, which are produced when the body is forced to metabolize fat over carbohydrates. One study showed that 40% of patients benefitted from the diet, with a 50% reduction in seizure frequency, and a 10% seizure free rate at 1 year follow up (8). The ketogenic diet has been shown to be effective for all types of epilepsy, both focal and generalized, though close adherence to the diet is crucial for effectiveness and it is best administered/managed at a center with such expertise. It is extremely restrictive, and unpalatable for many, especially adults however, and there are high drop out rates. An alternative, the low glycemic index diet, still heavy on fat and protein consumption but allows some complex sugars, has been tried as well with some positive results (9). More long-term data are needed to evaluate its effectiveness long-term in this population.

Many patients ask about medical marijuana for epilepsy. There are varying anecdotal reports from patients regarding its efficacy; some feel it helps their seizures, some find it worsens them, others find no effect. Though there is no definitive data available at this time, it is currently being responsibly researched in multi-center trials and may ultimately provide an adjunctive treatment if the results are favorable. More data will be needed, however, to determine which epilepsy types/ages/AED regimens respond best and, it will be very important to look at side effects and it has major interactions with many of our traditional AEDs. Devinsky's review summarized current thinking on marijuana for epilepsies as follows:

"We lack valid data on the safety, efficacy, and dosing of artisanal preparations available from dispensaries in the 25 states and District of Columbia with MMJ [medical marijuana] programs and online sources of CBD and other cannabinoids. On the other hand, open-label studies with 100mg/ml CBD (Epidiolex®, GW Pharmaceuticals) have provided additional evidence of its efficacy along with an adequate safety profile (including certain drug

interactions) in children and young adults with a spectrum of TREs [Treatment-Resistant Epilepsies]. Further, Phase 3 RCTs [Randomized-Controlled Trials] with Epidiolex support efficacy and adequate safety profiles for children with DS [Dravet Syndrome] and LGS [Lennox-Gastaut Syndrome] at doses of 10- and 20-mg/kg/day.” (10)

IV. Goals of pre-surgical evaluation: who is a good candidate for surgery?

The main three criteria for determining if a patient is a candidate for epilepsy surgery include 1) Seizures are focal-- the seizures emanate from one area in the brain which could be resected without leaving a deficit, 2) Seizures are drug-resistant-- defined as persistent seizures despite 2 therapeutic AED trials, and 3) Seizures are disabling-- defined by the patient. In order to be considered for surgery, continuous videoEEG monitoring is performed to capture the patient's seizures. Clinical semiology and ictal electrographic pattern are reviewed for concordance, as well as concordance with a lesion (on MRI, or PET), if present.

The presence of a lesion on MRI (such as mesial temporal sclerosis or a focal cortical dysplasia) is correlated with a higher chance of seizure freedom, but it is not mandatory to be considered for surgery. In fact, a study out of the Mayo group reported a series of 40 patients with temporal lobe epilepsy who had normal MRIs but otherwise concordant data who underwent surgery, and 60% were free of disabling seizures at 1yr, 47.5% were free of all seizures including auras (11). In addition, neuroimaging techniques in epilepsy have become quite advanced. Combinations of higher resolution MRI, PET, SPECT, MEG and other techniques allow for visualization of lesions that may not have been identified on single-modality imaging. Thus, the absence of a lesion should not defer practitioners from referring patients for surgical evaluation.

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