

## Epilepsy Management – Key Issues, Challenges, and Developments

a report by

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Across all ages, at a considerable expense of emotional and financial resources to society, epilepsy holds a significant share of neurological morbidity and mortality. Fortunately, the management of epilepsy has evolved due to great developments in the understanding of the pathogenesis of the disease, improvement in the tools for evaluation, and the availability of newer pharmacological and non-pharmacological measures for its treatment. This has resulted in better seizure control and improvement in quality of life (QOL) for a much larger number of afflicted individuals. While concepts in the pathogenesis of the disease are a key building block, the purpose of this review is to focus on the novel aspects of evaluation and management.

Therapy of epilepsy is based on a correct diagnosis of the epilepsy syndrome, appropriate choice of medication(s), early identification of medically refractory epilepsy, and consideration of epilepsy surgery in ideal surgical candidates. Among the options available in clinical practice, anti-epileptic medications and epilepsy surgery form cornerstones in epilepsy management; vagus nerve stimulation and ketogenic diet are the other two considerations that may benefit some individuals in whom good surgical or medication options do not exist. Other forms of magnetic or electrical stimulation of the brain do not have clearly defined roles yet.

### Anti-epileptic Medications

Prior to 1990, there were only six major anti-epileptic drugs (AEDs) available for controlling seizures. These included carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), primidone (PRM), valproic acid (VPA), and ethosuximide (ESM). These medications are effective and are still used in patients with epilepsy; however, as a group, they share some disadvantages. They have significant influence on hepatic enzymes (induction or inhibition), which lead to important interactions with commonly used medications as well as complications if combination AED therapy is warranted. Rapid metabolism of vitamin D and other steroid hormones due to hepatic induction may also lead to adverse effects in reproductive and bone health. The last decade has seen an unveiling of nine new anti-

epileptic medications in the quest of newer and safer treatment options. Eight of them (gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), topiramate (TPM), tiagabine (TGB), oxcarbazepine (OXC), zonisamide (ZNS), and felbamate (FBM)), with the exception of vigabatrin (VGB), have been approved by the US Food and Drug Administration (FDA) and are available for use in the US. All of these medications are indicated as add-on therapy in the treatment of epilepsy and there is gathering evidence supporting their use as monotherapy in select clinical syndromes. Indications for their use in pediatric age groups are also forthcoming due to a concerted effort to increase their availability across all age groups. In contrast to the older anti-epileptic medications, the newer agents share a more favorable side effect profile. The efficacy is not vastly different; however, a smaller risk of adverse effects give these medications a valuable role while formulating a management plan tailored toward the unique needs of any particular patient.

### Medically Refractory Epilepsy

Medically refractory epilepsy is a concept that is relative strictly to the context of its use. First and foremost, one must ensure that there is a 'true' resistance to medical treatment, and not a 'pseudo' resistance, which may result from an inappropriate choice of AED or an inadequate dose of an appropriate agent, incorrect diagnosis, or poor compliance with medications. Thereafter, in clinical practice (as is different from drug trials), the measure of resistance depends upon the number of drugs failed, despite their use over an adequate duration and in therapeutic doses. With an increased choice of medications it is impractical and – as data suggest – unnecessary to exhaust all possible AED regimens to establish medical refractoriness. In a study involving 470 patients of different age groups, 47% of the patients were treated successfully with the first anti-epileptic medication, 13% attained seizure freedom on the second anti-epileptic medication in contrast to only 4% of patients who responded to a third medication or combination drug therapy. Another study that looked at the AED responsiveness in 417 pediatric patients found that 58% of the children who did not respond to the first anti-epileptic medication,

continued to have seizures until the end of follow-up. Although systematic analysis of the effectiveness of subsequent AEDs was not carried out, the authors concluded that if the first AED is not efficacious, the outcome is less favorable.

It is therefore reasonable to conclude that in the face of two failed AEDs, there is little optimism for subsequent agents or combinations of agents to be effective, and this juncture in clinical practice ought to serve as a reminder for careful and detailed analyses of epilepsy syndrome for the identification of surgical candidates.

Adequate duration of AED treatment is unique in different clinical situations and a traditional approach of waiting two years may not be suitable for all patients. Some obvious circumstances where such a wait would be controversial include a low grade neoplasm causing epilepsy, or a surgically remediable syndrome in an infant with catastrophic epilepsy and developmental stagnation. A tailored approach, depending upon the clinical situation, must therefore be used.

### Epilepsy Surgery

Epilepsy surgery is fast becoming a treatment of choice for the management of good surgical candidates where the risk–benefit ratio is in favor of surgery. The earlier reluctance to consider epilepsy surgery stemmed from the fact that surgery is expensive and invasive and carries with it an inherent risk of complications. Improved diagnostic and surgical capabilities coupled with an increased awareness of the significant morbidity and mortality burden of uncontrolled seizures has shifted this tide. The results of a Canadian randomized controlled trial comparing medical therapy with epilepsy surgery may be regarded as a landmark study of recent times, which has upheld the superiority of epilepsy surgery for medically refractory temporal lobe epilepsy.

Identification of ideal surgical candidates is key for availing this treatment approach. Digital video electroencephalogram (EEG) evaluation enables acquisition and realtime analyses of large volumes of data and forms the basis of pre-surgical evaluation. Careful analyses of seizure semiology and EEG features help to initiate a hypothesis of focal compared with multifocal or generalized epilepsy. Brain magnetic resonance imaging (MRI) has superior resolution among the neuroimaging modalities and the anatomic detection of a focal epileptogenic lesion relies heavily on this imaging technique. Subtle cortical malformations are a common substrate of focal epilepsy and a high resolution MRI is instrumental for visualizing such anatomic detail *in vivo*. Presence of a lesion with well-defined margins on MRI, its location (hence surgical accessibility), and its underlying etiology

weighs heavily in prognosis. Supplemental data from functional neuroimaging techniques such as fluorodeoxyglucose positron emitted tomography (FDG-PET) and ictal single photon emission computed tomography (SPECT) may aid further in MRI negative or other focal epilepsy syndromes with complicated EEG findings. Invasive subdural grid recordings are used to better define a diffuse epileptogenic zone, and also to tailor a resection by mapping out the relationship of eloquent cortex relative to the epileptogenic zone. A convergence of data from clinical semiology, EEG, and neuroimaging findings portends good prognosis if the implicated epileptogenic zone can be removed safely and completely.

Most epilepsy surgical centers report 70% to 90% cure rates among surgically remediable epilepsy syndromes. This is a vast improvement over a medically refractory state, where the chance of a new AED to control seizures is less than 5% to 10%. Hippocampal sclerosis and smaller malformations in cortical development tend to be common focal substrates and surgical resection results in the highest seizure-free rates. Patients with mesial temporal epilepsy have a better chance for a seizure-free surgical outcome than those with neocortical temporal epilepsy, and patients with temporal lobe epilepsy have a better surgical outcome than those with extratemporal epilepsy. Promising results may be seen in focal epilepsy syndromes due to large hemispheric malformations, tuberous sclerosis, Rasmussen's encephalitis, neonatal/perinatal stroke, cerebral vascular malformations, and even in 'non-lesional' (i.e. normal brain MRI) cases if all other data is localizing strongly.

### Other Treatment Options

Ketogenic diet is a high-fat, low-carbohydrate and low-protein diet that has been used as an effective and safe medical treatment for seizures in patients with glucose transported deficiency, or pyruvate dehydrogenase deficiency and some patients who have generalized epilepsy with prominent myoclonic seizures. The effectiveness is modest; most patients may achieve a reduction in seizure frequency but only small subset of patients become seizure-free. Evidence suggests that the Atkins diet may also have a therapeutic role due to its ability to induce a ketotic state. Improved cerebral energy reserves and increases in the gamma-amino butyric acid (GABA) shunt activity are the hypothesized mechanisms that control seizures in the ketotic state. The diet is contraindicated in patients with metabolic disorders involving the respiratory chain (mitochondrial disorders) and pyruvate carboxylase deficiency. Adverse effects from the diet may involve reduced bone density, electrolyte disturbances, and those secondary to lipemia (cardiovascular (CV), liver, or hematopoietic dysfunction).

### Neural Stimulation

Vagus nerve stimulation is currently the only approved stimulation therapy. The vagus nerve has diffuse and widespread projections to the thalamus, amygdala, and different cortical regions. Its stimulation on the left side is safe (less risk of bradycardia) and by way of modulating cortical excitability via thalamocortical relay neurons it may favorably influence the generation of primary or secondarily generalized seizures.

A report of the therapeutic and assessment committee of the American Academy of Neurology (AAN) suggests that the degree of seizure control from vagus nerve stimulation (VNS) remains comparable to that of new AEDs. It may be utilized as a safe and effective measure in medically refractory patients who have generalized epilepsy or those patients with focal epilepsy who are poor surgical candidates.

Therapies such as transcranial magnetic stimulation, deep brain stimulation of different targets (thalamus,

subthalamus and hippocampus), or stimulation of neocortical seizure foci are at various stages of development that may emerge in the future as promising therapeutic alternatives.

### Timing of Surgical Intervention

The ability to predict medical refractoriness early in the course of epilepsy (after failure of two or three AEDs) brings the question of timing of surgical intervention for the appropriate surgical candidates with focal epilepsy, to the forefront. Prolonged exposure to seizures and anti-epileptic medications is also associated with a significant psychological morbidity. Rehabilitation is more difficult in patients who have a longer delay from onset of seizures to epilepsy surgery compared with those who do not. Plasticity of a young and developing brain is another important factor that weighs for an earlier intervention in the first few years of life. Prompt relief from severe epilepsy may provide the best and only chance for optimizing developmental outcome in an immature brain. ■

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