

## Drug Resistant Epilepsy- A Review for Non Neurologists

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### Abstract

Many patients present to the primary care physicians with seizures. A large number of patients do respond to this therapy. However, a significant number of patients do not respond to medical therapy. For a multitude of reasons, these patients are not offered surgical option. The possibly most probable cause is lack of knowledge and lack of access to the services. We hereby discuss the options in this review.

**Keywords:** Drug Resistant Epilepsy; Seizures

### Introduction

A large number of patients present to a doctor who is not specifically a neurologist. The patient is thereafter started on antiepileptic drugs and a long course of treatment and investigations begin (Figure 1). A large number of patients are well treated with these antiepileptic drugs. A significant proportion of patients however continue to have seizures despite all best efforts of treatment. These patients, often inappropriately labelled as Drug Resistant Epilepsy, should be referred to an epilepsy centre for further management. Yet there remains some confusion amongst doctors about this condition. We therefore bring forward this article for the benefit of the doctors, non-neurologists and primary care physicians, who form the first line of doctors treating these patients.

### Approach to Patient with Persistent Seizures

Primary physician gets a case of new onset seizure disorders



40% patients remain seizure free despite 1<sup>st</sup> and 2<sup>nd</sup> line antiepileptic drugs



Refer to Epilepsy Centre for accurate identification of type of seizures via history, examination, MRI and video EEG



Surgical and presurgical evaluation for a surgery as soon as possible, after a systematic medical trial and multidisciplinary comprehensive medical care.

**Figure 1:** Approach to Patient with Persistent Seizures.

## Discussion

Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used anticonvulsant drug schedules (whether as mono-therapy or in combination) to achieve sustained seizure freedom (by ILAE). This condition is also known as Medically Intractable Epilepsy [1].

Patients with focal seizures and those with focal seizures to bilateral tonic clonic seizures who have failed appropriate trials of first line anticonvulsant drug should be considered for referral to an epilepsy surgical centre. Surgery is currently an underutilized therapy in drug resistant epilepsy (AAN) [1].

### Following issues should be considered

1. The anticonvulsant drug should be considered appropriately and selected for the individual's seizures or epilepsy type.
2. Adequate dose should be used for a significant length of time prior to the discontinuation of medication trial. An inappropriate ceiling can occur if there is reliance on "therapeutic range" of blood level without taking into account the clinical scenario.
3. Anticonvulsant drugs should be well tolerated and free from disabling side effects.
4. The patient should be compliant to the anticonvulsant drug therapy. The discontinuation of drug due to side effects or non-compliance would not be considered as a failure.
5. Duration of the therapy should be adequate. Post treatment period can be estimated as 3 times longer than pre-treatment seizure frequency or a sustained freedom for 12 months, whichever is longer.
6. The definition stipulates failure of two drugs in monotherapy or combination therapy. Combining antiepileptic drugs with differing mechanisms of action in hopes of improved efficacy has not been proven consistently. It has however been reported that medications with action on sodium channels work well in combination with GABAergic drugs. Adequate polytherapy may produce a 50% reduction in seizure frequency in 30 to 40% patients of previously unresponsive patients.
7. Lifestyle factors contributing to seizure recurrence should be considered (e.g. lack of sleep) [1-6].

### Mechanisms of drug resistance include

- **Transporter Hypothesis:** Over expression of multi drug efflux transporters at epileptic focus.
- **Target Hypothesis:** Alteration of the cellular targets of antiepileptic drugs that lead to less sensitivity of these medications. The mechanisms of drug resistance are not completely understood [6,7].

### Negative predictors for seizure remission include

- a. History of status epilepticus.
- b. Number of failed drug therapies.
- c. Number of tonic clonic seizures.
- d. Neurological insults.
- e. Duration of epilepsy.
- f. Developmental disabilities.
- g. Early onset of epilepsy.
- h. Symptomatic aetiology.

Age plays a role and elderly are more likely to be seizure free on medications.

### Evaluation of Drug Resistant Epilepsy requires

1. Detailed history and examination.
2. Video EEG.

3. High resolution MRI.
4. Functional MRI.
5. PET/SPECT.
6. Invasive EEG
7. Neuropsychological imaging [6-11].

### Treatment options of Drug Resistant Epilepsy

**Resective Epilepsy Surgery:** Complete removal of lesion and epileptogenic zone should be attempted. Causes that are often considered for surgical treatment include follows-

- a. Hippocampal sclerosis
- b. Focal cortical dysplasia
- c. Vascular malformation
- d. Benign tumor
- e. Dual pathology [12].

**Goal of surgery:** Removal of epileptogenic area without causing a permanent neurological deficit.

Epilepsy surgery is considered a gold standard therapeutic option for intractable cases with focal lesion can be localized on presurgical evaluation. Patients with low grade glioma had best outcome followed by MRI visualized malformations of cortical development [12].

### Surgical options include

- a. **Anterior Temporal Lobe Resection for Epilepsy-** in medically intractable mesial temporal lobe epilepsy. Possible side effects include- infection, wounds, stroke, decline in verbal memory. Asymptomatic quadrantic visual field loss is noted in 55% people.
- b. **Lesionectomy-** efficacy in cavernous angioma or glioneural tumours.
- c. **Corpus Callosotomy-** typically used in children or patients with cognitive impairment. This disconnects pathways of seizure's propagation to decrease morbidity of seizures. Most frequently used in Lennox Gestaut syndrome.
- d. **Multiple Subpial Transections-** if resection of epileptic focus is not possible because of its proximity to eloquent cortex. It uses vertical incisions in the grey matter at 4 mm intervals to limit propagation of epileptic activity within eloquent cortex and to reduce seizure spread without disturbing functional integrity.
- e. **Hemispherectomy and Functional Hemispherectomy-** reserved for devastating epilepsy with pathology affecting an entire hemisphere. An entire hemisphere is disconnected or resected. Used in
  - i. Catastrophic epilepsy,
  - ii. Hemispheric malformation of development of cortex,
  - iii. Rasmussen's encephalitis,
  - iv. Sturge Weber syndrome,
  - v. Remote hemispheric vascular insult [12].

### Outcome of surgery depends on-

- Underlying cause of epilepsy.
- Vascular malformation.
- Low grade glioma.
- Dysembryoplastic neuroepithelial tumors.
- Cystic lesions.

These above have a good outcome.

- Cortical dysplastic lesions.
- Post traumatic gliosis.

These above have a high chance of recurrence.

- Bilateral MRI findings.
- Hippocampal sclerosis

These above have a poorer outcome

- History of febrile seizures.
- Disease duration.
- Preoperative seizure frequency.
- MRI lesions restricted to 1 frontal lobe.
- Complete resection.
- Regional or ictal scalp EEG pattern.

Lobar and multilobar resections are becoming more common in patients with tuberous sclerosis and intractable epilepsy. The surgery may have a positive effect on seizure control and cognitive function [12].

**Vagus Nerve Stimulation:** FDA approved it for adjunctive therapy in medically intractable epilepsy. The patients achieve 50 % or greater reduction in seizure frequency. It is used in children above the age of 12 years at this time. It might also be useful in primary generalized epilepsies, drop attacks, and Lennox Gastaut syndrome.

The generator is implanted below the clavicle and stimulating wire is attached to left vagus nerve.

Mechanism is proposed to be desynchronization of thalamocortical activity mediated by thalamic and brainstem nuclei. The exact mechanism is under evaluation.

Benefits are

- i. Decrease in seizure frequency.
- ii. Reduced intensity of seizures.
- iii. Reduced seizure duration.
- iv. Reduced severity of seizures.
- v. Reduced duration of post ictal period [12].

**Responsive Neurostimulation:** Electrodes are implanted near the foci via depth electrode or subdural strips. Seizure pattern detectors trigger cortical stimulation when a seizure is detected. It is approved by FDA for age of 18 years and above with medically refractory partial epilepsy with no more than 2 foci [12].

**Ketogenic Diet:** This has been proposed in treatment of epilepsy. High fat and low carbohydrate diet mimics starvation and induces urinary ketosis. Fats are long chain fatty acids or medium chain triglycerides (latter produces more ketones). Modified Atkin's diet may be used. In comparison to the ketogenic diet that have fat to carbohydrate and protein in a ratio of 4:1 or 3:1, modified Atkin's diet has a fat to carbohydrate ratio of 1:1. Calories and fluids are not restricted in modified Atkin's diet.

No less than 38% patients achieve a 50% reduction of seizures at 3 months.

**The mechanism of the diet may involve**

1. alterations of mitochondrial functions,
2. direct effects of ketones on neuronal function or receptors,
3. antiepileptic drug effects of fatty acids, or
4. glucose metabolism.

Long term outcome reports, however, show a high dropout rate of this diet [12].

**Cell Transplantation and Gene Therapy:** e.g. grafting of fetal cells in hippocampus. Gene therapy to enhance neuronal intubation in the brain appears more promising than attempts to reserve rare monogenic mutations leading to epilepsy [12].

**Radiosurgery with Gamma Knife** can be used in focal epilepsy when seizure focus is located in eloquent or surgically challenging brain regions that are associated with high incidence of complications after open surgery e.g. primary motor cortex, insula, hypothalamus. This has been used in

- a. arteriovenous malformations,
- b. cavernomas,
- c. tumours,
- d. mesial temporal sclerosis,
- e. hypothalamic hamartomas.

Anti-seizure effects can be delayed with unpredictable late complications [12].

**Conclusion**

Patients who are labelled to have Drug Resistant Epilepsy should be carefully evaluated. The episodes should be confirmed to be true seizures. The type of seizures should be well classified. Appropriate treatment should be then initiated. Adequate dose and duration of medicine should be allowed before adding or replacing the treatment. Once the patient is found to be compliant and avoiding other factors and triggers for seizures, treatment modality of surgery and other options should be offered as soon as possible by an epilepsy centre well versed and well equipped to perform such treatments. The treatments improve the quality of life (Table 1), even if they may not be able to completely cure the disease. The surgical options should therefore never be ruled out amongst patients not responding to medical therapy.

Lifestyle Modifications	Drug adherence Seizure precautions Avoid triggers
Medical co-morbidities	Sleep disorders Headache and Migraine Smoking Obesity Traumatic Injuries SUDS Symptomatic seizures Brain tumors Stroke and Brain injury Meningitis and Encephalitis Cerebral Palsy Multiple sclerosis Malformations of cortical development

Behavioural and Psychiatric co-morbidities	Depression Anxiety Psychosis Suicide ADHD Autistic disorders Cognitive impairment
Psychosocial Impact	Social functioning Education Employment Recreational activities
Long term Drug effects	Drowsiness and somnolence Birth defects Reproductive health and Sexual dysfunction Poor coordination Fatigue and weight changes Hormonal dysfunction Decreased bone density and osteoporosis

**Table 1:** Comorbidities and Effects on Health and Quality of Life Associated with Intractable Epilepsy.

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