

## Management Tips of Epilepsy: A Clinician's Guide

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Epilepsy is a ubiquitous disease and is known to antiquity. It is characterized by occurrence of recurrent seizures secondary to disease or dysfunction of the central nervous system. Seizures occur due to abnormal hyper synchronous discharges of cortical neurons and the clinical features depend upon the location and extent of the propagation of the discharging neurons. Acute symptomatic/provoked seizures are defined as clinical seizures occurring at the time of a systemic insult or in close temporal relationship with an acute CNS insult e.g. metabolic, toxic, structural, inflammatory or infectious causes. Epilepsy was defined conceptually in 2005 as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having two unprovoked seizures >24 h apart. Physician should be able to initiate management, alleviate misunderstandings and refer appropriately when required. The latest practical definition accepted by The International League Against Epilepsy (ILAE) considers epilepsy to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked (or reflex) seizures occurring >24 h apart;(2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;(3) diagnosis of an epilepsy syndrome. This revised definition of epilepsy brings the term in concordance with common use.

### Diagnosis

Diagnosis of epilepsy requires detailed history especially information from eyewitness regarding the semiology of seizure. Several conditions like convulsive syncope, transient ischemic attacks, parasomnias and psychogenic episodes(dissociative attacks) may mimic

seizures. A correct diagnosis, rational treatment, reassurance and family education can lead to improved quality of life for an epileptic patient. Though diagnosis of epilepsy is clinical, EEG is an important part of the workup. Neuroimaging preferably MRI (epilepsy protocol)is helpful to evaluate for structural lesions. Video EEG is the simultaneous recording of video and EEG of seizures in patients with epilepsy. It helps to localize the epileptic focus in the presurgical evaluation of epilepsy. It can also help to differentiate dissociative attacks from true epileptic seizures.

### Drug Therapy For Epilepsy- Basic Principles

Medical therapy for seizures is started if patient clearly has proven unprovoked seizures. The principle of AED therapy is to use appropriate mono therapy in full doses before a second drug is added if the response is suboptimal. When starting drug therapy one should start at a lower dose and should gradually titrate to full dose. Selection of the antiepileptic drug is based on the seizure type and side effect profile of the drug, co-morbid illnesses in the patient, and cost of long term therapy. Remarkable non-specificity of therapy is a striking feature of most partial and tonic – clonic epilepsies of adult life, regardless of cause. This is perhaps because the antiepileptic drugs act on the final physiological processes of epilepsy which are similar whatever the cause. Side effects vary, however, more than efficacy, and the choice of drugs is often influenced more by them. Certain AEDs themselves aggravate or precipitate seizures. Carbamazepine, phenytoin, and phenobarbitone can aggravate absence seizures. Carbamazepine, phenytoin, vigabatrin, and lamotrigine can aggravate myoclonic seizures. Benzodiazepine can exacerbate tonic seizures.

About 60% of all epilepsies respond to the first appropriate monotherapy. An additional 10% respond to addition of a second AED. The added value of seizure control of a third AED is to only 3-4% of patients. 25% of patients continue to have seizures

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**Choice of Antiepileptic Drug Therapy Based on seizure Type**

Type of seizure	Drug
Primary generalized tonic-clonic seizures	Valproate, lamotrigine, levetiracetam
Partial seizures, secondary generalized tonic-clonic seizures	Carbamazepine, oxcarbazepine, phenytoin, valproate, lamotrigine
Typical absence seizures	Valproate, lamotrigine, levetiracetam
Myoclonic seizures	Valproate, levetiracetam
Atypical absence, tonic and tonic seizures	Valproate, Lamotrigine, levetiracetam, Topiramate

despite 2 or 3 AEDs. This constitutes medically refractory epilepsy. Common substrates of refractory epilepsy like cortical dysplasia and cavernomas, mesial temporal sclerosis (MTS) can sometimes be identified only on 3 Tesla MRI with special imaging protocols. MTS constitutes over 50% of all refractory epilepsy. The typical history is of childhood febrile seizures followed by refractory focal seizures with dyscognitive features with rare secondary generalization. Many of these patients can be treated by anterior temporal lobectomy, after proper presurgical evaluation. Ketogenic diet consists of a fat to carbohydrate and protein ratio of 3:1 or 4:1. It may be tried in children with intractable seizures, with AED intolerance or side effects, and with specific metabolic defects, or as a bridge to control seizure when patient is considered for surgery.

**Single Unprovoked Seizure- When To Treat?**

5-10% of the population suffer from at least one seizure during lifetime. Not all first seizures mean the beginning of epilepsy. Risk of recurrence of seizure after first event is 40% during lifetime. Most recurrences occur early- 50% of seizures recur within first 6 months. 2 year risk of being seizure free is about the same whether or not AEDs are started after first unprovoked seizure. Most important indicators of recurrence include structural lesions on MRI (strongest predictor), abnormal EEG, partial seizure type, seizure in sleep, postictal motor paralysis and positive family history. Normal routine EEG doesn't rule out epilepsy. First EEG is abnormal in 30-50% of patients and 2 serial EEGs are abnormal in 70-80% of patients after first seizure.

**How To Discontinue Aed?**

Decision to withdraw AED in patient with controlled epilepsy needs expertise and has to be individualized. Continuing or discontinuing the treatment depends upon the risk-benefit ratio. JME may need low dose AED for lifelong. Successful withdrawal of AED is likely in childhood onset epilepsy, in patient with normal EEG, and in adult who is seizure free on AED for 2 or more years. The persistence of spike-wave in those with IGE is the most useful prognostic EEG feature, suggesting a higher chance of relapse. AED should be withdrawn slowly with reduction by 25% of daily dose every 5 elimination half-life. Taper a single AED over 4-6 wks. For the patient on 2 drugs first taper one drug and if seizure free, second withdrawal can be attempted. Of patients who are going to experience a recurrence of seizures on withdrawal, 50% do so during the reduction phase and 25% in the first 6 months after withdrawal.

**Newer-AEDS**

Rufinamide, lacosamide, clobazam, zonisamide and Ezogabine are the drugs which are recently approved in epilepsy. Lacosamide acts on slow inactivation of voltage gated Na channels. Rufinamide acts on fast inactivation of Na channels which is useful in Lennox-gastaut syndrome. Clobazam is benzodiazepine acting on chloride channels. Other drugs include brivaracetam, eslicarbazepine, stiripentol, perampanel and a few others.

**Recent Advances And Future Trends**

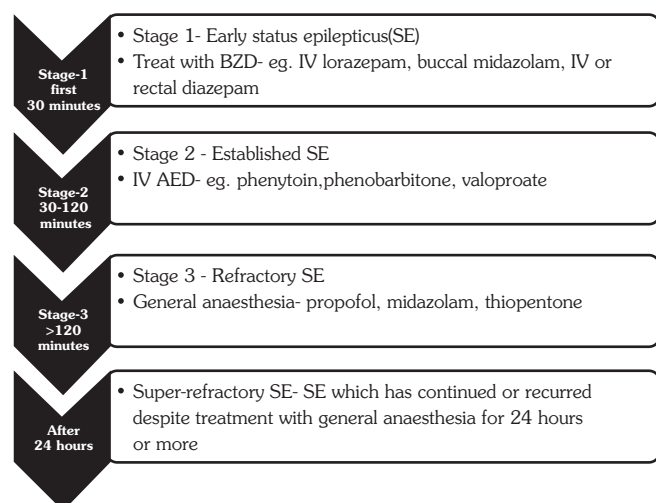
Vagus nerve stimulation has been used as an adjunctive treatment for medically refractory partial-onset seizures

in adolescents and adults. One third of patients had a 50% or greater reduction in seizure frequency. Gamma knife surgery, deep brain stimulation, gene therapy, polymer based therapy, and medical use of marijuana are also being considered for seizures.

### Status Epilepticus

As per latest definition given by neurocritical care society in 2012, status epilepticus is defined as >5 min of (a) continuous clinical and/or electrographic seizure activity or (b) recurrent seizure activity without recovery between seizures. Etiology is the main determinant of outcome of status epilepticus. (IV Benzodiazepines (Lorazepam / Diazepam / Midazolam) are clearly the first line of treatment. IV lorazepam is easily available and at dose of 0.1 mg/kg it has superior efficacy, short latency, prolonged effect >6 hours, and minimal respiratory depression, while diazepam has lower efficacy and effect lasts up to 20 minutes. IV midazolam is also short acting and requires additional drug/dosage)

**Figure-1 : Algorithm for Management of Status Epilepticus**



### Epilepsy in Elderly people

Epilepsy is a frequent and generally under – recognized problem in elderly people .It can be difficult to differentiate seizures from syncope, hypoglycemia, transient ischemic attacks, and transient global amnesia in them. Uncontrolled seizures are likely to be more hazardous in an elderly patient.

In elderly patients, choice of AED and dosing will have to be adjusted to co-morbid disease. Therapy should generally be initiated with lower doses than in the young adult.

Adequate calcium and vitamin D supplementation is essential especially with enzyme inducing drugs. Renal and hepatic function and plasma protein concentrations should be measured before therapy is started. Blood level measurements should be made at regular intervals, for relevant drugs, at least until stable regimens have been achieved. Drug combinations should be avoided especially in elderly where possible. Elderly patients are more vulnerable to drug induced impairment of gait and tremor. Initiate carbamazepine therapy slowly in individuals aged > 65 years, slowly increase the dose. The slow - release formulation causes fewer side effects. The lack of drug interactions, and the simple pharmacokinetics of levetiracetam are advantages in elderly people. Levetiracetam is useful and safe although they should be monitored for behavioral side effects. Lamotrigine is better tolerated in elderly but its clearance is reduced by a third when compared to young. The metabolism of phenytoin can be saturated at lower levels than in young. Frequent serum level measurements are essential. Valproate is effective for generalized tonic-clonic seizures in elderly but its half-life can be doubled in them. Encephalopathic side effects of valproate are more common in elderly. Chrono(slow release) formulation has doubtful advantage if any.

### Issues For Women With Epilepsy (WWE)

Estrogen has neuroexcitatory properties and progesterone has neuroinhibitory properties. Therefore, changes in endogenous and exogenous female hormone levels can influence seizure control. Enzyme inducing drugs increase metabolism of hormones. OC pills have significant drug interaction with carbamazepine, phenobarbitone, phenytoin, topiramate and lamotrigine. Oestrogen is enzyme inducer especially of glycosylation and decreases level of lamotrigine by 30%.Levetiracetam, gabapentin, zonisamide, and valproate don't affect contraception. Depot medroxyprogesterone levels are not affected by

enzyme inducing drugs. Infertility is particularly common in women taking polytherapy. Up to 60% women on valproate get PCOS, usually if drug is started below age of 26.

The major congenital malformations (MCM) most commonly associated with AED exposure include congenital heart disease, cleft lip/palate, urogenital defects and neural tube defects. MCM rates in the general population is around 2%, and women with epilepsy who are not receiving AEDs show similar rates. The lowest rates of malformation were seen with LTG doses of <300 mg/day(2%) and CBZ doses of <400 mg/day(3.4%). The risks of malformation were significantly higher at all evaluated doses of valproate and phenobarbitone. With AED exposure and pregnancy the rates vary between 3.1% to 9%. Usually MCM occurs before 60 days. Preconception

counseling and folate therapy is essential in WWE. High resolution Ultrasound screening or fetal MRI at 18-20 weeks gestation can identify many fetal anomalies. Fetal exposure to valproate is associated with lower IQ and increased risk of autism. Pre pregnancy seizure frequency has important relation with seizure recurrence during pregnancy. Seizure free period over previous 9 months provides over 90% chance of seizure free pregnancy. AEDs are excreted into breast milk to a variable degree. Due to the overall benefits of breast-feeding, mothers with epilepsy can be encouraged to breast-feed. If there is presence of lethargy or poor feeding in infant, change of AED should be considered.