Chapter 116

Indian Guidelines on Epilepsy

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ABSTRACT

Epilepsy is a common neurological disorder affecting about 50 million people worldwide. It has been considered as a public health problem by World Health Organization (WHO), the International League Against Epilepsy (ILAE) and a global campaign was launched against epilepsy in 1997. In India, it was seen that many a times management was suboptimal and antiepileptic drugs (AEDs) are not always chosen and used appropriately by clinicians. Certain important and specific areas of concern include initial diagnosis, drug treatment, management of children and pregnant women with epilepsy and management of poorly controlled seizures and status epilepticus (SE) with limited resources. Moreover, it was felt that there remains considerable scope for the development of better epilepsy services at both primary and secondary care level in a developing country like India. The need for "Guidelines for Epilepsy Management in India (GEMIND)" was discussed in the Indian Epilepsy Society General Body Meeting in the annual conference in 2005. A small core group from among members of the Indian Epilepsy Society was formed and the GEMIND was formulated through a series of meetings in 2008. These guidelines are expected to guide the medical practitioners in providing epilepsy care. However, it remains for the discretion of the physician to modify the guidelines as and when required in the individual patient.

INTRODUCTION

Epilepsy is one of the most common neurological disorders. India is home to about 10 million people with epilepsy (prevalence of about 1%);[1] this being higher in the rural (1.9%) as compared with the urban counterpart (0.6%).[2-4] The number of epileptologists and neurologists is very meager for rendering services to epilepsy patients in India. The burden of epilepsy as estimated using the disability-adjusted life years (DALYs) accounts for 1% of the total burden of disease in the world, excluding that due to social stigma and isolation, that people with epilepsy (PWE) in India face.[5] This in turn leads to escalation of the disease burden. Epilepsy is not benign, especially if not treated. Injury and death can result from poorly treated or untreated epilepsy. Status epilepticus is a serious and potentially life-threatening complication of epilepsy.

WHY DO WE NEED INDIAN GUIDELINES?

Most people with epilepsy are being diagnosed and treated by nonspecialists at both primary and secondary care levels. Therefore, in most of such situations, epilepsy management can be suboptimal. The Indian Epilepsy Society strongly felt for a need to have its own guidelines for the management of epilepsy in India (GEMIND). The guidelines were developed based on a consensus arrived by a group of experts on the good practice parameters relevant to epilepsy treatment in India. The recommendations of the expert group were peer reviewed.[6]

How will it Help?

The GEMIND are expected to help in improving medical decision making in India, mainly at a general physician level. The guidelines are only to be taken as recommendations for management of epilepsy patients. However, the treating physician is the best judge and treatment should be individualized to each patient.

DEFINING EPILEPSY

Epilepsy is a chronic disorder characterized by recurrent unprovoked seizures:

- An epileptic seizure refers to transient occurrence of signs and/or symptoms due to abnormally excessive or synchronous neuronal activity in the brain. The epileptic seizure may be characterized by sensory, motor or autonomic phenomena with or without loss of consciousness.
- All PWE have seizures but all those who have seizures do not have epilepsy. Seizures occurring in a setting of an acute illness or medical condition like high fever, hypoglycemia, etc. are classified as acute symptomatic seizures.

DIAGNOSING EPILEPSY

Detailed clinical history from the patient, the family members and the eye witness (if available) about the event are very important for correct diagnosis.

- Presence of an aura, e.g. motor and/or sensory phenomenon, fear, abdominal discomfort, etc. may help to determine seizure type and localize the site of origin of seizure.
- Ictus/event could consist of unilateral or bilateral tonic clonic movements, sudden jerking, deviation of eyes and head, alteration or loss of consciousness, and may be associated with injuries, tongue bite or incontinence.
- Postictally the patient may have confusion, drowsiness, headache or weakness.
- Video recording of the event on a mobile phone camera will be valuable.
- Special effort has to be made to elicit the history of sudden jerks (myoclonus).
- Careful physical and neurological examinations are important in making a correct diagnosis.
- One should record pulse, blood pressure and look for subcutaneous nodules and examine heart, optic fundi and focal

neurological signs. Developmental assessment should be done in all children.
- Investigations such as electroencephalogram (EEG) help in the diagnosis of seizures, while imaging procedures like computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain may reveal an underlying cause.

CLASSIFICATION

Epilepsies are broadly classified based on the seizure type, age of onset and possible etiology:
- Localization-related epilepsies are characterized by seizures that have a focal or partial onset and generalized epilepsies are characterized by generalized onset of seizures.
- Idiopathic epilepsies are those that are inherited or occur without identifiable pathologic cause.
- Symptomatic epilepsies are those associated with a known or suspected brain disease or lesion.
- Epilepsy syndromes are age specific and may begin during infancy, childhood or adolescence.

INVESTIGATIONS

Electroencephalogram is a noninvasive and widely available investigation for evaluating an individual with suspected seizures. Routine EEG is useful for diagnosis, classification of seizure type and the epilepsy syndrome. There are better chances of detecting abnormalities if EEG is done soon after the seizure or within 48 hours. A normal EEG does not rule out diagnosis of epilepsy and also epileptiform discharges in the EEG may occasionally be seen among healthy adults without history of seizures.

Long-term video electroencephalogram (VEEG) is a time consuming and relatively expensive method of investigating patients with difficult to control epilepsy. Continuous video and synchronized EEG recordings are usually done for more than 24 hours with documentation of at least three or more events. A short-term VEEG (1–2 hours) may be performed in patients in whom psychogenic nonepileptiform events are suspected.

Neuroimaging Studies

Neuroimaging (CT or MRI scan of the brain) is not mandatory for all PWE. Neuroimaging in epilepsy is useful in:
- Focal seizures
- Seizures suspected to be symptomatic in origin
- Difficult to control seizures (MRI using special epilepsy protocol).

Computed tomography scan should be the initial investigation in epilepsy patients in India.

Magnetic resonance imaging may be performed taking into consideration the patient's socioeconomic status and type of epilepsy.

Advanced epilepsy protocols and newer imaging modalities [functional magnetic resonance imaging (fMRI), single photon emission CT (SPECT), positron emission tomography (PET)] should be performed and interpreted by those working in specialized centers.

TREATMENT[7]

The aim of treatment is to control seizures with the most appropriate AED without causing any significant side effects.
Antiepileptic drug therapy should be started only after the diagnosis of epilepsy is confirmed.

Treatment should be initiated following the occurrence of two or more unprovoked seizures, after discussing the risks and benefits of treatment with the person/family members.

Treatment may be deferred under the following circumstances:
- Infrequent seizures with extremely long/several years interval between seizures
- Occurrence of brief (and infrequent partial sensory or myoclonic) seizures without underlying structural lesion.

Treatment of the first unprovoked seizure may be considered under the following circumstances:
- Prolonged focal seizure
- First seizure presenting as SE
- Presence of neurological deficit, hemiparesis, mental retardation, cerebral palsy, etc.
- Family history of seizures among parents, siblings or children
- Electroencephalogram abnormality
- Abnormality on brain imaging (CT, MRI)
- When the patient might have had a seizure before. This may not have been recognized by the patient and may be brought out only by a careful history
- High-risk jobs (professional or other activities that may endanger life)
- The individual and family do not accept the expected risk of recurrence.

Principles of Treatment

Treatment should be started with a single conventional AED (monotherapy). The formulation or brand of AED should preferably not be changed (variations in bioavailability or different pharmacokinetic profiles may increase the potential for reduced effect or excessive side effects). The dose should be slowly built up until seizure control is achieved or side effects occur.

If the initial treatment is ineffective or poorly tolerated then monotherapy using another AED can be tried. The dose of the second drug is slowly increased until adequate or maximum tolerated dose is reached. The first drug is then tapered off slowly.

Combination therapy (polytherapy or adjunctive or "add-on" therapy) can be considered when two attempts at monotherapy with AEDs have not resulted in seizure freedom.

Modified release formulations are convenient but expensive. Once-daily administration should be used with caution in pregnancy.

Choosing the Appropriate Antiepileptic Drug

Phenytoin (PHT), phenobarbitone (PB), carbamazepine (CBZ), oxcarbazepine (OXC) and valproate (VPA) are usually called "conventional" or "first-line drugs". The other AEDs are called "new" or "second-line drugs". It is preferable to use a conventional AED as the initial drug since those are less expensive and the side effects with long-term use are well-known **(Flow chart 1)**.
The newer AEDs can also be used when:
- There are contraindications to the first-line drugs due to coexisting illnesses
- The first-line drugs interact with other drugs; the person is taking (notably oral contraceptives, anticoagulants, antiretrovirals or immunosuppressants).

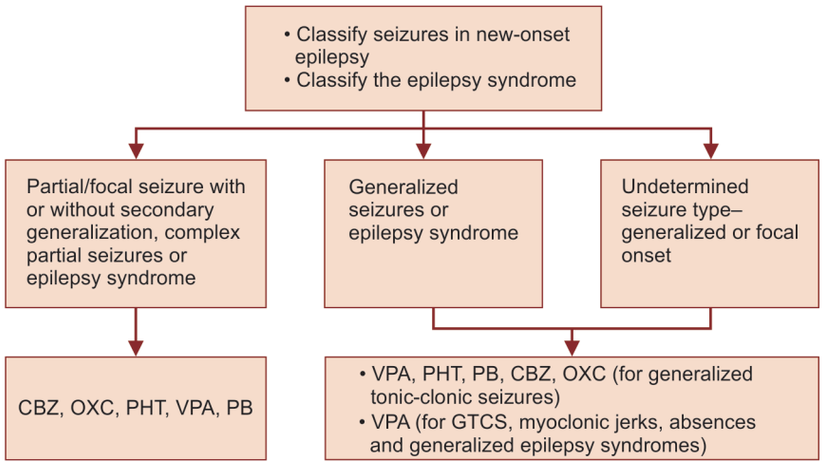
Indications for Monitoring AED Blood Levels

- Detection of AED noncompliance in case of uncontrolled seizures
- Documenting suspected AED toxicity
- Adjustment of AED dose while managing drug interactions
- Specific clinical conditions (e.g. SE, liver or renal disease and pregnancy).

Monitoring the Antiepileptic Drug Therapy

The following tests may be carried out as necessary:
- Complete blood count, liver enzymes and renal functions before starting AED

Flow chart 1: Algorithm for choice of antiepileptic drug (AED) among new-onset epilepsy patients



Abbreviations: CBZ, Carbamazepine; OXC, Oxcarbazepine; PHT, Phenytoin; VPA, Valproate; PB, Phenobarbitone; GTCS, Generalized tonic-clonic seizure

TABLE 1 | Initial and maintenance daily doses and important side effects of commonly used antiepileptic drugs (AEDs)

Antiepileptic drugs (AEDs)	Starting dose in average adults	Maintenance dose in average adults (mg/day)	Important side effects
Carbamazepine (CBZ)	100 mg BID	400–1000	Sedation, dizziness, ataxia, skin rash (occasionally Stevens-Johnson syndrome), hyponatremia, weight gain, seizure worsening in some epilepsy syndromes
Clobazam (CLB)	10 mg OD (HS)	10–30	Sedation, ataxia, somnolence, irritability, depression, weight gain, tolerance (reduced antiepileptic effect)
Lamotrigine (LTG)	25 mg OD (HS); lower dose VPA	100–300	Sedation, ataxia, dizziness, skin rash (occasionally Stevens-Johnson syndrome)
Levetiracetam (LEV)	250 mg BID	1,000–3000	Somnolence, dizziness, cognitive slowing, psychosis
Oxcarbazepine (OXC)	150 mg BID	600–1800	Sedation, dizziness, ataxia, headache, hyponatremia, skin rash
Phenobarbitone (PB)	60–90 mg OD (HS)	60–180	Sedation, ataxia, depression, memory problems, skin rash, hyperactivity in children
Phenytoin (PHT)	200–300 mg OD (HS)	200–400	Ataxia, sedation, gum hyperplasia, coarsening of facial features, hirsutism, memory problems, osteomalacia and bone loss, skin rash
Topiramate (TPM)	25 mg OD	100–400	Sedation, somnolence, cognitive problems, weight loss, word-finding difficulty, renal stones, seizure worsening
Valproate (VPA)	200 mg BID	500–2000	Anorexia, weight gain, nausea, vomiting, tremors, hair loss, polycystic ovarian syndrome, thrombocytopenia
Zonisamide (ZNS)	50 mg OD (HS)	200–500	Sedation, anorexia, renal stones, forgetfulness, skin rash, weight loss, distal paresthesia

Abbreviations: OD, Once daily; BID, Twice daily; HS, At night

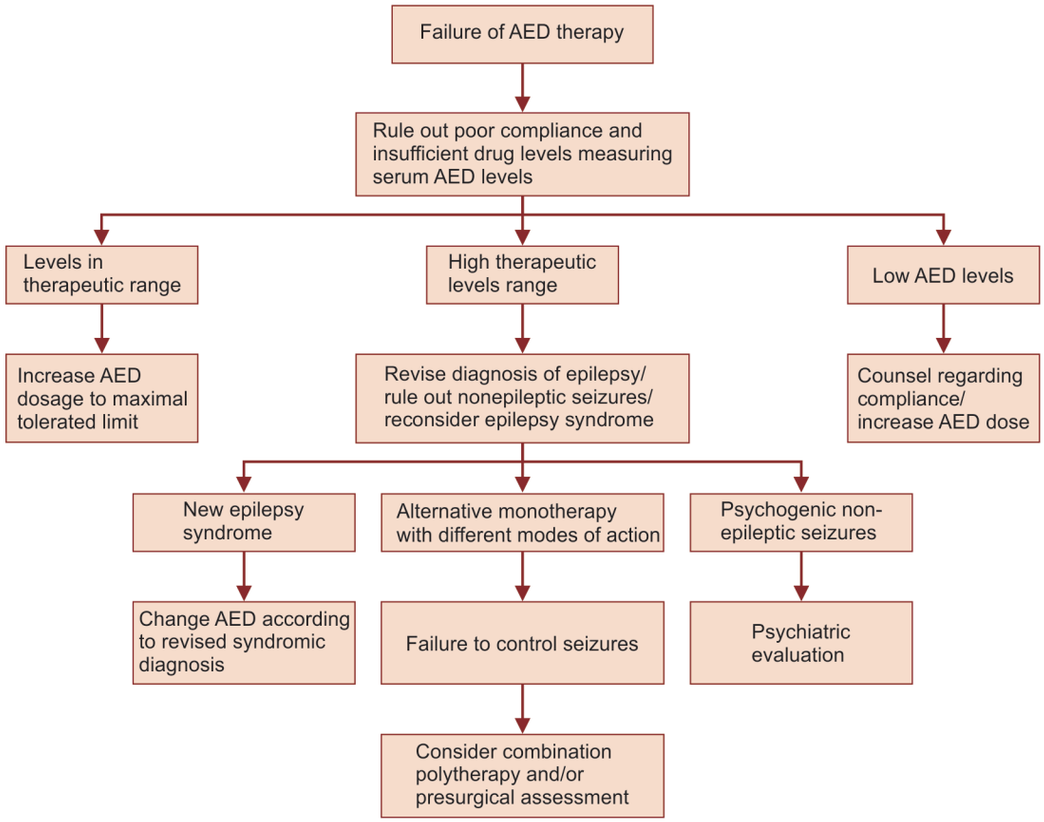
- Calcium (Ca^{++}), alkaline phosphatase (ALP) and other tests of bone metabolism every year for adults taking enzyme-inducing drug.

People with epilepsy should maintain a seizure diary and have regular follow-up. The first follow-up may be undertaken anytime within 2–4 weeks of initiation of treatment and subsequently at every 3–6 months, depending on the control of seizures and side effects **(Table 1)**. Lifestyle issues such as sleep, regular food intake, alcohol use, driving and pregnancy (if planned) should also be discussed.

Drug Interactions

A detailed knowledge of the pharmacokinetics of AEDs and other drugs is necessary to understand the drug interactions. The important points to remember are:

Flow chart 2: Algorithm for strategies in case of failure of initial treatment



Abbreviation: AED, Antiepileptic drug

- Certain AEDs (PHT, PB, CBZ and OXC) induce hepatic enzymes and enhance the metabolism of lipid-soluble drugs. These interact with other AEDs, oral contraceptive pill (OCP) and oral anticoagulants.
- Valproate inhibits hepatic enzymes and slows down the metabolism of concomitant AEDs and other drugs having hepatic metabolism causing toxicity and requiring dose adjustments.
- Drug interactions become important while using AEDs with theophylline group erythromycin, ciprofloxacin or ofloxacin; antitubercular drugs (like isoniazid and rifampicin are enzyme inducers and also hepatotoxic), antiretroviral drugs and mefloquine **(Flow chart 2)**.

Considering Stopping Antiepileptic Drug

Withdrawal in most cases after a seizure-free period of 2–3 years. The decision is mainly based on the type of epilepsy syndrome and cause of seizures and should be taken after discussion of the risks and benefits of withdrawal with the PWE and family. Antiepileptic drugs withdrawal should be avoided in certain epilepsy syndromes (e.g. juvenile myoclonic epilepsy) because of the higher risk of seizure relapse following AED withdrawal.

Antiepileptic drugs are usually withdrawn gradually over several months (at least 3–6 months or longer). There is possibility of seizure recurrence during and after withdrawal.

- The tapering may be performed at a slower rate for benzodiazepines (6 months or longer).
- One drug at a time in those patients who are on multiple AEDs.

If seizure recurs during or after AED withdrawal, the person may be advised to revert to their AED dose before reduction and seek medical help.

TREATMENT IN SPECIAL SITUATIONS

Women with Epilepsy

Women with epilepsy (WWE) who continue appropriate AEDs under proper supervision have more than 90% chance of having a normal pregnancy and children. Doctor should keep in mind the possibility of marriage and pregnancy in all WWE who are in the reproductive age group.

All WWE should be advised to plan their pregnancies. They should be cautioned that some AEDs may make OCPs ineffective. Barrier contraception is an alternative that can be considered.

All WWE in the reproductive age group should be started on folic acid (5 mg/day) at the time of starting AED. The risk of major fetal malformations is approximately 5% more than that among children born to WWE who are exposed to AEDs as compared to that of unexposed fetuses, which is around 2–3%. The risk is further reduced when the mother is using monotherapy (a single AED) at low dose along with folic acid. Based on the currently available data, there is no superiority for one AED over the other with regard to fetal malformations. Nevertheless VPA at higher doses carries higher risk for neural tube defects. Seizures may remain unchanged in 50% WWE or improve (25%) or even worsen (25%) during pregnancy. Thus, the situation needs to be carefully reviewed by neurologist and the patient should be maintained on the lowest effective dose.

If a woman had an offspring with malformation in the previous pregnancy, the AED therapy need to be carefully reviewed and if necessary, the AED could be changed prior to the next pregnancy.

Antiepileptic drugs should be continued in pregnancy. All pregnant WWE should be advised screening for fetal malformations by serum alpha fetoprotein at 16 weeks and by detailed ultrasound scanning by an experienced ultrasonologist at 18 weeks. If preterm labor is threatened in women taking enzyme-inducing AEDs, 48 mg betamethasone (double the normal dose) should be given over 48 hours.

All WWE should be given two doses of vitamin K 10 mg intramuscularly (IM) at 34 and 36 weeks of pregnancy, unless there is a contraindication for the same. All infants born to mothers taking AEDs should be given vitamin K 1 mg IM at birth.

Seizures during labor should be terminated as soon as possible using intravenous (IV) lorazepam (4 mg IV) or diazepam. If seizures persist, those should be managed as done for SE. If seizures recur during labor, particularly after prolonged remission, other etiological possibilities such as cortical vein thrombosis, eclampsia and other causes should also be considered. All WWE should be encouraged to breast-feed their babies.

Epilepsy in Children and Neonates

There are many subsyndromes and subtypes of epilepsies peculiar to neonates, infants and children. Subtle manifestations of seizures are common in neonates and infants and these must be looked for very carefully. Identifying the type and choosing the appropriate drug and the dosage is of utmost importance. Electroencephalogram and neuroimaging studies (MRI of brain) are required in most of the children. Although the basic principles of therapy are the same there are some special situations.

Febrile Seizures

Febrile seizures (FS) occur during fever between 6 months and 5 years of age in the absence of intracranial infection. Single FS occur in 3–5% children. Recurrent FS occur in about one-third to half the cases with FS. Recurrence is higher if the onset is within the 1st year of life. Febrile seizures may be simple or complex and this classification helps to prognosticate. Complex FS comprise only 15% of FS, are characterized by partial onset, duration more than 15 minutes or multiple episodes in the same illness, and have a poorer outcome compared to simple FS. Infections like meningitis need to be ruled out especially in those presenting in the 1st year. There is no consensus about prophylaxis. Parents can be taught to use rectal diazepam (0.5 mg/kg), preferably a liquid or suppository formulation or buccal midazolam (0.2–0.3 mg/kg) for acute termination of seizures lasting more than 2 minutes. Intermittent prophylaxis with oral clobazam (CLB) in a dose of 0.75 mg/kg for 2–3 days in two divided doses is most useful drug in preventing recurrence. However, it does not prevent future risk of developing epilepsy.

West Syndrome and Infantile Spasms

In West syndrome, corticotropin or corticosteroids should be used as first-line treatment. Such children are best treated by a specialist. Other drugs such as benzodiazepines, VPA, vigabatrin and topiramate are used as second choice.

Children with Cerebral Palsy, Mental Retardation and Learning Disability

Although cerebral palsy (CP) and mental retardation (MR) are nonprogressive or static problems, seizures can become uncontrolled or increase in severity and number, thus adding to the disability of patients and anxiety to caregivers. The risk of cognitive problems among PWE is higher due to the disease and AEDs.

Most AEDs can be used safely in such PWE. Caution is required while using PB (due to associated hyperactivity) and topiramate (TPM) (associated word-finding difficulty) in those in whom speech and language may already be affected. It is important on the part of treating physician to distinguish nonepileptic events which can be very difficult in children as compared to adults.

Epilepsy in Adolescents and Young Adults

Important points to remember are:

- Avoiding sleep deprivation, alcohol and substance abuse, driving, potentially risky leisure activities like rock climbing, horse riding, etc. prolonged television (TV) viewing, playing video games and dancing in dark rooms with flickering/flashing lights (discotheques).

Epilepsy in Elderly

Generalized tonic-clonic seizures dominate for metabolic or toxic etiologies, whereas partial seizures with or without secondary generalization are most frequent for vascular or other circumscribed brain lesions. A convulsive SE (tonic-clonic) is more frequent at an advanced age as compared to younger age group. Patients with nonconvulsive status epilepticus (NCSE) may not have clinical seizures and usually present with history of sudden change in mental status. Every elderly patient with epilepsy should undergo, at least a CT scan, though MRI is preferable as symptomatic epilepsy is common in elderly. The choice of AEDs in elderly depends on many factors: changes in liver, kidney, gastrointestinal (GI) system and brain itself. Bioavailability of the drug in elderly is altered. Existence of comorbid conditions in elderly may cause interaction with AEDs and other drugs leading to AED toxicity or other complications. Phenytoin, CBZ and VPA as well as most of the newer AEDs can safely be used in the elderly.

SURGERY IN EPILEPSY

All patients with medically intractable epilepsy (MIE) should be evaluated at a center performing epilepsy surgery. A patient having MIE with an identifiable lesion on imaging, correlated with electrophysiology [Electroencephalogram (EEG), Vidio EEG] is a potential candidate for epilepsy surgery. Even if imaging is negative, patients still can be surgical candidates on further investigation. Epilepsy surgery should be done only in specialized centers.

Surgery has a high chance of achieving seizure freedom (in 60–70% of cases) and a reduction in seizure frequency in the remaining 30–40% cases. When indicated it should be considered as early as feasible rather than an option of last resort.

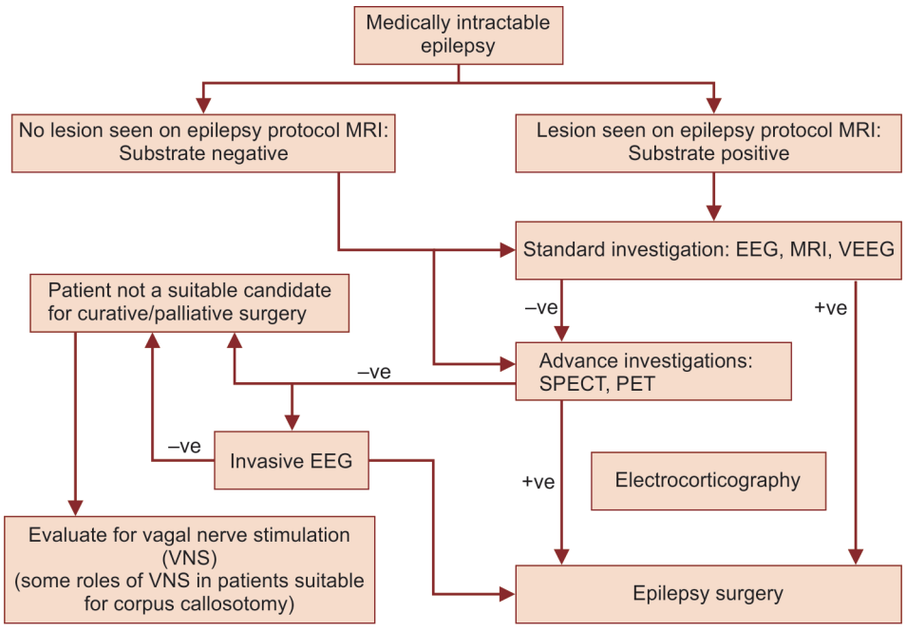
Epilepsy surgery may be resective or nonresective. Resective surgery includes lesionectomy (resection of the lesion and the surrounding epileptogenic area), amygdalohippocampectomy with or without temporal lobe resection, multilobar resection and hemispherectomy. Nonresective surgery includes multiple subpial transections corpus colostomy and vagus nerve stimulation (VNS).

MEDICALLY INTRACTABLE EPILEPSY

Medically intractable epilepsy (synonyms: intractable epilepsy, difficult to control epilepsy, refractory epilepsy, therapy resistant epilepsy) is defined as:

- Those in whom epilepsy is not controlled by two or more appropriate AEDs used in their optimal dosage.
- Adults (16 years or above) who continue to have seizures even after 2 years of treatment.
- Pediatric epilepsy patients can be labeled as MIE much earlier (sometime even within weeks of onset of seizures), if they present with epileptic encephalopathy, infantile spasms, catastrophic

Flow chart 3: Algorithm for approach to patients medically intractable epilepsy



Abbreviations: MRI, Magnetic resonance imaging; EEG, Electroencephalogram; VEEG, Video electroencephalogram; SPECT, Single photon emission computed tomography; PET, Positron emission tomography

onset of epilepsy, seizure frequency of more than one per month and disabling seizures **(Flow chart 3)**.

CONCLUSION

The guideline is intended to act as a working model for managing patients with epilepsy in India. Every medical practitioner needs to combine guidelines with his/her own skill, knowledge and experience keeping in mind the needs of individual patients. With so many new AEDs in the market, a physician might be tempted in trying them out but the first-line AEDs still remain the most preferred agents in India considering their wide availability, known long-term toxicity profile, wide experience with these agents and cheap price. Since a patient has to take these drugs for a long time and ensuring drug compliance is a key issue, appropriate choice of the drug is important.

The physician should choose the drug after taking into consideration the seizure semiology as well as the socioeconomic status of the patient.

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