

## **TREATMENT OF EPILEPSY**

- The aim of treatment is to control seizures with the most appropriate antiepileptic drug (AED) without causing any significant side effects.
- Treatment of epilepsy with AEDs should be started after confirming the diagnosis of epilepsy.
- Treatment should be initiated following the occurrence of two or more unprovoked seizures, after discussion about the risks and benefits of treatment with the person with epilepsy and his/her family members.

### **Treatment of the first unprovoked seizure**

Epilepsy should not be diagnosed after a single seizure. The average risk of developing a second seizure following a single unprovoked seizure is about 35-40%. Many individuals with a first seizure if left untreated may not have a second seizure. The risk of a third seizure following two unprovoked seizures is much higher.

Generally the first seizure is not treated. The individual and family are explained about the possible risk of recurrence and need for follow up. Patients with the first seizure may be treated in the following circumstances.

### **Circumstances in which a single seizure may be treated**

1. Prolonged focal seizure
2. First seizure presenting as status epilepticus
3. presence of neurological deficit, hemiparesis, mental retardation, cerebral palsy etc.
4. Family history of seizures among parents, siblings or children.
5. EEG abnormality
6. Abnormality on brain imaging (CT, MRI)
7. 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.
8. High risk jobs (Professional or other activities that may endanger life during a seizure)
  9. The individual and family do not accept the expected risk of recurrence

### **Treatment of newly diagnosed epilepsy**

- AED therapy is generally recommended after a second unprovoked epileptic seizure.
- AED therapy should be started only after the diagnosis of epilepsy is confirmed.
- AED treatment may occasionally 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.
  - Benign epilepsy with centro-temporal spikes (Rolandic epilepsy in children).

The decision in such situations should be taken by a specialist.

### **Principles of AED treatment**

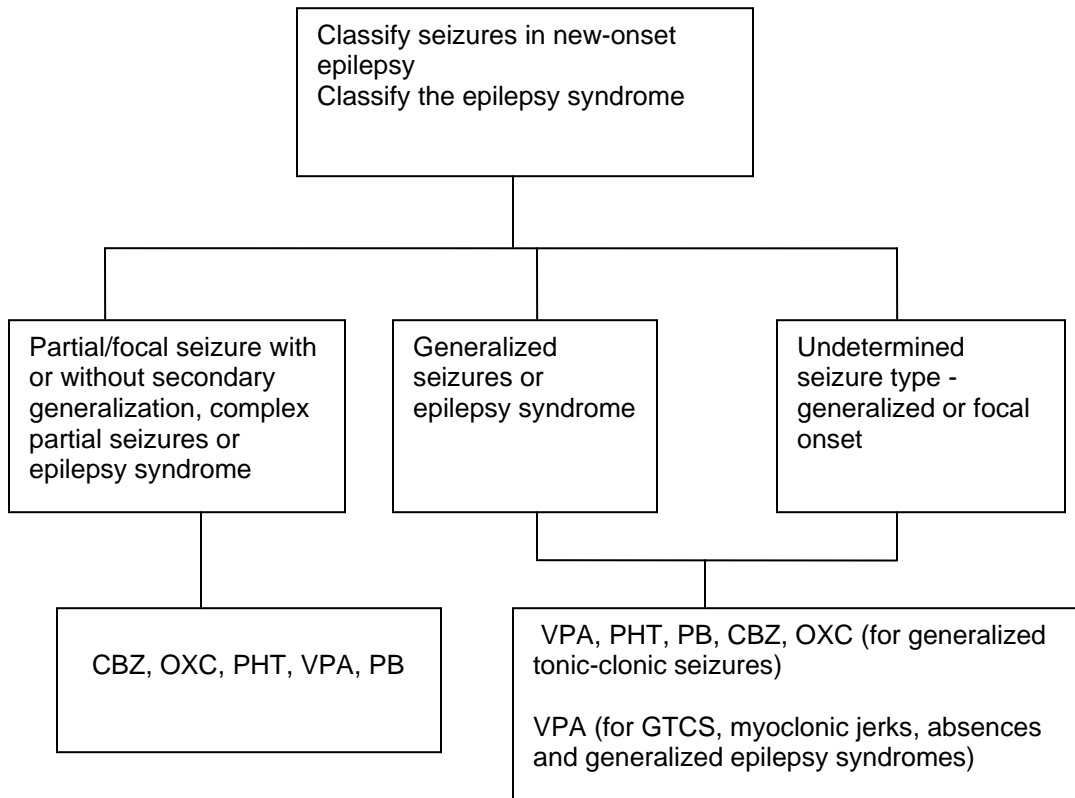
- The decision to start AED treatment should be made after discussion of the risks and benefits of treatment and taking into account the person's seizure type, prognosis, lifestyle and socioeconomic circumstances.
- Treatment should be started with a single conventional antiepileptic drug (AED monotherapy).

- Start with a low dose and gradually increase the dose until seizures are controlled 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.
- If the second drug is also unhelpful, the drug with lesser efficacy or tolerability should be taken off.
- 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.
- If seizures continue despite trial with two AEDs, patient should be referred to a specialist for evaluation.
- 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).
- Modified release formulations offer ease of administration due to less frequent dosing and better compliance. These are costlier than regular formulations.
- Once daily administration of AEDs should be used with caution during pregnancy.

## Choice of AEDs

- Phenytoin (PHT), Phenobarbitone (PB), Carbamazepine (CBZ), Oxcarbazepine (OXC), 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.
- The choice of AED is mainly based on the seizure type and epilepsy syndrome. For partial seizures, the initial choice can be CBZ, OXC, PHT, VPA or PB.
- For generalized onset tonic clonic seizures, the initial choice is VPA, PHT, PB, CBZ, OXC. For absence seizures VPA is the drug of choice. For myoclonic jerks, VPA and benzodiazepines are generally used.
- Prior to initiating treatment it is preferable to have baseline blood counts, liver enzymes and renal functions tested.

## Algorithm for choice of AED among new-onset epilepsy patients



**Table. Initial and maintenance daily doses and important side effects of commonly used AEDs**

AED	Starting dose in average adult	Maintenance dose in average adults (mg/day)	Important side effects
Carbamazepine (CBZ)	100 mg BID	400 -1000	Sedation, dizziness, ataxia, skin rash (occasionally Steven-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 anti-epileptic effect)
Lamotrigine (LTG)	25 mg OD (HS) Lower dose with VPA	100-300	Sedation, ataxia, dizziness, skin rash (occasionally Steven-Johnson syndrome)
Levetiracetam (LEV)	250 mg BID	1000-3000	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
Topiramate (TPM)	25 mg OD	100-400	Sedation, somnolence, cognitive problems, weight loss, word finding difficulty, renal stones, seizure worsening
Zonisamide (ZNS)	50 mg OD (HS)	200-500	Sedation, anorexia, renal stones, forgetfulness, skin rash, weight loss, distal paresthesiae

OD: Once daily

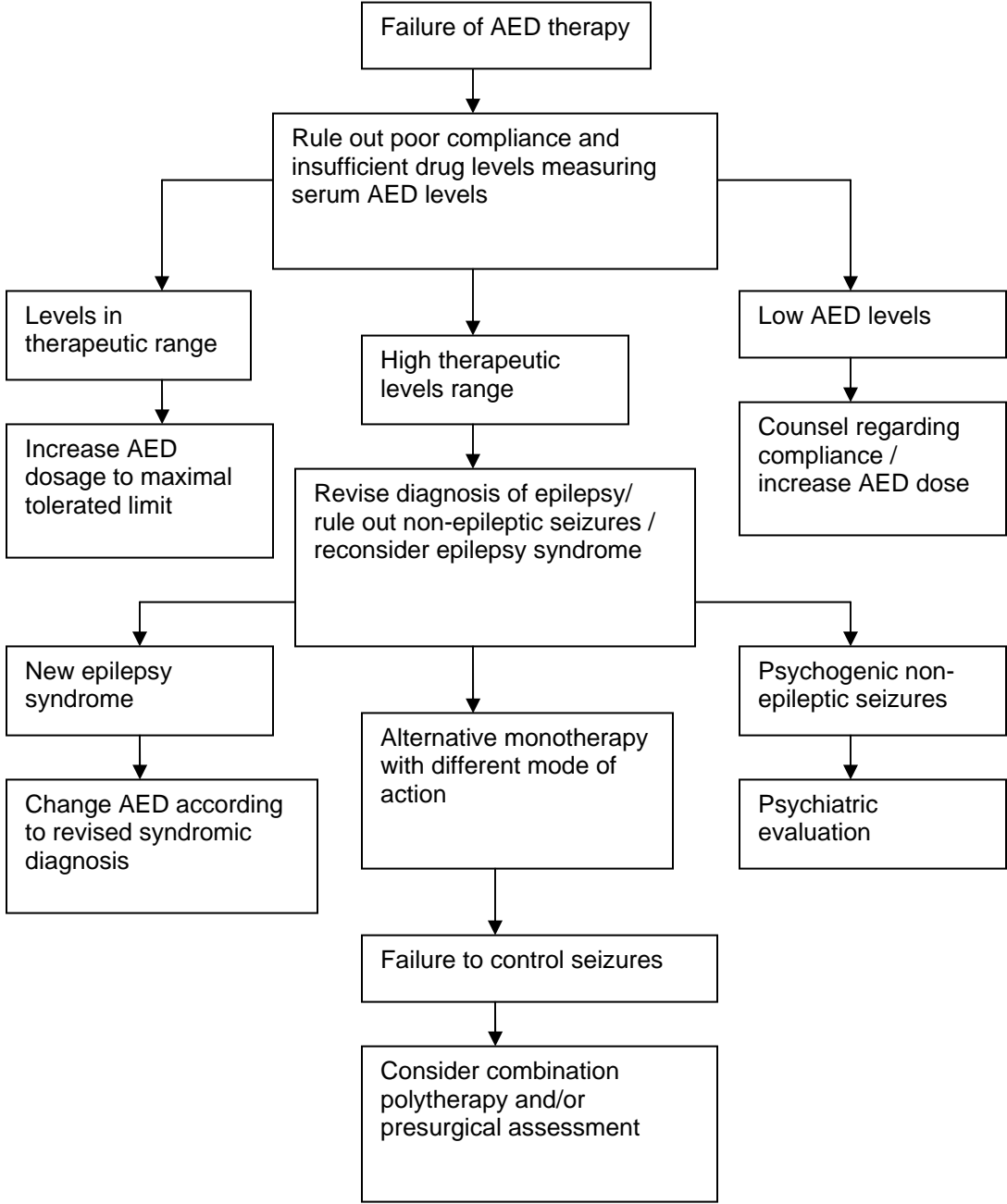
BID: Twice daily

HS: At night

## **Strategies in case of failure of initial treatment**

- Failure of an initial AED should prompt the treating doctor to ascertain the accuracy of the diagnosis of epilepsy, the seizure type or syndrome; the appropriateness of the drug for the particular seizure type, the adequacy of dosage, compliance of the individual and whether there are any remediable structural or other causes for epilepsy.
- All PWE should be asked to note down what happens before and during a seizure and to maintain a 'seizure diary'. They should be encouraged to make a record seizure on a cell phone camera. This will help the treating doctor in arriving at a correct diagnosis.
- Attempt should be made to optimize the AED therapy by using maximally tolerated doses, ensuring compliance and avoiding seizure precipitants.

**Algorithm for strategies in case of failure of initial treatment**



### **Role of AED level monitoring**

- Routine monitoring of AED blood levels is not recommended and should be done only when clinically indicated.

Indications for monitoring AED blood levels:

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

### **Routine laboratory tests during AED therapy**

The following tests may be carried out as necessary:

- Complete blood count, liver enzymes and renal functions before starting AED.
- Serum calcium, alkaline phosphatase and other tests of bone metabolism every year for adults taking enzyme-inducing drug.
- Asymptomatic minor abnormalities in blood test results are not necessarily an indication for changes in medication.

### **Role of newer AEDs**

The newer AEDs (Gabapentin, Lamotrigine, Levetiracetam, Tiagabine, Topiramate, Vigabatrin and Zonisamide) are recommended for the management of epilepsy in people who have not benefited from treatment with the

conventional AEDs or for whom the older AEDs are unsuitable because of intolerable adverse events. The new AEDS are almost as effective as the conventional drugs but do add significantly to the cost.

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, anti-retrovirals or immunosuppressants).
- Always consider factors such as cost and continued availability of medicines before starting newer AEDs.

### **Drug interactions**

There are many interactions between different AEDS and between AEDs and other drugs that the patient might be taking. A detailed knowledge of the pharmacokinetics of AEDS and other drugs is necessary to understand the drug interactions. The important points to remember are:

- Certain AEDs (PHT, PB, CBZ and OXC ) induce hepatic enzymes and enhance the metabolism of lipid soluble drugs. Enzyme induction results in rapid clearance and reduced efficacy of other drugs requiring adjustment of the dose of other drugs to a slightly higher level. These interact with other AEDs (necessitating higher dose of concomitant AEDs)

- oral contraceptives and oral anticoagulants.
- VPA inhibits hepatic enzymes and slows down the metabolism of concomitant AEDs and other drugs causing toxicity and requiring dose adjustments.
  - Drug interactions become important while using AEDs with theophylline group erythromycin, ciprofloxacin or ofloxacin; anti-tubercular drugs (like isoniazid and rifampicin are enzyme inducers and also hepatotoxic), anti-retroviral drugs and mefloquin.

### **Frequency of follow-up**

- People with epilepsy should maintain a seizure diary and have regular follow-up to ensure that the prescribed medication is taken as advised and to detect any adverse effects of AED. This will also avoid a situation in which they continue to take treatment that is ineffective or poorly tolerated.
- The first follow-up may be undertaken at anytime within 2-4 weeks of initiation of treatment. Subsequent follow-ups at every 3-6 months, depending on the control of seizures and side-effects.
- The doctor should review the seizure diary ( Appendix III) to assess efficacy tolerability and ensure AED compliance. Lifestyle issues such as sleep, regular food intake, alcohol use, driving and pregnancy (if planned) should also be discussed.
- PWE and their care givers should be provided information about the disease, maintaining seizure diary, counselling services, and timely and appropriate investigations.

- In patients with poorly controlled seizures or unacceptable side effects due to AEDs, consider referral to tertiary services for appropriate diagnosis, investigations and advanced treatment including surgery for epilepsy.

### **When to refer to a specialized 'Epilepsy Centre'**

An individual should be referred to a specialized epilepsy centre:

- Seizures controlled despite use of maximum tolerated dose of 2 AEDs
- Seizures are controlled even after 2 years of starting AEDs
- The diagnosis of seizure type and/or syndrome is not certain
- The individual experiences unacceptable side effects of medication
- Abnormal behaviour, progressive deterioration in the intellect, associated psychological and/or psychiatric co-morbidity
- There is a remediable structural lesion that could be the cause of epilepsy

### **Withdrawal of AEDs**

- Withdrawal in most cases after a seizure-free period of two to three 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.
- AED withdrawal should be avoided in certain epilepsy syndromes (e.g., juvenile myoclonic epilepsy) because of the higher risk of seizure relapse following AED withdrawal.

### **How to withdraw AEDs**

- AEDs 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).
- Withdraw 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.

### **PRACTICE POINTS**

- Establish the diagnosis of epilepsy before starting treatment.
- The choice of AED should be based on seizure type, epilepsy syndrome (appropriate drug), affordability and availability of AEDs.
- Initiate treatment with monotherapy. Use polytherapy with caution when monotherapy is not successful.
- The principle, “***start low and go slow***” should be followed for AED dosages.
- Maintain seizure diary, ensure regular follow up and AED compliance.
- Conventional AEDs are generally as effective as newer AEDs and should be the first line of treatment in most cases.
- Consider AED withdrawal after 2 years of seizure-free interval.
- When in doubt or in case of an unexpected situation, refer to a specialist!