Chapter

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Optimizing Management of Seizure Disorders

V NAGARAJAN

INTRODUCTION

Seizure disorders are met with by every consultant in practice almost everyday. In the management of seizure disorders, even though concerned with the Neurologist- it is mandatory that a consultant should be aware of the management on an elementary but firm basis. Before establishing EEG diagnosis especially in a country like India, wherein sophisticated management is expensive. The majority of population needs management on a clinical basis. The basic knowledge is necessary to exclude a structural lesion and knowledge to exclude them on clinical basis is absolutely necessary. The introduction of high cost investigations has extended the total cost of management of seizure disorder[1]. The knowledge of clinical assessment of seizure disorder definitely cuts down the cost of the diagnosis and management. The successful management of seizure disorder is often focused in the following 9 targets:

1. Diagnosis
2. When to start the anti-epileptic drug (AED)
3. Choosing medications
4. Initiating treatment
5. Awareness of interaction with patients
6. Detecting non-compliance
7. Side-effects of drugs in the management of epilepsy
8. AED blood level monitoring
9. Discontinuing the management finally.

CLINICAL DIAGNOSIS — SEIZURE SEMIOLOGY

Witnessing a seizure is important so as to recognize the seizure type. At least history could be obtained through the witness, who actually sees the seizure phenomenon. Especially, distinction should be made between focal epilepsy and idiopathic generalized epilepsy. A clear history from the patient regarding the aura and an eye-witness of the attack gives the most relevant diagnostic information and can be the mainstay of diagnosis.

- Focal onset, becoming a generalized seizure
- Seizures are most often due a structural cause. Idiopathic epilepsy seldom has a focal onset
- A clear picture of seizure events most often helps to arrive at correct diagnosis
- Remember, the EEG is not routinely indicated in all seizure disorders and should not be performed to exclude a diagnosis of epilepsy. The EEG is always supportive where clinical history indicates high probabilities of an epileptic seizure or epilepsy.

EEG should be supportive for the classification of seizures and syndromes of epilepsy and a necessity towards the management as well as to understand photo-paroxysmal response especially towards alcohol induced seizures.

Pharmacokinetics Nature of AEDs

The basic side-effects of AEDs are dependant on the pharmacologic character of the drugs (Table 1).

Enzyme inducing AEDs - CBZ, oxycarbamazepine, phenobarbitone, phenytoin, primidone, topiramate.

- Non-enzyme-inducing agents like acetazolamide, BDZ, ethosuximide, gabapentin, lamotrigine, levetiracetam, Tiagabine.

Table 1: Pharmacokinetics of established antiepileptic drugs

Drug	*Absorption (bioavailability)*	*Protein binding (% bound)*	*Elimination half-life (hours)*	*Route(s) of elimination*	*Comments*
Carbamazepine	Slow absorption (75-85%)	70-80	24-45 (single) 8-24 (chronic)	Hepatic metabolism Active metabolite	Enzyme inducer Metabolic autoinduction
Clobazam	Rapid absorption (90-100%)	87-90	10-30	Hepatic metabolism Active metabolite	Sedative Tolerance
Clonazepam	Rapid absorption (80-90%)	80-90	30-40	Hepatic metabolism	Sedative Tolerance
Ethosuximide	Rapid absorption (90-95%)	0	20-60	Hepatic metabolism 25% excreted unchanged	More rapid clearance in children
Gabapentin	Rapid initial absorption	0	5-7	Not metabolized, Excreted unchanged	Limited absorption at high doses
Lamotrigine	Rapid absorption (95-100%)	50-55	14-88	Hepatic metabolism by glucuronidation	Half-life dependent on co-medication
Phenobarbitone	Slow absorption (95-100%)	48-54	72-144	Hepatic metabolism 25% excreted unchanged	Enzyme inducer Sedative
Phenytoin	Slow absorption (85-90%)	90-93	9-40	Saturable hepatic metabolism	Tolerance Enzyme inducer
Sodium valproate	Rapid absorption	88-92	7-17	Hepatic metabolism	Elimination half-life concentration-dependent
Topiramate	Rapid absorption	15	12-30	Active metabolites Mostly hepatic metabolism with renal excretion. No active metabolites.	Enzyme inducer Concentration-dependent protein binding
Vigabatrin	Rapid absorption (60-80%)	0	5-8	Not metabolized 85% excreted unchanged	Cognitive slowing, kidney stones, weight loss.
Levetiracetam	Rapid absorption (100%)	< 10	7 – 7.5	Not metabolized 95% in urine, 0.3% in feces	Clearance increased by enzyme inducers. Visual field constrictions Non-enzyme inducer

IMAGING

- Brain imaging is not routinely indicated where there is a confident diagnosis of idiopathic generalized epilepsy especially where the response is rapid and controllable with first-line of AEDs.
- MRI is the imaging of choice, if imaging is needed in seizure disorders; but CT is indicated when there is contraindication for MRI[2].

GOAL OF PHARMACOLOGY

- Old thoughts revolved around the fact that the goal is only to achieve "Arrest of Seizures", irrespective of side-effects and complications
- Presently, emphasis is on enabling the epileptic patients to lead a normal lifestyle consistent with their capabilities with high quality life
- Presently, focus for quality treatment is with the accurate diagnosis of seizure type, measurement of seizure frequency, as well the severity of seizure episodes. Referral to a Neurologist is to begin the management but the maintenance if absolutely by the primary care physicians. It is evaluated by monitoring the side effects, and psychosocial problem of AEDs. Clinical implications are more to be considered in the treatment of seizure disorder[3,4].

Table 2 shows the various side-effects of commonly used AEDs in practice.

Diagnosis

- Observation — establish the seizure type. This determination is mandatory for selection of the proper AED.
- IALE classification is a helpful framework to follow to classify the seizure type. Moreover, the history which focuses over the triggering factors, behavior, environmental factors, which provoke the seizure episodes, has to be considered.

Table 2: Side-effects of established anti-epileptic drugs

Drug	*Dose-related side-effects*	*Idiosyncratic side-effects*
Carbamazepine	Dizziness Headache Nausea Drowsiness Neutropenia Hyponatremia Hypocalcemia Orofacial dyskinesia Cardiac arrhythmia	Morbilliform rash* Agranulocytosis Aplastic anemia Hepatotoxicity Photosensitivity Stevens–Johnson syndrome Thrombocytopenia Pseudolymphoma Teratogenicity
Clobazam	Drowsiness Dizziness Ataxia Aggression Hypersalivation Bronchorrhea Weight gain Psychosis	Rash
Clonazepam	Drowsiness Dizziness Ataxia Aggression (children) Hyperkinesia (children) Hypersalivation Bronchorrhoea Psychosis	Rash Thrombocytopenia
Ethosuximide	Anorexia Agitation Drowsiness Headache Lethargy	Rash Erythema multiforme Stevens-Johnson syndrome Lupus - like syndrome Agranulocytosis Aplastic anemia
Gabapentin	Ataxia* Fatigue* Diplopia* Paresthesia Amnesia	Increased Seizures*
Lamotrigine	Diplopia* Ataxia Insomnia Tremor* Nausea Vomiting Aggression Irritability	Rash* Stevens–Johnson syndrome Toxic epidermal necrolysis Liver failure Aplastic anemia Pancytopenia Multi-organ failure
Vigabatrin	Diplopia* Irritability* Depression* Psychosis Aggression Weight gain Stupor Tremor Impaired concentration	Visual Field Defects* Increased Seizures
Piracetam	Diarrha* Weight gain* Insomnia Depression Hyperkinesia	
Phenobarbitone	Fatigue* Listlessness* Tiredness* Depression*Insomnia (children)* Distractibility (children)* Hyperkinesia (children)* Irritability (children)* Aggression Memory disturbance Decreased libido Impotence Folate deficiency Neonatal hemorrhage Hypocalcemia Osteomalacia	Macropapular rash* Exfoliation Toxic epidermal necrolysis Hepatotoxicity Frozen shoulder Teratogenicity
Phenytoin	Nystagmus Ataxia Anorexia Dyspepsia Vomiting Aggression Depression Drowsiness Headache Paradoxical seizures Megaloblastic anemia Hypergylcemia Hypocalcemia Osteomalacia Neonatal hemorrhage	Rash Acne Gum hypertrophy Coarse facies Hirsutism Blood dyscrasias Lupus-like syndrome Reduced serum 1gA Pseudolymphoma Peripheral neuropathy Stevens-Johnson syndrome Dupuytren's contracture Hepatotoxicity Teratogenicity
Primidone	Listlessness* Depression* Psychosis* Decreased libido* Hyperkinesia (children)* Irritability (children)* Nystagmus Ataxia Folate deficiency Hypocalcemia Osteomalacia Megaloblastic anemia Neonatal hemorrhage+	Agranulocytosis Thrombocytopenia Lupus-like syndrome Teratogenicity
Sodium valproate	Tremor* Weight gain* Hair fall* Anorexia Dyspepsia Alopecia Peripheral edema	Acute pancreatitis Hepatotoxicity Thrombocytopenia Encephalopathy Teratogenicity Polycystic ovarian syndrome

Contd...

Table 2 contd...

Drug	*Dose-related side-effects*	*Idiosyncratic side-effects*
	Drowsiness Hyperammonemia Amenorrhea	
Topiramate	Anorexia Weight loss Paresthesias Renal stones	
Levetiracetam	Nervousness Solmlenence	Minimal drug to drug, as well interactions with other drugs. Sudden death syndrome rarely

Common triggers are sleep deprivation, alcoholic binge, acute stress[5]. Measures to limit the triggering factors, will potentiate the action of AED's.

TIME TO START THE AED

- If single seizure - Establish the probability of recurrent seizures. Up to 10% of general population may have a single seizure which is non-recurrent. A much smaller percentage only will have recurrent seizures. Hold caution in treating single seizures until necessity arises.
- As a rule, single absence seizure may be noticed by the relatives, and several absence seizures would have been missed. Hence treatment for AS is a must. So with the partial seizures and prominence towards treatment would be to a generalized conversion of partial seizures. Hence treat the partial seizures.
- Management required for all GTCS. The chance of a subsequent seizure episode varies from 16 to 61% in patients who experience single seizures[6].

Table 3 shows the differential diagnosis of Absence Vs Complex partial seizures.

Table 3: Differential diagnosis of complex partial and absence seizures

Presenting features	Complex partial seizure	Absence seizure
History	Febrile seizures, trauma, stroke, encephalitis	None of these
Age at onset	Any age	Childhood: rare in adults
Aure	Common	None
Duration	Minutes	Seconds
Post-ictal confusion	Often	None
Electroencephalogram findings	Focal sharp waves	Generalized spike and wave

Tabel 4: Differential diagnosis of primarily generalized and secondarily generalized tonic-clonic seizures

Presenting features	Primarily generalized	Secondarily generalized
History	Normal; no history of simple or complex partial seizures	Trauma, stroke, tumor, encephalitis; possible history of simple or complex partial seizures
Age at onset	Usually childhood or adolescence	Any age; if age > 30 yr, diagnosis is almost always secondarily generalized tonic-clonic
Aura	None	Common
Forced head and eye deviation	Rare	Common
Focal post-ictal Todd's paralysis	None	Sometimes
Electroencephalogram findings	Generalized spike and wave	Focal

Table 4 shows the differential diagnosis of GTCS Vs Secondary generalized seizures.

RULE-OUT

1. Persistent focal deficits after seizure
2. History of absence of brain insult
3. Seizures during sleep
4. Normal Inter-ictal EEG
5. Imaging studies are normal
6. Absent family history

If these are positive, no treatment need be given for a single seizure episode. Patient job concern, willingness to take treatment, etc. also plays a vital role in giving treatment for a single seizure episode.

HOW TO CHOOSE MEDICATIONS?

Mostly seizure control is good with 70 to 80% of patients with single AED. Appropriate and suitable AED enhance the chances of successful management of SD. Table 5 shows the appropriate choice of drugs for various types of epilepsy.

LOOK INTO OTHER FACTORS

- Contraindications
- Side-effects
- Dose frequency
- Mechanism of action
- Therapeutic delivery system
- Drug interactions.

Table 5: Dosage guidelines for established antiepileptic drugs in adolescents and adults

Drug	*Indications*	*Starting dose*	*Standard maintenance dose*	*Dosage interval*	*Target range*
Carbamazepine	Partial and generalized tonic-clonic seizures	200 mg	400-2000 mg	*od-qid	25-50 µmol/l (6-12 mg/l)
Clobazam	Partial and generalized seizures	10 mg	10-40 mg	od-bid	None
Clonazepam	Myoclonic and generalized tonic-clonic seizures	1 mg	2-8 mg	od-bid	None
Ethosuximide	Absence seizures	500 mg	500-2000 mg	od-bid	283-708 µmol/l (40-100mg/l)
Gabapentin	Partial seizures	300-400	1800-3600 mg	tid	None
Lamotrigine	Partial seizures and generalized tonic-clonic seizures	25	200-400	bid	6-16 mg/l
Phenobarbitone	Partial and generalized tonic-clonic, myoclonic, clonic and tonic seizures, Status epilepticus	60 mg	60-240 mg	od-bid	40-172 µmol/l (10-40 mg/l)
Phenytoin	Partial and generalized tonic-clonic seizures, Status epilepticus	200 mg	100-700 mg	od-bid	40-80 µmol/l(10-20 mg/l)
Primidone	Partial and generalized tonic-clonic seizures	250 mg	250-1500 mg	od-bid	23-55 µmol/l (5-12 mg/l)
Sodium valproate	All generalized seizures Partial seizures	500 mg	500-3000 mg	*od-bid	347-693 µmol/l (50-100 mg/l)
Topiramate	Partial and generalized seizures	25 mg	100-400 mg	Bid	6-74 µmol/l (2-25 mg/l)
Vigabatrin	Partial seizures	500 mg	1000-4000 mg	od-bid	None

* od or bid with controlled release formulation, modified from IIAE suggestions

SIDE-EFFECTS OF AEDs (Refer Table 2)

After selection of the AED, go with the accepted regimen.

Interaction with the patient regarding the management.

1. Interaction with the patient to alleviate the stress
2. Follow-up of management of stress situations
3. Compliance enquiry.

FACTORS INFLUENCING NON-COMPLIANCE

1. Adverse effects
2. Multiple inconvenient dosing
3. Violent as well disturbing side-effects
4. Usually present during the first six months of management.

How to Manage?

1. Long-acting preparations like "Chrono " and "Contin technology" preparations, which will help the patient to take OD or bid doses only[7]
2. Mentoring the AED blood levels will give an indication for the compliance.

THERAPEUTIC CONSIDERATIONS

- Age – Ageing changes the pharmacokinetics of drugs due to altered physiology of organs, and their pharmcodynamic dealing
- Solution – Titrate the dose of clinical clearance of side effects.

A short algorithm for management of Adult Seizure disorders (Fig. 1).

As suggested by Epilepsy Foundation – Preferred first line drug in primary care setting[8].

WOMEN AND EPILEPSY

- Women with epilepsy who are of childbearing age, need additional advise about issues such as contraception and pregnancy, as well as lactation. This is influenced by factors that produce potential teratogenicity of the AED, interactions with the oral contraceptive, cosmetic side-effects.

CONTRACEPTION – Combined Oral Contraception

- Usually women with epilepsy do not plan for pregnancy

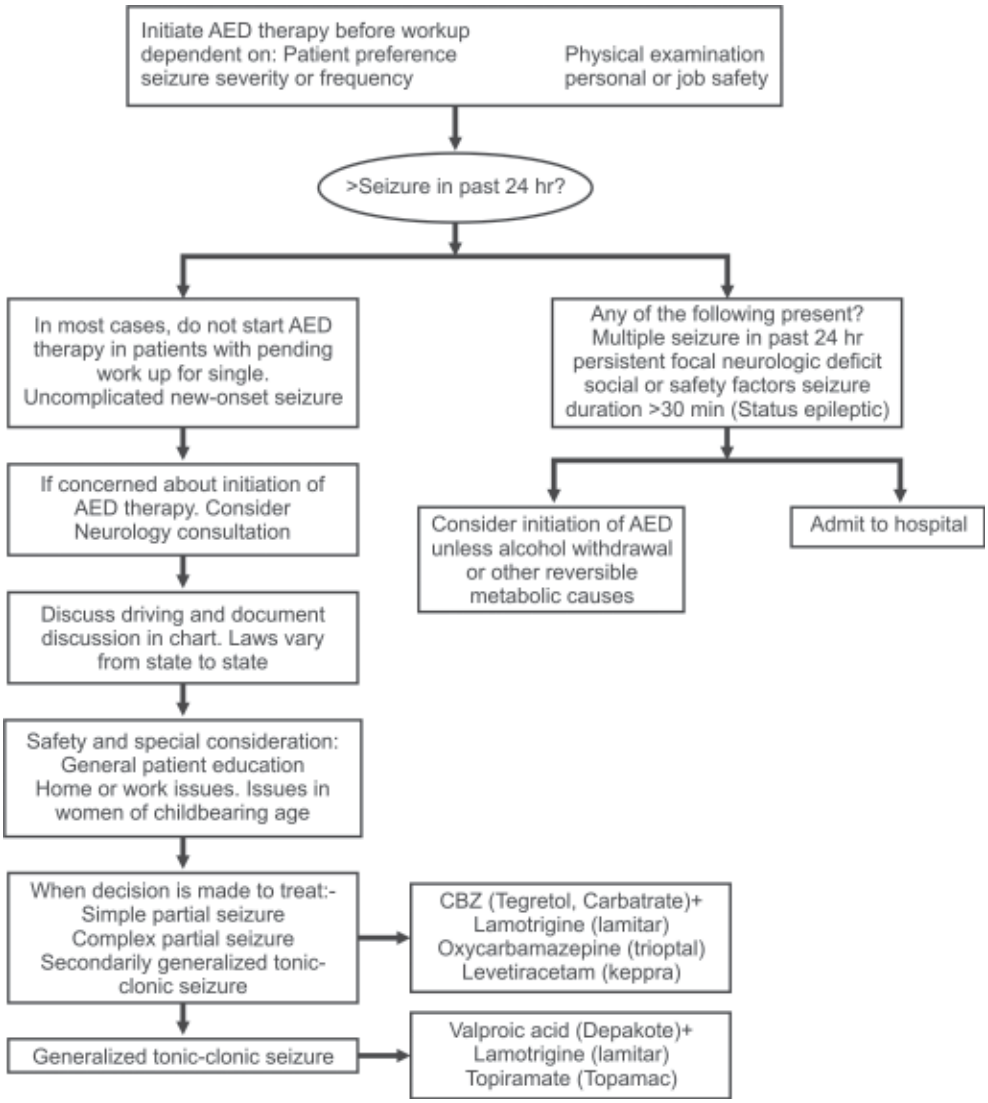

Fig. 1: Treatment algorithm for adults with confirmed epilepsy antiepileptic drug

- Women taking AEDs which induce hepatic enzymes are at increased risk of breakthrough bleeding and COC failure, estimated at up to 7 per 100 women years, due to accelerated estrogen metabolism[9-11].
- Current guidelines recommend a COC containing a minim of 50 micrograms estrogen to reduce this risk, increasing to 80 or 100 micrograms if breakthrough bleeding occurs. AEDs which do not induce hepatic enzymes do not alter the efficacy of the COC[12]. (Evidence level 2-4).
- The understanding would be to use non enzyme inducing AEDs, when a women epileptic is on oral contraception.

Action of AEDs on Hepatic Enzymes (Table 6)

Hepatic Enzyme induction plays a crucial role in deciding the dosage of the medications as well as drug interactions with many drugs used concurrently with AEDs.

A complete list is given in Table 5 for reference.

Guidance on Oral Contraceptives for Women on AED

- The 'progesterone only' oral contraceptive is not recommended for women taking enzyme-inducing AEDs, as progesterone metabolism is enhanced with the enzyme inducing AEDs.

Table 6: Role of AEDs on hepatic enzymes

AEDs which induce hepatic enzymes	*Non-enzyme inducing AEDs*
Carbamazepine	Acetazolamide
Oxcarbazepine	Benzodiazepines
Phenobarbital	Ethosuximide
Phenytoin	Gabapentin
Primidone	Lamotrigine
Topiramate	Levetiracetam
	Tiagabine
	Valproate
	Vigabatrin

- Depot injections of progesterone may be used with enzyme inducing AEDs, but should be given every 10 weeks. Progesterone implants are not suitable for women taking enzyme inducing AEDs.
- The dose of Levonogestrol for emergency contraception should be increased to 1.5 mg and 750 micrograms 12 hours apart in woman taking enzyme inducing AEDs.
- Women with epilepsy should be reassured that most of them will have a normal pregnancy and delivery
- Information about the risk of epilepsy and AEDs in pregnancy and the need for Folate and vitamin K should be given to all women in childbearing age and repeated at review appointments.

RISK TO FETUS FROM MATERNAL EPILEPSY

- Even though enough risk are observed due to status epilepticus due to anoxia, injury, etc to fetus, it is not well established. But risk to the woman with injury, rarely death in a seizure in the pregnancy with seizures has been reported[13]. Evidence level 3.
- Women should be made aware of the risk of uncontrolled seizures to both themselves, and to the fetus.
- Risk to fetus from AEDs, would be major and minor fetal malformations which occur more commonly in infants exposed to AEDs during pregnancy especially during the first trimester[14,15].
- But the overhaul risk of fetal abnormalities due to AEDs are observed only to be 2% but manifold with high-dose of single AEDs[16,17].
- The risk with valproate may be higher than with CBZ, lamotrigine. Polytherapy, particularly. with certain combinations of therapy, may carry a higher risk than monotherapy, especially when combined with newer AEDs and Valproate[18].

IMPLICATIONS OF CLINICAL ORIENTED MANAGEMENT OF AEDs

1. Seizure freedom without adverse effects in school-going patients, and especially elderly patient with epilepsy
2. Right diagnosis and right formulations with tailoring the dose according to the seizure frequency and minimal side effects with avoidance of drug interactions
3. Low-dose and increase steadily to avoid adverse effects based on the patient response, not on the so called "therapeutic rays" which normally do not correlate with toxicity or side effects.
4. Counseling, supportive management would achieve better goal with the cure, with normal lifestyle.

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