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A BRIEF REVIEW OF GUIDELINES FOR THE MANAGEMENT OF EPILEPSY PATIENTS- INDIAN PERSPECTIVE

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ABSTRACT

Epilepsy is very commonly prevalent neurological disorder and a wide array of pharmacological and non-pharmacological modalities are available for its treatment. Epilepsy is classified into several subtypes and syndromes and treatment varies according to the diagnosis, continuous research continues for new drugs. Guidelines for the management of epilepsy have been issued by several bodies. This is a concise summary of various guidelines of epilepsy particularly National Institute for Health and Care Excellence *(*NICE*)*, International league against epilepsy, American academy of neurology and Guidelines for Management of Epilepsy in India *(*GEMIND). There is a brief discussion on the classification, diagnosis and management of epilepsy in view of its presentation as unprovoked, provoked or status epilepticus with special focus on newer/second generation antiepileptic drugs. Role of non-pharmacological modalities are also discussed.

INTRODUCTION

Epilepsy is one of the most common and chronic neurological disorders characterised by repetitive attacks of seizures. Seizure is an abnormal & high frequency discharge from cerebral neurons. Hence person with a single seizure or recurrent seizures due to correctable cause does not necessarily have epilepsy. All Patients with Epilepsy have seizures but all those who have seizures do not have epilepsy. The epileptic seizure may be characterized by sensory, motor or autonomic phenomena with or without loss of consciousness.

Incidence & Prevalence- Accounts for 1% of the total burden of disease in the world and 1% of prevalence rate in Indian population.[1] It is common in Rural (1.9%) than urban (0.6%) population. Males are affected more than female in the age group of < 18 years and > 65 years.

Consequences of untreated Epilepsy - Epilepsy is not benign, especially if not treated. There is a threat of serious Injury and death in poorly treated or untreated patient of epilepsy. Serious and potentially life-threatening complication of epilepsy is Status Epilepticus.

Indian scenario in epilepsy management- In India, most of the patients with epilepsy are being diagnosed and treated by non-specialists because of scarcity of specialist at both primary and secondary care levels. This results in suboptimal level of treatment. Hence Indian Epilepsy Society has developed its own guidelines **GEMIND** for the management of epilepsy in India.[2]

This will help in improving medical decision making in India, mainly at a General physician level.

Etiology– Some common etiological factors are as follows. Genetic/heredity play significant role in Epileptic syndrome.

- Brain lesions :Tumors & birth trauma
- Infections : Meningitis & abscess
- Hypoxia : ↓ O2 content of blood
- Sudden withdrawal of drug of abuse : Alcohol & Barbiturates
- Post stroke & operative procedure on Brain
- Complications during pregnancy or birth - PIH
- Parasitical infection – Neurocysticercosis.

Diagnostic criteria– Medical history with Presence of recurrent, unprovoked seizures & for correct diagnosis detailed clinical history required from the patient, family members and eye witness.

Electroencephalogram (EEG) - It should be done soon after the seizure or within 48 hours and helps in classification of seizure type & epilepsy syndrome. Normal EEG does not rule out diagnosis of epilepsy.

VEEG (video electroencephalogram) – It is done in the patients of difficult to control epilepsy.

Radio imaging is not mandatory for all patients but needed in the patients with Focal seizures, Suspected-symptomatic in origin and when difficulty in controlling seizures. Magnetic resonance imaging (MRI) is followed by Computed tomography (CT scan).

EVALUATION OF A SEIZURE PATIENT

Evaluation and management of first unprovoked seizure - In India, incidence of patient presenting with unprovoked first seizure is very high. Hence it is important that clinicians know how to manage this clinical situation. Following steps clinician should follow while managing the seizure patients. First is to take detailed history and neurological Examination for confirmation of the event as a seizure. Other conditions can be mistaken or mimic with the episode of seizure are Syncope, Breath holding spells, Panic attack, Transient ischemic attack, Psycologenic (Hysteric) episode, Hypoglycemic episode, Gastro-esophageal & esophageal reflux, Movement disorders and Non-epileptic spells.[3]

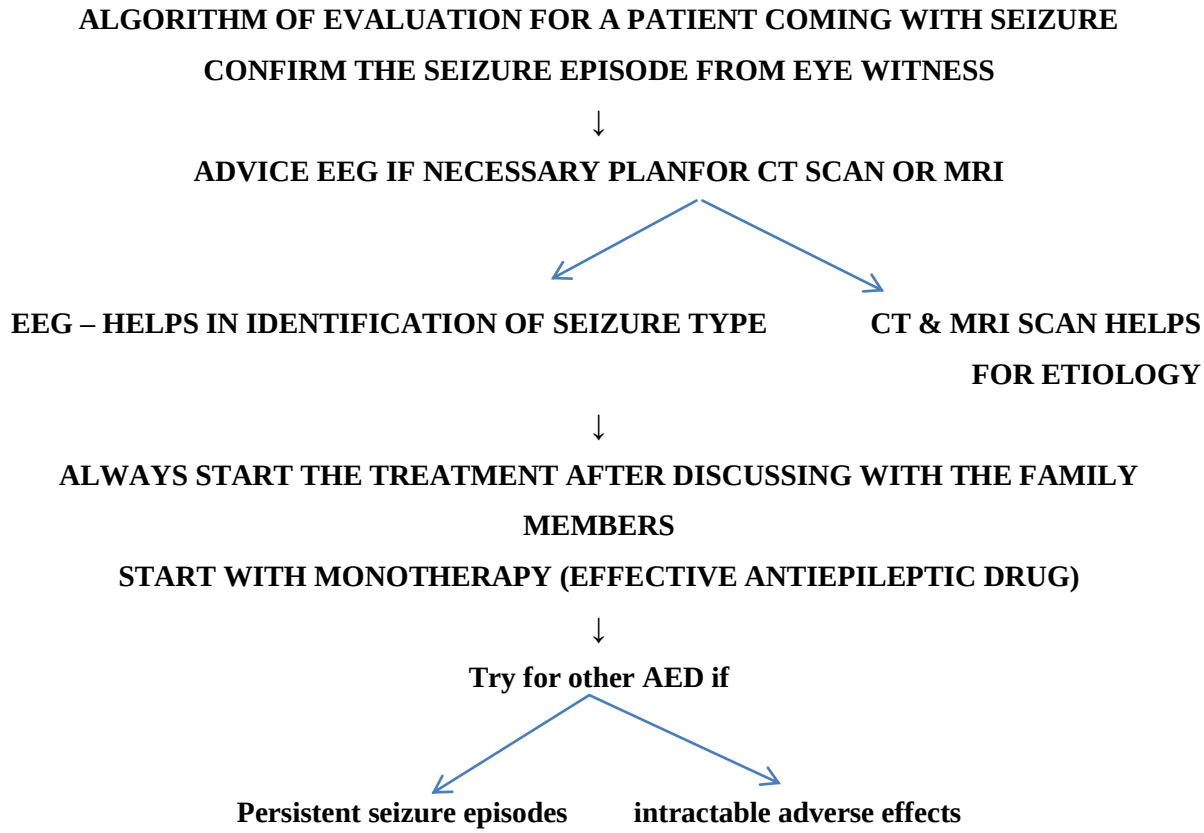
Blood investigations to be done are Blood glucose to rule out hypoglycemic episode, Serum electrolytes to know the Na^+ status, Serum creatinine, LFT, Blood count, Lumbar puncture in specific situation to rule out infectious causes and if patient is febrile.

DIFFERENCE BETWEEN SYNCOPE & SEIZURE

FEATURES	SYNCOPE	SEIZURE
Precipitating factors	Common	rare
Occurrence	Awake, mostly when upright	Awake or asleep
Aura	Common	uncommon
Onset	Less abrupt	abrupt
Jerking of limbs	Occasional	frequent
Incontinence	Rare	common
Post- ictal recovery	rapid	slow
Post- ictal confusion	uncommon	common
EEG	Usually normal	May be abnormal

DIFFERENCE BETWEEN HYSTERIC EPISODE & SEIZURE

FEATURES	PSYCHOGENIC EPISODES	EPILEPSY
Age and gender	Usually young, more common in women	Any age
Precipitating factors	Emotional disturbances	Lack of sleep, poor drug compliance
Occurance in sleep	No	yes
Duration	Minutes to hours	Seconds to minutes
Movements	Vocalization pelvic thrusting, bizarre flinging of limbs	Tonic or tonic clonic jerks
Eyes	Forcibly closed, resistance to opening	open
Injuries including tongue	Infrequent bite	frequent
Post ictal confusion, headache, sleep	Uncommon	common
Pattern of attacks	Variable	stereotyped
EEG/ video EEG	Normal	Usually abnormal



CLASSIFICATION OF EPILEPSIES & EPILEPSY SYNDROMES

Broadly classified based on seizure type, age of onset and possible etiology.

Localization-related epilepsies: focal/partial onset and generalized epilepsies.

Idiopathic epilepsies: Inherited or occur without identifiable pathologic cause.

Symptomatic epilepsies: Associated with a known or suspected brain disease or lesion.

Epilepsy syndromes: Age specific and may begin during infancy, childhood or adolescence.

Significance of classification- It is important to have proper diagnosis of epilepsy for starting the appropriate treatment and improvement of quality of life, as certain drugs may even aggravate particular seizure type.

Example: Juvenile myoclonic seizure is type of epilepsy which usually starts in the adolescent age & characterized by Myoclonic jerks/Generalised tonic clonic seizures/ Absence seizure. In this case proper diagnosis of seizure type is important, as misinterpretation may leads to starting with Carbamazepine.

ILAE 2017 CLASSIFICATION OF SEIZURE TYPES[4]

A. FOCAL ONSET	B. GENERALIZED ONSET	C. UNKNOWN ONSET
I. Awareness a. aware b. impaired awareness	I. Motor a. Tonic clonic b. Other motor	I. Motor a. Tonic clonic b. Other motor
II. onset Motor onset Non motor onset	II. Non motor(absence)	II. Non motor
III. Focal to bilateral tonic clonic		III. Unclassified

Focal seizures/partial seizures – Epileptic focus start in an area on one side of the brain(one hemisphere). **Generalized seizures/Primary generalized –**Epileptic focus start in both the hemisphere. **Unknown onset:** If the onset of a seizure is not known. **Focal to bilateral / secondary generalized seizure:** A seizure that starts in one side or part of the brain and spreads to both sides.

Awareness – Simple to evaluate than consciousness and of importance during a seizure because it is one of the main factors affecting a person's safety during a seizure. **Focal aware/ simple partial:** Awareness remains intact, even if the person is unable to talk or respond during a seizure. **Focal impaired awareness/ complex partial seizure:** Awareness is impaired or affected at any time during a seizure. **Unknown:** If it is not possible to know if a person is aware or not. **Generalized seizures:** It is presumed to affect a person's awareness or consciousness in some way. **Focal motor seizure:** It has some type of movement occurs during the event. For example twitching, jerking, or stiffening movements of a body part or automatisms means automatic movements such as licking lips, rubbing hands, walking, or running. **Focal non-motor seizure:** This type of seizure has other symptoms that occur first, such as changes in sensation, emotions, thinking, or experiences.

Auras: The term aura to describe symptoms a person may feel in the beginning of a seizure. It's important to know that as it is the start of the seizure. **Generalized seizures:** can be motor or non-motor. **Generalized motor seizure/Generalized tonic-clonic seizure/Grand mal-** Characterized by stiffening (tonic) and jerking (clonic). The other forms of generalized motor seizures may occur.

Generalized non-motor seizure/ Petit mal/Absence: These are primarily absence seizures. These seizures involve brief changes in awareness, staring and automatic or repeated movements like lipsmacking.

Epileptic encephalopathies/syndromes in Infancy and Early Childhood: Severe brain disorders: epileptic electrical discharges contribute to progressive psychomotor dysfunction. Seen in early age and manifest with EEG paroxysmal activity that is often aggressive, seizures that are commonly multi-form and intractable, cognitive, behavioral and neurological deficits and sometimes early death.

Few West syndrome, Lennox–Gastaut syndrome, Early myoclonic encephalopathy, Ohtahara syndrome, Dravet syndrome.

MANAGEMENT OF PATIENT WITH EPILEPSY

Various treatment modalities available are

Pharmacological: Antiepileptic drugs

Nonpharmacological: Surgical intervention, Vagal nerve stimulation,

Other interventions: Yoga and Meditation, Ayurveda, Ketogenic diet, EEG biofeedback, Herbs

Aim of treatment: To control seizures withmost appropriate AED without causing any significant side effects, Prevent recurrence&Restore the quality of life (Update),To be started only after confirming diagnosis of epilepsy, To be Initiated following :The occurrence of two or more unprovoked seizures& After discussing the risks and benefits of treatment with the person/family members.

Indian Epilepsy Association (IEA) affiliated to International Bureau of Epilepsy (IBE), and Indian Epilepsy Society (IES) affiliated to International League Against Epilepsy (ILAE), are the two major epilepsy societies in India. IEA and IES consist of medical doctors and professionals from the fields of epilepsy. The role of IEA and IES is to form a task force to liaise with traffic authorities, public health officials, epidemiologists, and importantly, sister organizations, such as the Indian Academy of Paediatrics and Indian Medical Association, with the aim of preventing epilepsy.[5]

First unprovoked seizure – Treatment should be started in following situations- Prolonged focal seizure, First seizure presenting as Status Epilepticus, Presence of neurological deficit, hemiparesis, mental retardation, cerebral palsy, Family history of seizures among parents, siblings or children, Electroencephalogram abnormality, Abnormality on brain imaging (CT, MRI) and High-risk jobs.[6]

First unprovoked seizure, initiation of antiepileptic drug therapy in adult and paediatric patients and its benefits

The decision to initiate AED in after first unprovoked seizure is more beneficial in adults compared with the children. In adults this reduces the 2 year seizure recurrence after first seizure. It has no additional beneficial effect on seizure remission after 3 years & effect on quality of life. Immediate start of AED in paediatric patient is recommended.

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.

PRINCIPLES OF PHARMACOLOGICAL TREATMENT

As per the various standard guidelines (Nice and Gemind)– AED therapy should be individualised and should consider age, type of epilepsy, co-medication & co-morbidities, convenience & preference of the individual & care taker. AED therapy should be initiated in adults on the recommendation of a specialist.

Monotherapy: Treatment should be started with a single antiepileptic drug. Priority should begiven to the conventional antiepileptic over the newer one for initiation of the treatment since the safety profile of the newer one is not well established & relatively cheaper. In case of failure with first monotherapy (adverse effect or continued seizure) start with another AED monotherapy, which may be an alternative first-line or second-linedrug) Caution isneeded during the changeover period. The diagnosis of epilepsy needs to be critically evaluated if events continuedespite an optimal dose of a first-line AED.

Combination /Add on/Adjuvant therapy: It should be considered when two attempts at Monotherapy with AEDs have not resulted in seizure freedom. 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. Combining drugs with different mechanisms of action, such as those which prolong Na+ channel inactivation with those facilitating GABA appears more appropriate.

Dose escalations: The dose should be increased slowly until seizure control is achieved or intolerable side effects occur.

Drug formulation: The brand/ formulation of AED should preferably not be changed as they may vary in bioavailability or pharmaco kinetic profiles and care needs to be taken to avoid reduced effect or excessive side& AED have low therapeutic index. Example: In 1968 there was sudden outbreak of Phenytoin toxicity in well stabilized epileptic patients when Dilantin Na capsules excipient was switched from Calcium sulphate to lactose. As lactose have faster wetting property & increased the dissolution rate of the formulation. Modified release formulations are convenient but expensive but using carbamazepine, offer controlled-release carbamazepine preparations.

While prescribing AED to women and girls of present and future childbearing potential, discuss the increased risk of congenital malformation and neurodevelopmental impairments in an unborn child i.e. teratogenicity. Available literature shows teratogenic risk of various antiepileptic drugs- Valproic acid > Phenytoin >phenobarbitone =primidone> carbamazepine >oxcabamazepine >Topiramate >Ethosuccimide =lamaotreigine. AED should not be stopped during pregnancy, should be continued in MED & regular USG monitoring.

Withdrawal of AED: Physician can consider withdrawal of AED after a seizure-free period of 2–3 years (70% children & 60% Adults).[7] The decision is mainly based on the type of epilepsy syndrome, normal neurological examination, EEG, cause of seizures and should be taken after discussion of the risks and benefits of withdrawal with the PWE and family. Most recurrences occur in first 3 months of drug withdrawal &advised to revert to their previous regimen. Antiepileptic drugs are usually withdrawn gradually over several months over 3–6 months or longer especially with benzodiazepines. The tapering may be performed at a slower rate for (6 months or longer), one drug at a time in those patients who are on multiple AEDs.

Drug interactions & drug monitoring: Most AED arecytochrome P450 enzyme inducers except valproic acid which is enzyme inhibitor. Hence pharmacokinetic interactions among anticonvulsants are common. They also have high PPB there by displacement drug interaction are seen with them. Most of the AED have low therapeutic index hence dose adjustments guided by therapeutic drug monitoring are warranted.

Choosing the Appropriate Antiepileptic Drug: AEDs are divided into

- ***First generation/conventional*** - phenytoin (PHT), phenobarbital (PB), carbamazepine (CBZ), valproic acid (VPA)and clobazam (CLB)

- ***Second generation/Newer***- vigabatrin, felbamate, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide
- ***Post second generation***- lacosamide (LCM) and eslicarbazepineacetatebrivaracetam, carabersat, carisbamate, DP-valproic acid, eslicarbazepine, fluorofelbamate, fosphenytoin, ganaxolone, lacosamide, losigamone, pregabalin, remacemide, retigabine, rufinamide, safinamide, seletracetam, soretolide, stiripentol, talampanel, and valrocemide.[8,9]

Most of the guidelines for Epilepsy Management recommend Conventional AED as first-line drugs because of cost effectiveness and known safety profile as mentioned above. Choice of drug depends primarily on seizure types as given in Table.1.

	GTCS SEIZURES	***FOCAL SEIZURES***	***ABSENCE SEIZURES***	***MYOCLONIC, ATONIC SEIZURES***
FIRST LINE	***Valproic Acid*** ***Lamotrigine***	***Carbamazepine*** ***Oxcarbazepine*** ***Phenytoin*** ***Lamotrigine*** ***Levetiracetam***	***Valproic Acid*** ***Ethosuximide*** ***Lamotrigine***	***Valproic Acid*** ***Lamotrigine*** ***Topiramate***
ALTERNATIVES	***Phenytoin*** ***Carbamazepine*** ***Oxcarbazepine*** ***Topiramate*** ***Phenobarbitone*** ***Felbamate***	***Topiramate*** ***Valproic Acid*** ***Gabapentin*** ***Lacosamide*** ***Phenobarbital*** ***Felbamate***	***Lamotrigine*** ***Clonazepam***	***Clonazepam*** ***Felbamate*** ***Clobazam*** ***Rufinamide***

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: To check noncompliance in case of uncontrolled seizures, Documenting suspected AED toxicity, For dose adjustment in case of drug interactions, Specific clinical conditions (e.g. SE, liver or renal disease and pregnancy).

Non pharmacological treatment of Epilepsy: Surgery for epilepsy: Indications/Potential PWE for surgery- A patient having MIE with an identifiable lesion on imaging, correlated with electrophysiology, Medically intractable epilepsy/Refractory epilepsy/ Therapy resistant epilepsy, Patients in whom epilepsy is not controlled by two or more appropriate AEDs used in their optimal dosage. Adults who continue to have seizures even after 2 years of treatment.

Pediatric epilepsy patients: Presenting with epileptic encephalopathy, Infantile spasms, Catastrophic onset of epilepsy. Seizure frequency of more than one per month. Disabling seizures. **Benefits of surgery-** Seizure freedom in 60– 70% of cases, Reduction in seizure frequency in the remaining 30–40% cases.[10] **Prerequisites-** In indicated patients should be considered as early as feasible rather than an option of last resort, Should be done only in specialized centres only. **Type of surgery**-Epilepsy surgery may be resective or nonresective. Resective- lesionectomy - resection of the lesion and the surrounding epileptogenic area Amygdalo-hippocamp-ectomy-with or without temporal lobe resection, multilobar resection. Hemispherectomy. **Non-resective surgery** includes: multiple subpial transections ,corpus colostomy, vagus nerve stimulation.

Yoga & Meditation- Various clinical trials have proved that yoga have shown to slow the production of stress hormone & increase level of serotonin.

Psychological interventions- Psychological interventions like relaxation, cognitive behaviour therapy, Biofeedback may be used in children and young people with drug-resistant focal epilepsy. They are used in conjunction with AED therapy &are not an alternative to Pharmacological treatment. Theymay be associated with an improved quality of life in some people but have notbeen proven to affect seizure frequency.

Ketogenic diet- This approach is mainly used in pediatrics patients with refractory epilepsy. This is high fat & low carbohydrate. It induces ketosis &increase leptin production. This suppresses seizure. It is unpalatable & need supervision from dietician &paediatrician.

EEG biofeedback - This is a neurotherapy. It suppresses seizure activity by voluntary control of EEG rhythm**.**

Provoked seizure - This type of seizure are secondary to structural or metabolic/toxic damage to the brain may be up to seven days following the brain insult.

ETIOLOGICAL CLASSIFICATION

Structural - Head injury, Stroke, Brain tumours, Neurocysticercosis

Metabolic - Alcohol related, Liver, Renal

Management of seizures due to structural injury

Head injury- it increases the risk of seizures. Phenytoin prophylaxis is recommended only in severe head injury. It should be given in a loading dose by intravenous route. Further continuation after seven days of insult does not provide additional benefit.

STROKE- Lamotrigine and gabapentin are the first line drugs. Phenytoin and phenobarbitone cause osteoporosis and delayed neurological recovery. It increases the risk of seizure particularly cortical and haemorrhagic. Single seizure does not require treatment. Post- operative prophylaxis not recommend. Enzyme inducers like phenobarbitone, cbz and phenytoin may interact with antiplatelets, anticoagulants and hypolipidemics. Central venous thrombosis has high incidence of seizures, even status epilepticus. Post episode one year prophylaxis is recommended.

NEUROCYSTICERCOSIS- It is a common cause of provoked seizures in India. For Single enhancing lesion AED is given for at least 6 months. On repeat MRI after 3-6 months, if lesion disappears taper off AED over 8-12 wks. Carbamazepine and phenytoin are the most frequently used AEDs because of their cost.[11]

STATUS EPILEPTICUS

This refers to continuous seizures/continuous repetitive seizures with impaired consciousness interictal period.

This is divided in two types: Convulsive status epilepticus – continuous convulsive seizures lasting >5 mins. Nonconvulsive status epilepticus – Change in mental status from baseline for atleast 30 min with ictal discharge on EEG.

Management: Convulsive status epilepticus is an emergency as it is associated with sever metabolic disturbances. **General management-** Secure airway, breathing& circulation. **Evaluation**-physical, neurological and blood investigation.

AEDs - as early as possible as below

I.V.Benzodiazepine

Inj.Lorazepam 0.1mg/kg/iv Alternatives are Midazolam/Clonazepam

↓

Inj.Phenytoin/Fosphenytoin 20mg/kg/i.v. (for long term seizure control)

↓

If this fails patient is shifted to higher center with ICU & artificial ventilation facilities.As they may require administration of intravenous general anaesthetics like Midazolam, Propofol and thiopentone Na.

↓

In case of Non convulsive SE AEDs like Valproic acid, Levetiracetam, Topiramate in early referactory case.[12]

Women and girls with epilepsy- Must be given accurate information and counselling about contraception, conception, pregnancy, caring for children and breastfeeding because AEDs have potential to cause contraceptive failure, congenital malformation in the foetus & post delivery complications.

Contraception- AEDs like phenytoin, carbamazepine, phenobabitone and topiramate has enzyme inducing properties. Patient should be advised to either alternative method of contraception /Higher dose OC pills/depot preparation injections.

Pregnancy- It is recommended that AEDs should be continued during pregnancy. It is observed that seizure frequency is increased in 30% cases.[13,14] Potential harm of seizure on mother and foetus is greater than the teratogenic effect of AED. It is recommended that AEDs should be given in minimum effective dose especially monotherapy with proper USG monitoring & serum α feto protein for screening of foetal malformation. All pregnant patients with AEDs should receive folic acid 5mg daily till delivery. This reduces the risk of neural tube defect. All pregnant patients with AEDs should receive two doses of vitamin K 10mg/IM at 34 weeks &36 weeks of pregnancy & also it should be given in the dose of 1mg/IM to the infant at birth.

As per the guidelines - The recommended AEDs during pregnancy are carbamazepine, Lamotrigine and Levetiracetam.

Febrile seizure- It occur during fever between 6months to 5 years of age in absence of intracranial infections. Reccurrence occur in 1/3rd to ½ of the patient.

Treatment- Rectal Diazepam 0.5mg/kg, Buccal Midazolam 0.2 mg/kg,Oral Clabazam 0.75mg/kg for 2 -3 days to prevent recurrence, Prophylactic AEDs not recommended, only if seizure persist beyond 6 years of age.

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