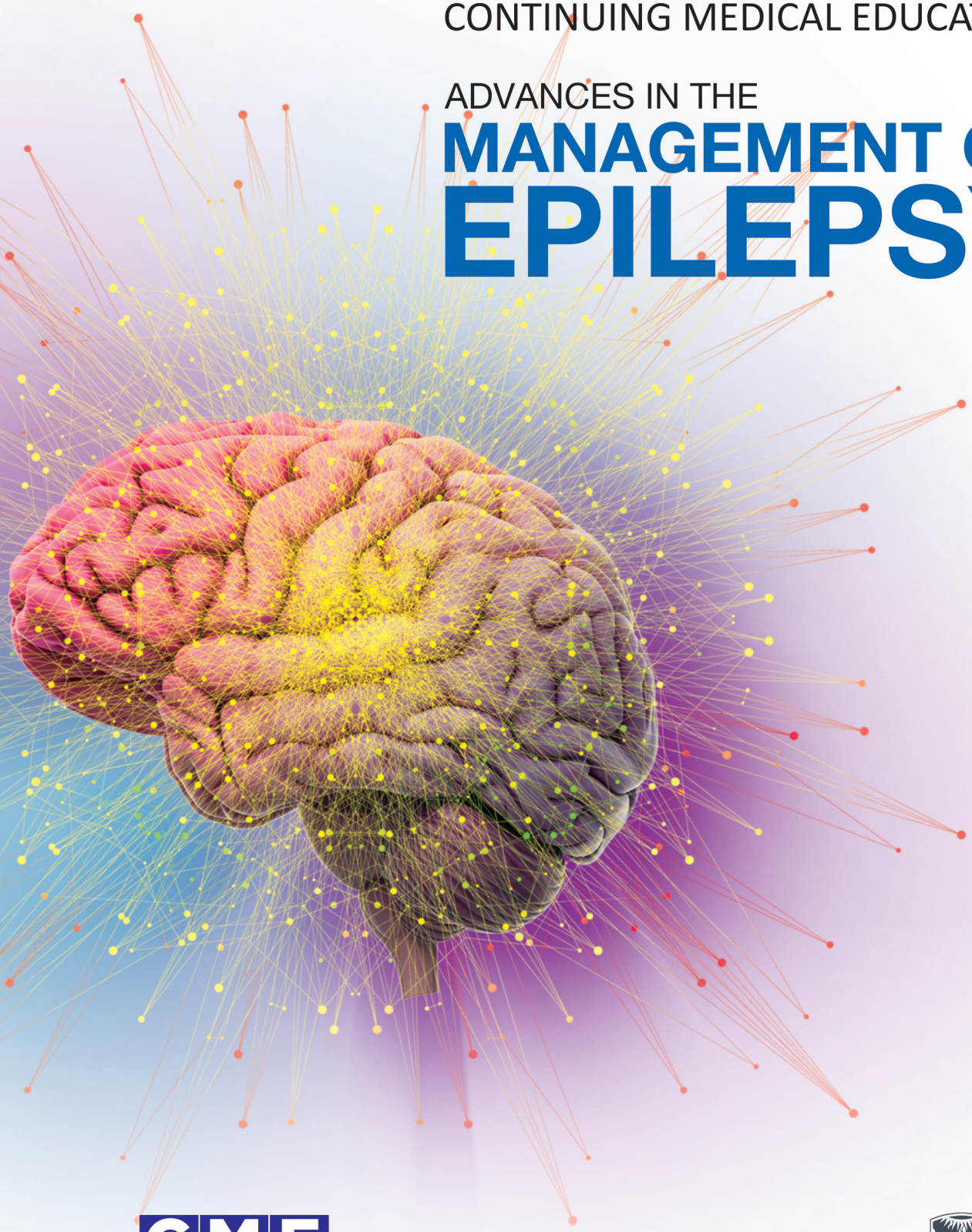
CONTINUING MEDICAL EDUCATION

ADVANCES IN THE MANAGEMENT OF EPILEPSY



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Program Information

Need for this program

Epilepsy is the most common neurological condition that continues to be poorly understood and managed, and has important medical, psychological and social consequences. Given the high burden of the disease, it is very likely that primary care physicians will continue to provide care for these patients. Generally, diagnosis of a particular seizure type, and of a specific type of epilepsy, directs the diagnostic workup of these patients and their initial therapy. However, there may be variation in the quality of care provided by primary care practices to individuals with such chronic illnesses. A physician's lack of updated information about epilepsy could be the cause of an incorrect and/or suboptimal clinical control. This CME activity is an attempt to update primary care physicians on the general concepts related to classification and types of epilepsy, the diagnostic and management approach in patients with epilepsy, including special populations that may require additional considerations, together discussing the antiepileptic drugs (AEDs) treatment.

Learning objectives

- To identify the current burden of epilepsy, and its classification
- To understand the pathophysiology and diagnostic approach for epilepsy
- To review the current management approaches for epilepsy, including specific subgroups

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None declared

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Participants are requested to attempt the self-assessment questionnaire after completing their module and mail the questionnaire along with the feedback form to: info@cmecom.in. Those participants who successfully attempt the questionnaire with a score of 60% or better will be eligible to receive a CME certificate.

ADVANCES IN THE MANAGEMENT OF EPILEPSY

BURDEN OF EPILEPSY IN INDIA

Epilepsy is a common, chronic neurological disorder characterized by recurrent epileptic seizures,[1] with high prevalence in developing countries like India, and posing enormous health, social, and economic burden. The prevalence rates of epilepsy – determined through population-based surveys – have shown considerable variation across different regions of the country.[2] However, despite regional variations, the huge burden of the disease is clearly documented. Estimates suggest that of the 70 million persons with epilepsy worldwide, 80% live in low- and middle-income countries with limited resources.[3] Amongst these, India is home to nearly 12 million persons with epilepsy, which contributes to almost 1/6th of the global burden.[4] Furthermore, amongst this national cohort, a differential distribution pattern is being noticed, with higher rates reported for the male gender, rural population, and low socioeconomic status; a finding which could be significant considering the Indian demographic position. This huge burden of epilepsy in India is expected to continue in the coming years possibly due to socio-demographic transition, huge treatment gap, vicious cycle between economic burden and poor disease outcome, and continuing perception, stigma, and discrimination of epilepsy across the country despite improvement in educational and social parameters over time.[5]

Need to target epilepsy at the primary care level in India

Overall, the epilepsy scenario in India typically signifies the need to give priority for this eminently preventable and manageable public health problem in healthcare delivery, and build capacity at all levels of human resources for its management.[4,6,7] Especially, this would require significant efforts to be positioned at the primary care level, given the higher rates of prevalence of epilepsy in rural areas,[2] limited availability of neurologists in primary care,[7,8] and the huge treatment gap and poor prognosis of the disease.[9] Given that a majority of persons with epilepsy in developing countries are diagnosed, treated, and followed up by primary care doctors, a substantial proportion of the current large treatment gap could be minimized by educating the primary care physicians about the diagnosis of epileptic seizures, cost-effective antiepileptic drugs (AEDs) treatment, and need-based referral for specialized care.[10] This would allow a rational and need-based distribution of patients between primary, secondary and tertiary care, thereby improving the access and quality of epilepsy care. A recent cross-sectional study[11] from India in fact showed that many epilepsy patients seeking tertiary care actually do not need it. Delivering first-line AEDs through primary healthcare can be a possible way to help decrease the treatment gaps and tertiary-care burden in resource poor, developing countries.[12]

DEFINITION OF EPILEPSY

In clinical practice, it is important for the physicians to identify the distinction between seizure, epilepsy, and convulsion as they are not synonymous (Table 1).[1] The term epilepsy was conceptually defined in 2005 as "a brain disorder characterized by an enduring predisposition to generate epileptic seizures; practically applied as having two unprovoked seizures more than 24 hours apart". In 2014, the International League Against Epilepsy (ILAE)

Table 1: Seizure vs. epilepsy vs. convulsion	
Seizure	• Always a symptom of abnormal function in the central nervous system rather than a disease in itself • May be initiated in a normal brain by acute insults such as alcohol withdrawal, low blood sodium, or certain toxins
Epilepsy	• A chronic condition in which seizures occur repeatedly because of an underlying brain abnormality which persists between seizures
Convulsion	• A forceful involuntary contraction of skeletal muscles, and is a physical manifestation of a seizure

Source: Bowman J, et al. Epilepsy. Encyclopedia of Life Sciences 2001; Nature Publishing Group. Available at: http://physiology.elte.hu/gyakorlat/cikkek/Epilepsy.pdf [Accessed on: 10/8/2018]

altered this practical definition making it applicable for special circumstances not meeting the two unprovoked seizures criteria. According to this revised definition, epilepsy is now considered to be a "disease" of the brain defined by any of the following conditions:[13]

- At least two unprovoked (or reflex) seizures occurring >24 hours apart
- One unprovoked (or reflex) seizure and a probability of further seizures similar to general recurrence risk (at least 60%) after two unprovoked seizures, occurring over next 10 years
- Diagnosis of an epilepsy syndrome.

Examples of evidence that increases the probability of having additional seizures include: (a) epileptiform activity on electroencephalogram (EEG), or (b) a potential epileptogenic abnormality on brain imaging.[14] Furthermore, epilepsy is considered to be resolved if an individual had an age-dependent epilepsy syndrome but is now past the applicable age, or if someone has remained seizure-free for the last 10 years and off anti-seizure drugs for at least the last 5 years. It is however important to note that "resolved" is not necessarily identical to the conventional view of "remission or "cure."

THE NEW 2017 CLASSIFICATION FOR SEIZURES AND EPILEPSY: PROVIDING A DIAGNOSTIC FRAMEWORK

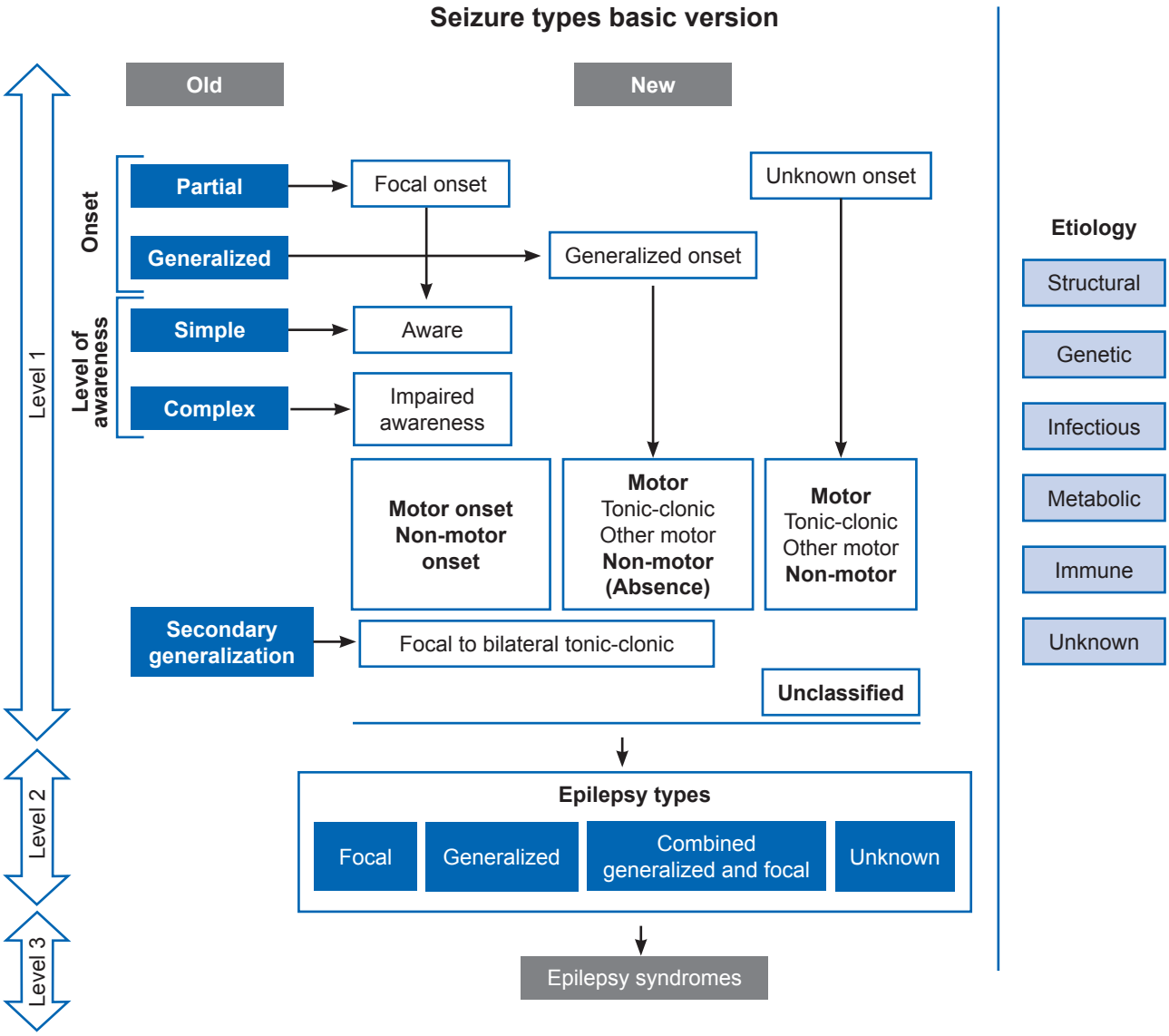
The ILEA constructed classifications for seizures and epilepsy at several time points (in 1981, 1985 and 1989) to provide a namable diagnosis/etiology, improve understanding, enhance discussion, and enable investigation of the treatments, responses, and typical clinical courses for different types of seizures and epilepsy.[14] Recently, in 2017, this classification was updated utilizing several important additions, thus providing a new operational classification of seizures and epilepsies. This new classification allows for inclusion/classification of previously unclassifiable seizure and epilepsy types, thereby greatly reducing the number of unclassifiable cases.[14-16] The classification applies to seizures in both adults as well as children (except for neonatal seizures), and has both a basic and expanded version depending upon the needs and expertise of individuals utilizing it; *per se*, the basic version is a tapered form of the expanded version and is expected to be more useful for doctors in general practice.

Basic version of seizures classification – relevant to general practice

The new ILEA classification of seizure type revises the old system but maintains the primary distinction of focal- vs. generalized-onset seizures.[17] According to the basic version of this new classification, seizures are defined by onset as: "focal" (synonymous with the old term "partial"), "generalized" [when both hemispheres (potentially asymmetrically) are activated at the seizure onset, according to behavior and EEG], "unknown" (when the onset is unknown but other manifestations are known), or "unclassifiable" (few events are clearly seizures, yet unclassifiable).[14]

Focal seizures: As an option, focal seizures are further classified as "aware" (synonymous with the old term "simple") or "impaired awareness" (synonymous with the old term "complex") seizures. However, it is important to note that "impaired awareness" is not synonymous to "loss of consciousness". "Impaired awareness" should be included if awareness is impaired at any time during a focal seizure - this is an exception to the "rule of first," where the first symptom or sign defines the seizure type, even if more prominent features occur later. If awareness is not known, then this level of classification should be omitted when classifying the seizure type. The next step in basic classification for a focal seizure - after considering the level of awareness - involves defining the onset as "motor" or "non-motor." The now called "focal to bilateral tonic-clonic seizures" is synonymous with the old term "secondarily generalized seizures", and has been named such in order to restrict the term "generalized" to seizures of generalized onset (Figure 1).[14]

Figure 1 **Classification of seizure and epilepsy types – Diagnostic considerations**



Source: Falco-Walter JJ, et al. The new definition and classification of seizures and epilepsy. *Epilepsy Research* 2018;139:73–79.

Generalized seizures: Since awareness is impaired in most cases of generalized seizures, the term "aware" vs. "impaired awareness" is omitted when classifying generalized seizures. Nonetheless, the designation of "motor" vs. "non-motor (absence)" is used. Generalized motor seizures can be further classified as "tonic-clonic" or "other motor."[14] The term "tonic" describes prolonged muscular contraction, while "clonic" describes rapid alternating succession of contractions and partial relaxations of a muscle.[18]

Unknown onset seizures: Unknown onset seizures can be further classified as "tonic-clonic" or "other motor." The nature of seizure onset is crucial – a seizure whose onset was not witnessed, followed by tonic-clonic activity should be labeled as "unknown onset to bilateral tonic-clonic seizure".

Epilepsy types/classification

The classification of epilepsy type is broader in scope than the seizure classification, and applies to all age groups. Therefore, after classifying the seizure type, clinician should aim to identify the patient's epilepsy type, and

where possible, their epilepsy syndrome. In general, in order to classify the epilepsy type, a patient must meet the definition of epilepsy; those not meeting the criteria for epilepsy (e.g., single seizure) should be classified as to a seizure type and classification should end there. Furthermore, even if criteria for epilepsy are met, there can be patients whose seizure type is classifiable but epilepsy type is unclassifiable.

Typically, classification of epilepsy type considers the possibility of having multiple seizure types, and incorporates information about the overall clinical picture. Accordingly, epilepsy types are classified as: (i) focal (ii) generalized (iii) combined generalized and focal, and (iv) unknown (Figure 1). In order to place a patient into one of these categories, one needs to use the classification of all types of seizures that a patient has, and then map those in total to one of these four categories.[14]

"Combined generalized and focal epilepsy" is a new group that has been devised considering that there are epilepsy syndromes, such as Lennox-Gastaut syndrome, wherein it is usual to have both generalized and focal seizures. Regardless, an epilepsy type should not be confused with an epilepsy syndrome, which refers to some "clusters of signs and symptoms customarily occurring together".[14,19]

ETIOLOGY OF EPILEPSY

Etiology of epilepsy is a major determinant of its clinical course, and has critical implications on its management and prognostic counseling.[20] Therefore, the clinician is encouraged to consider the etiology of patient's seizures from the very first contact. If etiology is not clear at initial presentation, it should be reconsidered at all further decision points.[14,21] The ILAE Task Force has defined six etiological categories for epilepsy, selected because of their potential therapeutic consequences. These categories are: (i) structural, (ii) genetic (iii) infectious (iv) metabolic (v) immune, and (vi) unknown.[14,22] The categories are not hierarchical and more than one might frequently apply; i.e., a seizure or an epilepsy can belong to more than one etiological subgroup.[23] In general, "unknown" is the most common etiology as a cause is often unidentifiable in most of the patients with epilepsy.[1]

PATHOPHYSIOLOGY OF EPILEPSY

The pathophysiology of epilepsy and seizures is diverse, accounting for the many different types of seizure disorders. However, one common phenomenon seen across epilepsies is a disrupted balance between the inhibitory (via GABAergic signaling) and the excitatory (via glutamatergic signaling) drive at the synaptic level, in favor of the latter, which can transform normal neuronal circuits into epileptic circuits (epileptogenesis) and contribute to generation of seizures (ictogenesis).[24-26] Interictal spikes commonly observed on EEG recordings from epilepsy patients could associate with a large depolarization and subsequent outbreak of action potentials in the individual neurons. The shift towards excitatory transmission occurs due to both selective loss of inhibitory GABAergic neurons after precipitating epileptogenic insults [e.g., stroke and traumatic brain injury (TBI)] and the reorganization of neuronal circuits that favor hypersynchrony of neuronal populations.[27]

The deficit in GABA-mediated signaling and augmentation of glutamatergic transmission thus represents a simple basis for pathophysiology and pharmacotherapy of the disease; though it is now being increasingly accepted that the neuropharmacological basis of epilepsy is far more complex and multifaceted, and could involve a diverse group of biologically active substances.[28-30] Further research will possibly delineate relative contributions of different cellular mechanisms to the different types of seizures and epilepsy.[1]

CLINICAL PRESENTATION IN EPILEPSY

In patients with epilepsy, repeated occurrence of sudden, excessive and/or synchronous discharges in cerebral cortical neurons can result in a variety of clinical signs, including disruption of consciousness, disturbance of sensation, movements, impairment of mental function, or some combination of these.[1] Patients may also experience a variety of common clinical symptoms such as headache, numbness or tingling in a specific body part, confusion, sore muscles, unusual sensations (smell, taste), extreme tiredness, and loss of bladder or bowel control.[31] Furthermore, besides the physical signs, psychiatric symptoms may also be commonly seen in epilepsy patients; as an instance, interictal depression in individuals with epilepsy has been found to be more prevalent as compared to the general population or among those with other chronic disorders.[32] An epilepsy syndrome is characterized by a cluster of symptoms and signs customarily occurring in combination.[33]

Oftentimes, the appearance of clinical signs and symptoms could help in localization of the epileptogenic zone. Typically, the sign needs to be one of the earlier components of seizure in order to have localizing value since

later signs or symptoms are considered to be more likely due to the ictal spread.[34] Such seizure semiology is however subjective, and requires standardization among evaluators. Patients may experience a variety of paroxysmal events and/or semiological signs that do not represent a dominant part of a seizure or they present in the post-ictal period only, such as dystonic posturing [a sustained (>10 seconds), forced, unnatural positioning of an upper extremity on one side of the body with a clear rotational component], ictal speech (presence of clearly intelligible speech when patient already shows unresponsiveness and/or has clear distal automatisms), post-ictal aphasia, unilateral eye blinking, or ictal nystagmus.[34]

DIAGNOSIS OF EPILEPSY

The accurate diagnosis of epilepsy is essential to avoid misdiagnosis or an incorrect diagnosis, and for selection of an appropriate treatment. Effective classification of epileptic seizures should therefore be the first step when encountering a patient suspected to have epilepsy.[35] As illustrated in figure 1, the new classification of epilepsies includes several diagnostic levels: from seizure type to epilepsy type; diagnosis of epilepsy syndrome; and etiology. Typically, according to the new classification, after diagnosis of seizure type, the next step is diagnosis of epilepsy type; the third level is that of epilepsy syndrome where a specific syndrome diagnosis – with treatment and prognostic implications – can be made.[21,23]

Clinical history

In general practice, clinical history plays a significant role in correct diagnosis, and hence detailed history about the event should be sought from the patient, the family members and the eye witness (if available).[36] The "Guidelines for Epilepsy Management in India (GEMIND)" suggest that information should be sought for aura, ictus/event, and the post-ictal condition.[34,37] Patients and the relatives should be asked to describe what happens immediately before, during, and following the episode, and given an opportunity to answer this open-ended question in as much detail as they can without interruption (Table 2).[38]

- Presence of an aura may help to determine seizure type and localize the site of origin of seizure.
- The ictal event could consist of tonic-clonic movements, sudden jerking, deviation of eyes and head, alteration/loss of consciousness; also, it may be associated with physical injuries, tongue bite or incontinence.
- During post-ictal phase, patient may have confusion, drowsiness, headache or weakness.

Further features to be established include type of seizure and timing; past medical history should also be probed to gain information on previous syncopal events or possible seizures. History of trauma or symptoms of infection (e.g., stiff neck, fever, and headache) also helps in directing the evaluation. Patient should also be asked about medication, illicit drug, and alcohol use.[39] Once a putative diagnosis of a

Table 2: History taking in epilepsy: Possible questions to be presented to the patient and the witness

Present history	Past history
• When did the patient experience first seizure in life? • Does patient experience some kind of a warning or unusual feeling at the onset, or immediately before the seizure? • What happens during the seizure? • What happens immediately following the seizure? • Is there any diurnal variation? • Are there any known factors that trigger the seizure? • What is the frequency of seizure? • What has been the maximum seizure-free period since the onset of seizure? • Are there more than one kind of seizures? • Are there any injuries related to the seizures?	• Was the patient product of a normal full-term pregnancy, labor, and delivery? • Was there any asphyxia or respiratory distress at the time of birth? • Were the developmental milestones appropriate for age? • Is there any history of febrile seizures? • Is there any history of infections such as meningitis, encephalitis, and Lyme disease? • Is there any history of head injuries, especially associated with depressed skull fracture, intra-cerebral hemorrhage, loss of consciousness and prolonged amnesia? • History of brain tumor? • History of cerebrovascular accident?

Source: Ahmed SN, et al. An Approach to the Evaluation of a Patient for Seizures and Epilepsy. *Wisconsin Medical Journal* 2004;103(1):49-55.

seizure is made, the next question is whether the seizure was provoked or not.

Physical examination and investigations

History taking should be followed by careful physical examination, which should include assessment of the level of consciousness and orientation, and the cardiovascular and nervous systems. Additionally, in a patient who has fully recovered from a first seizure, it is recommended to measure plasma glucose and electrolytes; since the most common laboratory findings associated with a seizure generally include abnormal sodium and glucose levels.[39] For seizures with no known causes, simple blood tests can be an important aid in identifying the etiology, especially with certain metabolic and toxic encephalopathies.[40] Therefore, tests for measuring electrolytes, creatine kinase (CK), creatinine, liver and renal function tests should be performed on at least one occasion. Test for prolactin may help to differentiate psychogenic non-epileptic seizures from epileptic seizures in adults and adolescents.

Imaging

EEG is recommended for patients presenting with a seizure. It is a non-invasive and widely available investigation for evaluating an individual with suspected seizures, and has been the most important test in the diagnosis of epilepsy.[1,41] Chances of detecting abnormalities in EEG are better if it is done soon after the seizure or within 48 hours. Epileptiform activity includes several stereotyped phenomena like spikes and sharp waves, which are strongly associated with seizures.[47] However, it is important to note that a normal EEG does not rule out a diagnosis of epilepsy, while epileptiform discharges may also occur occasionally in healthy adults without history of seizures.[37] EEG should therefore be used to confirm, but not to exclude, a diagnosis of epilepsy.

Other imaging investigations, such as computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the brain, are not mandatory for all patients with epilepsy, but can be useful in focal seizures, seizures suspected to be symptomatic in origin, and difficult to control seizures, and in possibly revealing an underlying cause.[37] Referral to a higher center of care should be considered if the patient has not fully recovered.[36] MRI is the best method for structural imaging and is preferable to CT if readily available within an acceptable time period, in a patient who has fully recovered. If MRI is not readily available, or in an individual who has not fully recovered, CT should be used; CT is also preferred in acutely ill patients.[42] In India, it is recommended that in case requiring neuro-imaging, CT scan should be the initial imaging investigation, and decision for MRI may be based on patient's socioeconomic status and type of epilepsy.[37,43]

DIFFERENTIAL DIAGNOSIS OF SEIZURES

Misdiagnosis of epilepsy is a common problem, majorly attributable to poor history taking and overreliance on laboratory testing. This not only can have significant consequences for the affected individual, but can also exert enormous financial costs on the healthcare system. It is therefore prudent to not only appraise the risks of a false negative diagnosis, but also that of a false positive diagnosis.[44-46] The initial step while encountering a patient suspected to have epilepsy and assessing a possible seizure, assuming that the patient has recovered and is not in an emergency situation, is to identify whether the paroxysmal events are epileptic seizures.[35]

The differential diagnosis of epilepsy could possibly include all causes of episodic impairment of awareness, aberrations of mental function, falls, sensory/motor phenomena and generalized convulsive movements, which are common presenting symptoms of epileptic seizures.[35] Furthermore, there are several seizure imitators which can be fatal if missed; for example, cardiac syncope due to arrhythmias, valvular abnormalities or ischemia, hypotension, hypoglycemia and transient ischemic attacks (TIAs).[36]

Historic features suggestive of seizure include tongue biting, presence of an aura, sensation of epigastric fullness, post-ictal confusion, and focal neurologic signs; whereas events precipitated by an emotionally stressful event or preceded by light-headedness, prolonged standing, sweating, chest pain, or palpitations are more likely to be syncopal.[39] Furthermore, eye closure throughout the event is rare in true seizures but common in pseudoseizures, while a history of fibromyalgia or chronic pain syndrome is predictive of pseudoseizures. A history of trauma, neurologic or developmental disorders or a family history of epilepsy may also help to narrow down the differential diagnosis.[39]

EVALUATION OF A PATIENT WITH A FIRST SEIZURE

Evaluation of the patient who has experienced a seizure is often most revealing when conducted soon after the seizure, and should be frequently repeated to determine

whether or not any observed deficits are transient. Certain signs, such as post-ictal weakness, aphasia, or sensory dysfunction, are useful in providing lateralizing and sometimes localizing information.[47] There is no standardized algorithm for evaluation of every patient with a first seizure. Instead, a careful history and physical examination should determine laboratory testing and imaging decisions.[39]

As mentioned earlier, the history should include events directly preceding the seizure, number of seizures in past 24 hours, length and description of seizure, focal aspects, and length of post-ictal period.[48] Need for laboratory testing in a patient with a first seizure is based on patient's age and clinical context, and may include blood glucose, blood counts, and electrolytes. Those patients with a new-onset seizure should undergo an EEG and, with certain exceptions, MRI. A CT scan is useful if an acute process is suspected (e.g., intra-cerebral hemorrhage). Some common exceptions to the need for neuroimaging include children with uncomplicated febrile convulsions or with firm clinical and EEG findings consistent with well-defined idiopathic syndromes.[47]

APPROACH TO TREATMENT OF EPILEPSY

Despite its varied etiology (unknown and known), majority of epilepsies are manageable in nature,[4] and this presents a significant therapeutic opportunity. The diagnosis facilitates decision about whether to treat or not since not all epilepsies require treatment. Hence, treatment decisions must be individualized.[14] In patients with a first unprovoked seizure who have a normal (or non-focal) examination and normal (or non-specific) neuroimaging, the risk of seizure recurrence is lower, and AED therapy may be reasonably deferred until after a second unprovoked seizure.[49] However, in patients with a first unprovoked seizure who are found to have a central nervous system (CNS) abnormality on neuroimaging, such as a brain tumor, scar tissue from an old head injury, or CNS infection, the risk of seizure recurrence is high, and most clinicians would start treatment after the first unprovoked seizure. Herein, patient concerns also weigh heavily in deciding the treatment initiation after a first unprovoked seizure.[49]

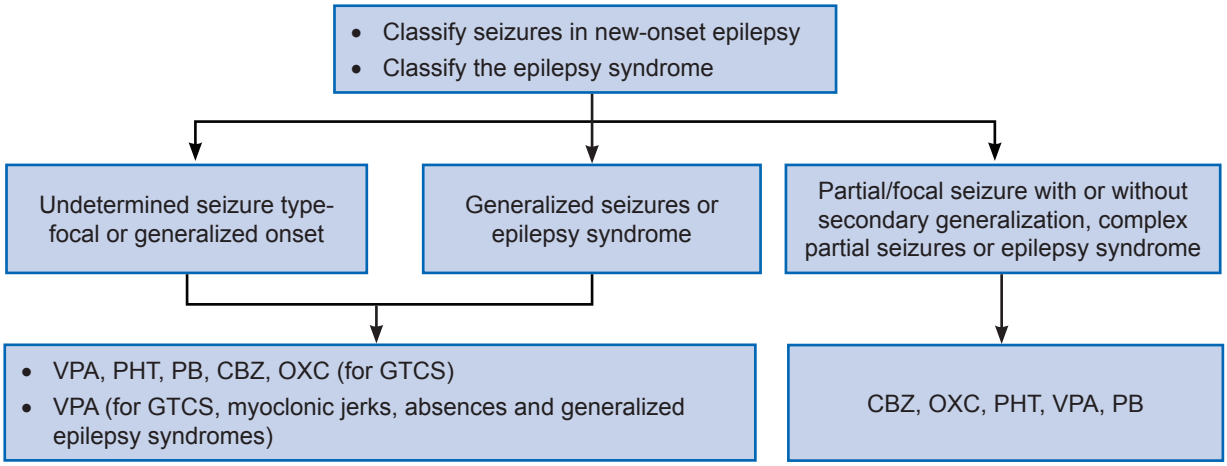
A significant opportunity in epilepsy is that many patients (approximately 50-70%) can have seizure control using a single medication (monotherapy).[47,50] Monotherapy is also desirable because it decreases the likelihood of adverse effects, avoids drug interactions, and may be less expensive than polytherapy. The GEMIND also suggests that treatment should be started with a single conventional AED (monotherapy), and dose be slowly built-up (titrated) until seizure control is achieved or side effects occur. Furthermore, it is important for physicians to note that the formulation or brand of AED should preferably not be changed since variations in bioavailability or different pharmacokinetic profiles may increase the potential for reduced effect or excessive side effects.[37] If the initial treatment does not prove effective or is poorly tolerated, then monotherapy using another AED can be tried; in which case, dose of the 2nd drug needs to be slowly increased until reaching adequate or maximum tolerated dose, and the 1st drug is then tapered off slowly. Although there is no clear supportive evidence, the second AED should have a different mechanism of action from the first. In patients who continue to have seizures even after two attempts of AEDs' monotherapy, combination therapy can be considered.[37] The following tests may be carried out before starting an AED as necessary: complete blood count (CBC), liver enzymes, and renal functions.

Choice of AED therapy

In more than 60% of patients with epileptic seizures who require treatment with anticonvulsants, AEDs help to accomplish the goal of achieving a seizure-free status without adverse effects.[51] The choice of AED, however, needs to be individualized for each patient based on factors such as the type of seizure, presence of an epilepsy syndrome, use of other medications, co-morbidities, lifestyle, and patients' preference.[48,52] In addition, it should consider the fact that different AEDs have widely different dose ranges, pharmacokinetics, and therapeutic ranges of blood concentrations. As a general rule, the drug of choice in any case should have the best efficacy (ability to stop seizures) and lowest likelihood of adverse effects.[47,50,53]

A conventional AED, such as phenytoin, phenobarbitone, carbamazepine, oxcarbazepine and valproate, may be considered as the initial drug since those are less expensive and have well-known side effects that may occur with their long-term use (Figure 2; Table 3 and 4). In patients with coexisting illnesses or those receiving other drugs such as anticoagulants, oral contraceptives, anti-retrovirals or immunosuppressants, newer AEDs can be used.[37] The newer AEDs have several unique features; for instance, levetiracetam undergoes no hepatic metabolism or protein binding, and therefore have no important pharmacokinetic interactions with other AEDs, an advantage for combination therapy.[51] Table 5 shows the initial and maintenance daily doses of some commonly used AEDs.

Figure 2 **Choice of AED among patients with new-onset epilepsy**



Abbreviations: VPA-valproate; PHT-phenytoin; PB-phenobarbitone; CBZ-carbamazepine; OXC-oxcarbazepine; GTCS-generalized tonic-clonic seizure

Source: Roy MK, et al. Chapter 116. Indian guidelines on epilepsy. Available at: http://www.apiindia.org/medicine_update_2013/chap116.pdf [Accessed on: 13/08/2018].

Table 3: AED options by seizure type

Seizure type	First-line AEDs	Adjunctive AEDs
Generalized tonic–clonic	Carbamazepine; Lamotrigine; Oxcarbazepine; Sodium valproate	Clobazam; Lamotrigine; Levetiracetam; Sodium valproate; Topiramate
Tonic or atonic	Sodium valproate	Lamotrigine
Myoclonic	Levetiracetam; Sodium valproate; Topiramate	Levetiracetam; Sodium valproate; Topiramate
Focal	Carbamazepine; Lamotrigine Levetiracetam; Oxcarbazepine; Sodium valproate	Carbamazepine; Clobazam Gabapentin; Lamotrigine; Levetiracetam; Oxcarbazepine; Sodium valproate; Topiramate
Prolonged or repeated seizures	Buccal midazolam; Rectal diazepam; Intravenous lorazepam	

Source: Epilepsies: diagnosis and management. NICE Clinical Guideline 137. Updated: April 2018. Available at: https://www.nice.org.uk/guidance/cg137 [Accessed on: 27/8/2018].

AEDs in specific patient populations

Pregnancy: Many women with epilepsy can safely become pregnant, though they are at a higher risk of obstetric complications, such as difficult labour, prematurity and low birth-weight, than normal women.[54] The possibility of pregnancy should therefore be kept in mind in women with epilepsy in the reproductive age. Pregnancy, if desired, should always be planned as some AEDs may interact with oral contraceptives and make the latter ineffective.[54] To minimize the risk of contraceptive failure, a woman using any combined hormonal contraception, or a combined oral contraceptive pill, or a progesterone-only pill should be prescribed an AED that does not induce hepatic enzymes. Levetiracetam or lamotrigine may be a reasonable alternative in women of childbearing age.[55]

In general, AEDs should be continued in pregnancy. However, therapy needs to be carefully reviewed if the woman had an offspring with malformation in previous pregnancy; and if required, AED could be changed prior to the next pregnancy. Although several AEDs are available, their use in women during pregnancy remains a dilemma for the treating clinician, especially concerning the safety data. Some AEDs like valproate may in fact show a dose-related effect, increasing the risk of major fetal malformations; added to the risk of major congenital malformation are concerns over more subtle neurodevelopmental disturbances. This risk may

Table 4: Side effects of commonly used AEDs	
AEDs	**Side effects**
Phenytoin	Ataxia, sedation, gum hyperplasia, hirsutism, memory problems, osteomalacia, skin rash, diplopia, fatigue
Phenobarbitone	Sedation, ataxia, depression, memory problems, skin rash, hyperactivity (in children)
Carbamazepine	Sedation, headache, dizziness, blurred vision, ataxia, skin rash, hyponatremia, weight gain, seizure worsening
Oxcarbazepine	Sedation, dizziness, ataxia, headache, hyponatremia, skin rash, fatigue
Clobazam	Sedation, ataxia, somnolence, irritability, depression, weight gain, tolerance
Valproate	Anorexia, weight gain, nausea, vomiting, postural tremors, hair loss, polycystic ovarian syndrome, thrombocytopenia
Topiramate	Sedation, somnolence, cognitive problems, weight loss, difficulty in word-finding, renal stones, seizure worsening
Lamotrigine	Sedation, headache, ataxia, dizziness, insomnia, skin rash
Levetiracetam	Somnolence, dizziness, cognitive slowing, psychosis
Zonisamide	Sedation, fatigue, anorexia, dizziness, renal stones, forgetfulness, skin rash, weight loss, distal paresthesia

Sources: 1. Roy MK, et al. Chapter 116. Indian guidelines on epilepsy. Available at: http://www.apiindia.org/medicine_update_2013/chap116.pdf [Accessed on: 13/08/2018]. **2.** Ahmed SN, Spencer SS. An Approach to the Evaluation of a Patient for Seizures and Epilepsy. *Wisconsin Medical Journal* 2004;103(1):49-55.

Table 5: Starting and maintenance daily doses of commonly used AEDs		
AEDs	**Starting dose***	**Maintenance dose***
Phenytoin	200–300 mg OD (HS)	200–400 mg/day
Phenobarbitone	60–90 mg OD (HS)	60–180 mg/day
Carbamazepine	100 mg BID	400–1000 mg/day
Oxcarbazepine	150 mg BID	600–1800 mg/day
Clobazam	10 mg OD (HS)	10–30 mg/day
Valproate	200 mg BID	500–2000 mg/day
Topiramate	25 mg OD	100–400 mg/day
Lamotrigine	25 mg OD (HS)	100–300 mg/day
Levetiracetam	250 mg BID	1,000–3000 mg/day
Zonisamide	50 mg OD (HS)	200–500 mg/day

*in average adults

Source: Roy MK, et al. Chapter 116. Indian guidelines on epilepsy. Available at: http://www.apiindia.org/medicine_update_2013/chap116.pdf [Accessed on: 13/08/2018]

be alleviated by using monotherapy at low dose along with folic acid. Therefore, women with epilepsy planning to have a child should preferably be treated with a single AED,[54] and be started on folic acid (5 mg/day) at the time of starting AED; though once-daily administration of AED should be used with caution in pregnancy. Newer-generation AEDs may confer improved safety in this patient population. A population-based cohort study[56] of more than eight lakh live-born infants in Denmark found that first-trimester exposure to newer-generation AEDs lamotrigine, oxcarbazepine, gabapentin, topiramate, or levetiracetam was not associated with an increased risk of major birth defects.

All pregnant women with epilepsy should be additionally advised screening for fetal malformations at 16 weeks of gestation. All women with epilepsy should be given two doses of vitamin K 10 mg intramuscularly (i.m.) at 34 and 36 weeks of pregnancy, unless there is a contraindication. Infants born to mothers taking AEDs should also be given vitamin K 1 mg i.m. at birth. If seizures occur during the labor, they should be terminated using intravenous (i.v.)

lorazepam (4 mg i.v.) or diazepam. In general, breast-feeding should be encouraged in all women with epilepsy.[57]

Children: Generally, in a child with first seizure episode, AED should not be used, but a detailed discussion with parents is required.[58] Home management of seizures includes use of rectal diazepam/buccal or nasal midazolam in seizures lasting for more than 5 minutes.[59] Nonetheless, long-term AED treatment should be started after the 2nd seizure. The drug should be started in low doses and increased gradually up to a maximum dose till seizure control is achieved or side effects appear. The dosage needs to be adjusted to the child's daily activity, with preference to extended release formulations in twice a day dosing. If no control is obtained with maximum doses of 1st drug, then a 2nd first-line drug is initiated and the first drug tapered. In most cases of epilepsy, AED is withdrawn after 2 years of seizure freedom. However, in case of adolescent onset or abnormal EEG after 2 years, which are predictors of relapse, drug should be withdrawn after 4 years. Drug withdrawal is over 3-6 months, and one drug should be withdrawn at a time in case the patient is on polytherapy.[58]

Reflex or provoked epilepsy

Seizures can be provoked by several factors, such as acute metabolic disturbances, treatment with certain drugs, and drug withdrawal (for example alcohol, benzodiazepines, and barbiturates). As follows, the risk of recurrence of such provoked seizures can be reduced by eliminating the provocative factor.[55] Seizures may also be provoked following an acute condition such as head injury, encephalitis, cerebral infarction, craniotomy and cerebral hemorrhage. While treatment can reduce the risk of such provoked seizures in certain cases, there is a lack of evidence showing the benefits of prophylactic treatment. If AED treatment is started following occurrence of provoked seizures, it should be used only in short term, unless unprovoked seizures occur later.[55]

Febrile convulsions/Infantile spasms

Febrile convulsions in children occur during fever between 6 months and 5 to 6 years of age in absence of an intracranial infection; such a child should not be labeled as having epilepsy.[37,54] CNS infections like meningitis need to be ruled out especially in children presenting in the 1st year of life. Parents of a child with febrile convulsions are advised to reduce the fever as early as possible by: (i) tepid sponging whenever temperature touches 100°F, and (ii) immediately administering medicines to lower the temperature. Covering the child with a blanket should be avoided, as it makes the body temperature to rise further.[54] While there is no consensus about prophylaxis in these patients, rectal diazepam (0.5 mg/kg) or buccal midazolam (0.2–0.3 mg/kg) can be used for acute termination of seizures lasting more than 2 minutes. Intermittent prophylaxis with oral clobazam (0.75 mg/kg in two divided doses) for 2 to 3 days is useful in preventing recurrence, though it does not prevent the future risk of developing epilepsy.[37] In infantile spasms, a corticosteroid (prednisolone) or vigabatrin can be used.

Patient counseling

Counseling by providing appropriate information about epilepsy has a potential to improve the self-management skills and increase individuals' sense of empowerment, promote adaptation to disorder, and enhance overall quality-of-life (QOL).[18] Information should therefore be conveyed in ways that are understandable and considering the culture. Counseling is also important because people with epilepsy are prone to not only physical comorbidities but also psychological comorbidities, such as anxiety and depression, which can negatively impact their QOL.[3] This burden could be related directly to the disease, or to the discrimination or stigmatization that can affect peoples' education, work, and marriage opportunities.

Counseling may also play a role in enhancing compliance. Therefore, before starting an AED, the patient should be informed about adverse effects and the realistic probability of drug's efficacy.[47] Adherence to prescribed AED regime should be strongly encouraged, and patient be asked to report any adverse effects that might compromise the adherence; missing a dose or taking twice the dose are both undesirable. Additionally, patients should be aware of the "withdrawal seizures", i.e. an abrupt discontinuation of AEDs may cause an increase in the number of seizures. Patients can be asked to keep an adequate stock of drugs with them and store the daily quota in a small container so that no dose is missed. Also, given the risk of drug interactions, patients should be asked about their current medications for any comorbidity.

Furthermore, patients should also be given verbal and written advice about driving and lifestyle changes,[42] and advised to avoid typical precipitants (e.g., alcohol, sleep deprivation). As an adjunctive, psychological interventions (e.g., relaxation, cognitive behavior therapy) may be used in conjunction with the AED therapy in adults.[52] Table 6 lists some essential advice that should be provided to epilepsy patients and their families.

Table 6: Essential information to be provided to epilepsy patients and their families

Advice to patients about their lifestyle	Advice to care-givers/families
• Driving: Avoid driving when sleepy or for an extended period • Working: Avoid working with heavy and dangerous machines • Daily activities: Avoid daily activities like cooking when tired, or has not had adequate sleep or when an aura occurs • Rural areas: Take adequate precautions while drawing water from a well or working with machines used in agriculture.	• Prevent injury to the patient • Do not attempt to force open the patient's mouth if clenched. This may break the teeth • Do not force the patient to drink anything until he/she regains full consciousness • There is no need for an extra dose of AED • Stay with the patient and provide reassurance till he/she regains consciousness • Seek medical assistance if seizure persists for more than 10 minutes or if it recurs.

Source: Epilepsy: A Manual for Physicians. World Health Organization Regional Office for South-East Asia, New Delhi. World Health Organization (2004). Available at: http://apps.searo.who.int/PDS_DOCS/B0769.pdf [Accessed on: 28/8/2018].

Dietary therapy for epilepsy

There are no special dietary restrictions for epilepsy. In fact, even the belief that consuming "cold" items of food such as ice cream or fruits such as banana will cause seizures is a misconception. However, certain special diets such as the high fat diet known as "ketogenic diet" have been found to be of some help in children with intractable epilepsy. Ketogenic diet is a stringently controlled high fat and low protein/carbohydrate diet given with/without a restricted fluid intake to maintain ketosis on a long-term basis.[58,59] Children and young people with epilepsy can therefore be referred to a tertiary care center for consideration of a ketogenic diet if their seizures do not respond to appropriate AEDs. Ketogenic diet can be used with both vegetarian and non-vegetarian diets at any age, for all types of seizures, and can improve hyperactivity and aggression in almost all patients. However, compliance with this diet is challenging since it is costly, extremely difficult to follow, and may not be liked by the patient. Furthermore, there are certain adverse effects, such as constipation, nausea, acidosis, drowsiness, weight loss, and nutritional deficiencies, which are transient and usually occur early in the diet but needs to be carefully monitored. The diet should be discontinued if there is no benefit in 3-6 months of use; though, in responders, it may be continued for 2-3 years after which it is gradually tapered.[58,59]

Long-term monitoring of AEDs

Routine monitoring of the AED levels is generally not recommended since it does not reduce the adverse effects or improve effectiveness. However, there are certain clinical scenarios which require monitoring of AED levels. These include founding of individual therapeutic concentrations once desired clinical outcomes have been reached, identifying clinical toxicity, and assessing compliance. In addition, monitoring of the AED levels may be required for guiding dosage adjustment in situations with increased pharmacokinetic variability (e.g., in patients at extremes of age, when a new drug formulation is considered, and during pregnancy).[48]

Test for calcium, alkaline phosphatase and other tests of bone metabolism should be done every year for adults taking an enzyme-inducing drug.[37] It is strongly advised that people with epilepsy maintain a seizure diary and have regular follow-up. The first follow-up may be undertaken anytime within 2 to 4 weeks of treatment initiation and subsequently at every 3 to 6 months, depending on the clinical control of seizures and treatment tolerance.[37]

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