

SEA-MENT-134
Distribution: General

Epilepsy: A Manual for Physicians



World Health Organization
Regional Office for South-East Asia
New Delhi

Acknowledgements

This document is based on contributions from experts in the WHO South-East Asia Region, including the following: Dr P. Satishchandra, Dr G. Gururaj, Dr Q.D. Mohammed, Dr N. Senenayake, Dr O. Silpakit and Dr P.A. Dekker.

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1. INTRODUCTION

Epilepsy is a common but serious brain disorder. It is universal, with no age, sex, geographical, social class or racial boundaries. Epilepsy imposes a large economic burden on health care systems of countries. There is also a hidden burden associated with stigma and discrimination against the patient and even his/her family in the community, workplace, school and home. Many patients with epilepsy suffer severe emotional distress, behavioural disorders and extreme social isolation. Thus, the Regional Office for South-East Asia (SEARO) of the World Health Organization (WHO) has decided to give high priority to the control of epilepsy in the community.

2. WHAT IS EPILEPSY?

Epilepsy can be defined as “the occurrence of transient paroxysms of excessive or uncontrolled discharges of neurons, which may be due to a number of different causes leading to epileptic seizures”. The actual presentation or manifestation differs among individuals, depending upon the location of the origin of the epileptic discharges in the brain and their spread.

A person should only be diagnosed as having “epilepsy” if there are recurrent manifestations i.e. there should be at least two or more unprovoked similar episodes at least 24 hours apart. Hence, the first episode of a seizure is called a “single seizure” and not epilepsy.

Epilepsy can also be divided into active and inactive epilepsy, with active epilepsy being defined as two or more epileptic seizures in the last five years that are unprovoked by any immediate identified cause.

An epileptic seizure is an event in which an individual is not aware of the surroundings, either completely or partially. Various motor movements, such as shaking of limbs; sensory phenomenon, such as electric shock-like sensation over a specific area; behavioural experiences, such as fear or confusion or autonomic disturbances such as excessive secretion of saliva or bladder/ bowel incontinence could occur in association with this altered sensorium. The epileptic seizure occurs all of a sudden as a “bolt from the blue” and ceases on its own, just as suddenly. Usually it is very brief, lasting from a few seconds to minutes. Only in very rare cases will it be continuous, resulting in “status epilepticus”, i.e. a seizure lasting more than 30 minutes or recurrent seizures without the individual regaining consciousness between attacks. However, often patients or their relatives describe a single attack that lasted for hours. This is invariably due to the fact that patients are drowsy or confused soon after cessation of the seizure, a state described as post-ictal phenomenon. This phenomenon may last for a few hours, rarely for more than a day, but the eyewitness often confuses this as part of the attack and reports it as a long duration of seizure.

3. WHAT IS NOT EPILEPSY?

Since the diagnosis of epilepsy involves long-term management and carries a lot of social and psychological stigma, one needs to differentiate it from other common conditions resembling it. More often than not, fainting episodes known as “syncope” are wrongly diagnosed as epilepsy, while in small children breath-holding spells during a temper tantrum are often erroneously classified as being epileptic in origin.

3.1 Non-epileptic “Seizure-like” Attacks/Pseudoseizures

These are also called psychogenic or hysterical seizures. They are more common in women usually during puberty and early adulthood and do not respond to any drugs. Usually, these are “dramatic” and “bizarre”, and last longer than true seizures.

Sometimes, a patient suffering from epilepsy may, in addition, start getting pseudoseizures which may be very difficult to differentiate from true seizures. A careful observation of one such attack aids diagnosis, although sophisticated tests may sometimes be required to differentiate the conditions. About 20% of those diagnosed to have epilepsy even in the best of centres may actually have pseudoseizures.

Conditions mimicking seizures
Non-epileptic “seizure-like” attacks/pseudoseizures Syncope or fainting Some forms of stroke (e.g. transient ischaemic attacks) Some sleep disorders (eg. sleep apnoea) Night terrors Emotional outbursts Breath-holding spells Hypnagogic (hypnic) jerks

Differences between epileptic seizures and non-epileptic “seizure-like” attacks/ pseudoseizures		
	Epileptic attacks	<i>Non-epileptic attacks</i>
A. Clinical features		
Resemble classical seizure patterns	Yes	<i>No</i>
Tongue biting	Yes (sides of tongue)	<i>Rare (tip of tongue)</i>
Duration	Short	<i>Long</i>
Postictal phenomenon	Present	<i>Absent</i>
Injury	Yes, sometimes severe	<i>Rare, less severe</i>
Occurs in sleep	Yes	<i>No</i>
Can be precipitated by suggestion	No	<i>Yes</i>
B. Laboratory tests		
EEG during the attack	Abnormal discharges	<i>No change</i>
EEG after the attack	Slowing pattern	<i>No change</i>
Antiepileptic drug usage	Suppress seizures	<i>No change (may worsen)</i>
<i>Serum prolactin levels (during generalized attacks)</i>	<i>Raised</i>	<i>No change</i>

3.2 Syncope

Syncope is much more common than epilepsy, and the main differences from epileptic seizures are shown in the table below. There is loss of consciousness due to a sudden decrease in the cerebral blood flow.

Differences between epileptic seizures and syncope		
	Epileptic attacks	Syncope
Precipitant Circumstances	Unusual (often lack of sleep) any	<i>usual (emotion, pain) usually upright position, crowded, hot surroundings, emotionally stressful situations</i>
Onset	sudden or aura	<i>gradual</i>
Motor phenomena	tonic or tonic-clonic movements with characteristic amplitude and frequency	<i>flaccid, uncoordinated clonic jerks of low amplitude</i>
Respiration	stertorous, foaming	<i>shallow, slow</i>
Incontinence	common	<i>rare</i>
Tongue-biting	common	<i>rare</i>
Vomiting	unusual	<i>often</i>
Injury	common	<i>rare</i>
Post-ictal	drowsy, confusion, sleep	<i>usually rapid recovery without confusion</i>
Duration	<i>minutes</i>	<i>seconds</i>

3.3 Transient Ischaemic Attacks

These attacks occur in an older age group and are caused by a transient reduction in blood supply to parts of the brain, usually secondary to arteriosclerosis of the cerebral and carotid arteries. Disturbances of consciousness may be associated with focal paralysis, disturbance of speech or loss of vision which occurs for minutes or hours. More prolonged symptoms may indicate a more serious cerebrovascular accident (stroke).

3.4 Sleep Apnoea

Sleep apnoea is a disturbance of the respiration during sleep, with interruption of respiration for about half a minute or longer. This can occur many times in one night. The patient is not aware of these spells.

3.5 Night Terrors, Nightmares and Sleep Walking

These are often familial and occur in childhood, mostly between the ages of 4 and 14. Nightmares occur during REM phase of sleep. Night terror (pavor nocturnus) and sleep walking occur during deep sleep.

3.6 Emotional Outbursts

Swoons and tantrums, might be confused with simple partial or complex partial seizures. In a swoon, the patient slowly drops to the floor, with closed eyes, followed by lying inert on the floor with peculiar eyelid flickering. Swoons are a way of avoiding difficult situations, unpleasant thoughts or memories. In a tantrum, the subject throws himself to the floor screaming, thrashing about and kicking. Often the subject bites himself or even bites onlookers. Tantrums frequently occur in children particularly immature or brain damaged people as an expression of anger and frustration.

3.7 Breath-holding Spasms

These occur in infants and children between one and five years old. They are usually caused by anger in children who cannot restrain their emotions. There is a sudden arrest of respiration followed by cyanosis, unconsciousness and sometimes twitching lasting a few seconds. The attack stops spontaneously and never results in brain damage.

3.8 Hypnagogic (Hypnic) Jerks

Jerks (hypnagogic startles, hypnic jerks) when falling asleep are not rare, but often are mistaken for epilepsy.

4. PHASES OF A SEIZURE

Four components of a seizure can be distinguished. Not all seizure types will have all these stages. The presence or absence and the nature of these stages are important for diagnosing the seizure type.

4.1 Prodromal Phase

This phase begins a few hours or even days before the actual seizure and should not be confused with the aura. Prodromal symptoms include: headache, irritability, insomnia, bad temper, depression or increased activity.

4.2 Aura

An aura precedes the seizure by seconds or a few minutes. It is the beginning of the seizure and signals the focal onset of the seizure. The symptoms depend on the location of this focus. The feelings of the aura are often vague and indescribable, leading to extreme fear. Strange epigastric sensations, dreamlike experiences, unpleasant smells, etc. may occur. The patient remembers the aura very well, and although he/she will not always be able to recount it, he/she can affirm the presence of it, as it happens before consciousness is lost.

4.3 Seizure (Ictus)

In most seizures there is a loss of consciousness, and the patient is therefore not able to give any information about the actual ictus. For this we are dependent on witnesses who have seen the actual seizure. The patient has no memory of the seizure.

4.4 Post-ictal Phase

This phase may be absent, brief or may last several hours, and sometimes even days. There is usually a deep sleep and waking up with headache, tiredness, irritability, vomiting, confusion,

muscular aches or ataxia. Transient paralysis of a part of the body, known as Todd's paresis may occur for a few hours or days. Altered speech or aphasia may occur when the dominant hemisphere of the brain has been involved. Altered behaviour and emotional outbursts may occur, and if patients are restrained or interfered with, they may become violent.

5. CLASSIFICATION OF EPILEPTIC SEIZURES

Epilepsy can broadly be divided into two categories: idiopathic where there is no known cause, and secondary seizures where there is known cause.

Seizures can be either generalized or partial (or focal). In generalized seizures, both halves of the brain are simultaneously affected. In partial seizures, the abnormal electrical discharge starts from a focus in one side of the brain. Later, this may spread to the other side. This spread is called secondary generalization.

5.1 Generalized Seizures

In generalized seizures, patients suddenly stop what they are doing, the eyes and head turn to one side and the body becomes stiff. This is usually followed by several jerks of the hands and legs, groaning and frothing from the mouth. During the episode, the tongue may be bitten or severe injury can result from a fall or an accident. Sometimes the patient may pass urine or stools. The body relaxes after a few minutes and the patient sleeps for a variable period. The patient is completely unaware of the seizure. Such seizures can also occur in sleep.

Generalized seizures consist of many different seizure types, of which the primary generalized tonic-clonic seizure (GTCS) is the most common.

Tonic-clonic seizure

In a generalized tonic-clonic seizure the patient loses consciousness, falls down, sometimes with a scream, and develops a generalized stiffness (the tonic phase). Breathing stops, as all the muscles of the trunk are in spasm, and the patient becomes cyanotic, the head is retracted, the arms flexed and the legs extended. After a while, this tonic phase is followed by the clonic phase, when the muscles alternately contract and relax, resulting in clonic movements. During this jerking the patient might bite his tongue, pass urine, or sometimes stool. The clonic phase may last several minutes. When all the jerking stops and the patient regains consciousness, he may feel very tired and have a headache and confusion. He has no memory of what happened, and may find himself on the floor in a strange position. Often he falls into a deep sleep. The frequency of the seizure may vary from one a day to one a month or once a year, or even once every few years. Either the tonic phase or the clonic phase can predominate in the seizure. Generalized tonic-clonic seizures can also occur due to secondary generalization in partial epilepsies.

Clonic seizures

These seizures are generalized seizures, where the tonic component is not present, only repetitive clonic jerks (clonic jerks are repetitive rhythmic flexing and stretching of limbs). When the frequency of jerks diminishes the amplitude of the jerks does not diminish.

Tonic seizures

Tonic seizures are sudden sustained muscle contractions, fixing the limbs in some strained position. There is immediate loss of consciousness. Often there is deviation of eyes and head towards one side, sometimes rotation of the whole body.

Absence seizures

These are short periods of loss of consciousness lasting only a few seconds (not more than half a minute). They are of sudden onset, there are usually no, or only minimal motor manifestations. There is a blank stare, brief upward rotation of the eyes and an interruption of ongoing activity. The child is unresponsive when spoken to. It is suddenly over, and the child continues what he was doing before the seizure. The child has no memory of these seizures. During such an absence seizure the child does not hear what the teacher is saying, and as they occur very often the child cannot follow the lessons any more. Unless the teacher is aware of this condition, he will scold the child for daydreaming and inattentiveness. Most parents are unaware of these small seizures, and even when they observe them, do not think them important and will not mention them to the doctor. Unless these children also suffer from generalized tonic-clonic seizures they are not brought to a doctor as people are unaware that these absences are epileptic seizures. Absences are easily provoked by hyperventilation. They should not be confused with brief complex partial seizures. Typical absences occur in school-aged children and can occur many times a day.

Myoclonic seizures

These seizures consist of sudden, brief, shock-like muscle contractions, either occurring in one limb, or more widespread and bilateral. They may be single jerks, or jerks repeated over longer periods. They are often seen in combination with other seizure types occurring in special epileptic syndromes.

Infantile spasms

Patients have flexor spasms of the head, bending of the knees and flexion with abduction of the arms. They occur in the first year of life, and are very difficult to treat.

5.2 Partial Seizures

Partial seizures are divided into two groups, simple partial seizures where consciousness is maintained, and complex partial seizures where there is an impairment of consciousness.

Simple partial seizures

In simple partial seizures, some patients may experience either motor or sensory phenomena. Such seizures arise from a specific area of the brain, with the patient being fully or partly aware of the event. In motor seizures, the focus is in the primary motor cortex. There are twitchings, starting in a distal part of the extremity, or in the face. The twitching may remain localised, or spread up the whole extremity and even become completely generalized to involve the whole body. Sensory seizures have their focus in the post-central gyrus (primary sensory cortex). There might be feelings of tingling, pins and needles, cold or heat, or numbness of a limb. Sometimes there may be strange feelings with visual signs, or hearing or smelling sensations. Autonomic seizures are associated with foci in the temporal lobe. There maybe: a sensation rising from the epigastrium to the throat, palpitations, sweating or flushing. The psychic symptoms may consist of changes in mood, memory, or thought (thinking). There may be distorted perceptions (time, space, or person) or problems with language. Structured hallucinations could occur (music, scenes). These simple partial seizures are usually only recognized as epileptic seizures when they develop into generalized seizures.

Complex partial seizures

Here the patient has impaired consciousness, but NOT complete loss of consciousness. He is slightly aware of what is going on, but he cannot respond to anything, neither can he change his behaviour during an attack. The seizure usually starts with an aura which can be of many types such as, a strange feeling in the stomach rising up to the throat and head, or a sensation of light, smell, sound or taste or with changes in perception, e.g., of time (time seems to pass too slowly or too fast), of light or sound or space. The surroundings may suddenly seem completely strange and different in scale (things seem larger or smaller than usual), or there is déjà vu (a sensation of things having happened before). These feelings can cause the patient a great deal of anxiety. Sometimes the seizure occurs with hallucinations or with psychomotor symptoms such as automatisms e.g., pulling at the clothes, chewing, lip smacking, or repeated aimless movements. These automatisms may become very complex, the patient is able to perform difficult tasks, or travel somewhere, but later not remember having done such a thing. He suddenly regains full consciousness and finds himself in a completely different place. During such an automatism the patient may become aggressive and violent when restrained. There is slow recovery after a complex partial seizure, with a period of confusion. After the attack, there is complete amnesia regarding the attack. These seizures were previously called 'psychomotor seizures', and as the localization of the abnormal discharge is often in the temporal lobe, the epilepsy is often called 'temporal lobe epilepsy'. However, the focus could also be in the frontal lobe.

During his lifetime, a patient does not necessarily have only one type of seizure. The type may change over the years, depending on the age and maturation of the brain. Moreover, one patient may have a combination of different seizure types.

Rashmi is an eight-year-old girl, studying in class III, with normal physical and mental development. She has had four or five seizures in the last one year. During these episodes, she complained of a sense of fear, ran to hold her mother, stared at a particular spot and smacked her lips. During this time, she was not responsive and the experience lasted for about one minute. Following this, she remained confused for 10–15 minutes. Later, neither did she remember the incident nor was she able to recollect what had happened.

Rashmi has complex partial type of epilepsy.

The doctor–patient interview

Ms S: Doctor, I am so worried about my 15-year-old daughter. She has had spells of odd behaviour, following which she loses consciousness. This has happened five times.

Doctor: Ms S, can you please tell me when it started?

Ms S: It happened suddenly about three months ago. She mentioned an odd feeling in her stomach, and before we realized it, she had lost consciousness.

Doctor: Can you please explain a little more? Do you remember the date? What time was it? What was she doing when she complained of that feeling?

Ms S: It was about six in the evening. She had returned from school and was relaxing in a chair with a book in her hand, when all of a sudden she complained of an odd sensation in the stomach. She had a dazed look on her face and started behaving in a strange manner, touching the chair and the book. She didn't answer when called, and appeared to be in a dazed state of mind. This was about three months ago. But I don't remember the date.

Doctor: Did you call her by her name? Did she respond? By any chance, did you notice any movements of the lips or jaw?

Ms S: Now that you ask me, I recollect that she was muttering something. She was moving her jaw as if she was eating something! (Ms S proceeds to demonstrate the movements).

Doctor: *What happened next?*

Ms S: She walked around without any specific purpose, and didn't respond when called. Then suddenly, she fell down unconscious, and started moving both limbs vigorously. It was uncontrollable, like a fit. This went on for two minutes. She was frothing at the mouth, and had soiled her clothes. It was very frightening! We placed a key in her hand, but it didn't help.

Doctor: *Did she hurt herself? Did she bite her tongue?*

Ms S: We all held her tightly, hence, she didn't get hurt. But saliva, froth and blood were drooling from her mouth. Yes, she had bitten her tongue.

Doctor: *When did she regain consciousness?*

Ms S: She slept for an hour and when she woke up, she complained of muscular pain and exhaustion. She has had four such episodes in the last three months.

Doctor: *When was the last attack?*

Ms S: The last attack was about seven days ago.

Doctor: *Did your daughter have any convulsions following fever when she was less than six years old?*

Ms S: No, she did not have any such convulsions.

This patient has generalized tonic-clonic type of epilepsy.

6. DIAGNOSIS OF EPILEPSY

It is essential that patients with episodes such as described above be accompanied by a witness who can describe the episodes in detail. More often than not, epilepsy can be diagnosed on the basis of reports of patients and eyewitnesses. No laboratory test can replace a clear description provided by the eyewitness. Electroencephalography (EEG), which records electrical activity from the surface of the head can, in some cases, support the diagnosis. When epilepsy is diagnosed, it is necessary to document the type of epilepsy, determine the cause, evaluate the intelligence and social background of the patient. This information is extremely useful for further patient management.

Those who develop epilepsy for the first time require investigations to identify the underlying cause. These investigations include EEG, and imaging tests such as CT scan or MRI of the brain.

7. PREVALENCE OF EPILEPSY

Approximately 50 million people are affected by epilepsy globally. About 40 million or 80% are assumed to live in developing countries. Multiple studies worldwide indicate that the prevalence of epilepsy globally is in the range of 5 to 8 per one thousand population. Methodological issues in addition to definitions and case ascertainment may explain some of the variations of prevalence estimates.

India: Studies from different parts of the country reveal that the problem varies from 8.8/1 000 in Bangalore, 5/1 000 in Mumbai, 3/1 000 near Kolkata to 4/1 000 in New Delhi.

Sri Lanka: In a survey in the Kandy district, it was observed that 9 out of 1 000 people had epilepsy.

Thailand: A survey of nearly 3 000 people in Thailand revealed that 50 had probable epilepsy.

Bangladesh: Though there are no national statistics, it is estimated that there are at least 1.5–2.0 million people with epilepsy.

The problem will be similar in countries such as Bhutan, DPR Korea, Maldives and Nepal as these countries share similar sociocultural and demographic characteristics. If these figures are applied to any local population, it will be possible to know the approximate number of people requiring help in the given geographical area.

The exact difference in the number of cases and the causes of seizures between urban and rural areas is not clearly known. A recent study in Bangalore, India, reported that the problem is nearly 2½ times higher in rural areas as compared with urban areas. The exact reason for this rural-urban difference is not known; lack of facilities for good antenatal/postnatal care, birth injury, malnutrition and childhood infections are probably responsible. The burden of epilepsy in rural areas is likely to be more than in urban areas as access to services is limited.

Epilepsy occurs across all sections of society. While there are no systematic studies on the subject, it is possible that a greater number of people from the lower socioeconomic sections of society will be affected by epilepsy.

8. NATURAL HISTORY OF EPILEPSY

With currently available drug treatment and good compliance, an affected person can be seizure-free for life. In nearly 60–70% of such individuals, epilepsy is short-lived and once remission has occurred, a subsequent relapse is not common. Long-term studies have indicated that the relapse rate over a period of time is about 1% per year for persons who have remained seizure-free for more than two years with adequate treatment. The condition remains active in a small proportion of affected individuals. Such individuals have recurrent seizures, a poor prognosis and require lifelong management.

9. MORTALITY IN PATIENTS WITH EPILEPSY

The risk of premature death in people with epilepsy is 23 times higher than the general population. The exact cause of the increased risk is not known in most cases i.e. the cause of sudden unexpected death in some patients. However, some deaths are related to the circumstances around a seizure such as a serious accident during a seizure.

10. PRECIPITATING FACTORS, CAUSES OF SECONDARY SEIZURES AND RISK FACTORS

In some patients there are certain precipitating or triggering factors for epilepsy, for example:

- Loss of sleep: Sleep deprivation is a definite precipitating factor for some, and hence needs to be avoided.
- Flickering lights: In a few patients, flickering bright lights, such as in discotheques may precipitate seizures. If a patient's seizures are precipitated by such lights, these should be avoided. However, not ALL people with epilepsy need to avoid bright, flickering lights.
- Alcohol abuse: Excess consumption of alcohol may lead to seizures. Seizures may also occur when recovering from an episode of excess alcohol consumption.

Patients should carefully identify their own precipitating factors and report them to the treating physician. Once a triggering factor is recognized, it should be avoided.

A few common causes of secondary/provoked seizures in different age groups	
<p>Newborn Birth injury Metabolic abnormalities Congenital abnormalities Genetic causes</p> <p>School-age child Genetic causes Infection Fever Injury</p> <p>Adult (26–50 years) Alcohol abuse Infection Tumors Injury Stroke</p>	<p>Infant (less than one year of age) Birth injury Infection Fever</p> <p>Young adult (15–25 years) Genetic causes Infection Metabolic abnormalities Tumour</p> <p>Elderly (50 plus) Stroke Tumour Injury Alcohol abuse</p>

Possible risk factors and their contribution	
Risk factor	Contribution to risk of seizure
Febrile seizures (repeated)	3–20% develop recurrent seizures (epilepsy)
Family history of epilepsy	Not known clearly, may increase risk
Brain infections	5–10% will have seizures at the time of infections
Brain injuries	5–10% will have seizures at the time of injury and another 10% during later years
Cerebrovascular disorders	5–15% develop seizures
Mental retardation or cerebral palsy	10–20% have seizures
Brain tumours	The majority will have seizures
HIV/AIDS	60% will have seizures at some time
Alcohol abuse	Heavy usage and withdrawal seizures
Drug abuse	Depends on type and dose of drug
Metabolic conditions: hypocalcaemia, hyponatraemia, hypoglycaemia	Variable: depends on severity of condition and age of patient

11. EPILEPSY AND HEREDITY

Some forms of epilepsy, but certainly not all, are hereditary, i.e. inherited due to genetic defects. Seizures are an important manifestation of more than 150 single-gene disorders. In certain parts of India, for example, South India, consanguineous marriages (uncle–niece) are in practice. This type of marriage should not be encouraged in the event of a family history of epilepsy. Genetic counselling may be necessary for such families.

12. INFANCY AND EPILEPSY

Infants below the age of one year may have prolonged seizures, sometimes lasting up to thirty minutes or one hour. Since these seizures may be bizarre and fragmented, it is difficult to make a correct diagnosis. Child specialists need to be knowledgeable about the different types of childhood seizures. The common causes for seizures during infancy are birth injury, metabolic disturbances and brain infections. In addition, there are certain special forms of epileptic syndromes, such as infantile spasms. These need to be diagnosed and properly treated to prevent the development of mental handicaps and intractable epilepsy.

13. FEBRILE CONVULSIONS

Some children less than six years of age are prone to convulsions when they have high fever. These are known as febrile convulsions and the child should not be labelled as having epilepsy. Parents are advised to reduce the fever as early as possible by: (1) tepid sponging whenever the temperature touches 100°F and (2) immediately administering medicines to lower the temperature. Many parents cover their children with a blanket during the fever. It is not unusual to see parents bringing completely covered children to the clinic. This should be avoided, as covering the child with a blanket makes the body warmer and the body temperature to rise further. Apart from this, rectal/oral diazepam should be administered at the onset of fever. Generally, these children do not require antiepileptic drug treatment, since febrile convulsions are a benign condition, disappearing spontaneously after six years of age, by which time the brain is fully mature.

14. EPILEPSY AND WOMEN

14.1 Catamenial Epilepsy

Approximately two-thirds of women with epilepsy complain of an increase in seizure frequency at the time of menstruation. The term “catamenial epilepsy” is applied if the seizures are immediately prior to or during the menstrual cycle. These seizures could be hormone-related, due to fluid and electrolyte imbalance or increased stress during this period. Sometimes physicians prescribe acetazolamide for women with catamenial epilepsy for about 1 week during the periods.

14.2 Oral Contraceptives and Antiepileptic Drugs

Women with epilepsy who use oral contraceptives should be warned about the decreased efficacy of these agents, as antiepileptic drugs interact with oral contraceptives. Women who experience breakthrough bleeding need to practice a barrier method for the rest of the cycle, since the bleeding is an indication that the agent may not provide adequate protection against pregnancy.

14.3 Pregnancy and Epilepsy

Approximately two-thirds of women with epilepsy can safely become pregnant. In some women, the pregnancy has no effect on epilepsy, in some it improves epilepsy, but in one-third of women with epilepsy, there is a worsening of their epilepsy status. This could be due to many reasons, such as fall in the serum antiepileptic drug levels due to the physiological changes/growth of the foetus. Some women may not take antiepileptic drugs regularly during pregnancy because of fear that their unborn child may be harmed. Premature labour and other obstetric complications are said to be higher in women with epilepsy.

A hormone-related cause could also be the reason for the worsening of the epilepsy. The risk of foetal malformations is three times higher in pregnant women than the general population on multiple drugs. Women with epilepsy planning to have a child should preferably be treated with a single antiepileptic drug. Generally, neurologists recommend carbamazepine as the safest anti-convulsant during pregnancy. However, patients need to continue on a relatively safe antiepileptic drug and understand that if drugs are reduced, there is a risk of seizure recurrence and frequent seizures in the mother may affect the unborn child. Women with epilepsy are usually advised to use folate supplementation before and during pregnancy, till delivery. This is believed to prevent neural tube defects in the child.

14.4 Problems in Babies Born to Mothers with Epilepsy

The chances of perinatal problems such as difficult labour, prematurity and low birth-weight are a little higher in the case of pregnancies of women with epilepsy than in normal pregnancies. The risk of jaundice during the neonatal period could also be higher in these children. Congenital malformations in newborns are sometimes associated with pregnant women who have been treated for epilepsy with anti-epileptic drugs such as phenobarbital, valproic acid, phenytoin and carbamazepine.

14.5 Breastfeeding

This practice should be encouraged in SEAR Member Countries to overcome protein-calorie malnutrition among children. As antiepileptic drugs do pass through the breast milk to the child, the latter could experience some side effects. The mother should be cautioned about these possibilities. Only those women who are on some newer antiepileptic drugs are not allowed to breastfeed their babies. Specific side effects of antiepileptic medications on the baby being breast fed are shown in Annex 1.

15. EPILEPSY IN THE ELDERLY

As longevity is increasing in most South-East Asian countries it is not uncommon to find epilepsy among the elderly. Special precautions should be observed when treating epilepsy in this age group. Some specific suggestions for the elderly are given below.

Some dos and don'ts for the elderly with epilepsy

- Avoid multiple drug therapy.
- Antiepileptic drugs might cause increased drowsiness, so one needs to be careful, especially when outside the house alone.
- Kidney and liver damage are not uncommon and hence proper dosage of the medications needs to be calculated.
- The elderly are prone to dehydration and electrolyte imbalance, particularly in tropical countries, which may affect antiepileptic drugs.
- More often than not, elderly people are on other medications. Hence, drug interactions need to be considered before the proper antiepileptic drug can be chosen.

16. TREATMENT GAP

The difference between the number of people with active epilepsy and the number of people who are being appropriately treated in a given population at a given point in time, expressed as a

percentage is known as the “treatment gap”. It has been estimated that 90% of people with epilepsy in developing countries are inadequately treated. From the point of view of the person suffering from epilepsy, fear of stigmatization, cultural beliefs, lack of knowledge and illiteracy contribute to the fact that people with epilepsy or their proxies do not seek treatment. Other potential factors contributing to the treatment gap include economic issues, distance to health facilities, inadequate supply of antiepileptic drugs and lack of prioritization by health authorities.

Treatment gap noticed in select SEAR Member Countries	
Yelandur, South India	<i>78% untreated at first contact</i>
Bangalore, South India	<i>10% (urban) and 24% (rural) were not on treatment</i>
Kashmir, North India	<i>75% not on treatment at first contact</i>
Kandy, Sri Lanka	<i>50% initiated on treatment for the first time</i>

Poor seizure control contributes to the impact on disability of persons with epilepsy. Social isolation, dependence, low educational performance, poor employment opportunities, loss of productivity, and personal injury are all intangible costs adding to the burden of epilepsy.

Many people with epilepsy seek treatment from faith healers or religious healers for which they spend large sums in cash or kind, but with no beneficial effects. According to a prevalence study in Silivri, Turkey, 65% percent had visited religious figures at the onset or during the course of the disease. In a more recent study from Gambia, among persons with lifetime epilepsy, it was shown that traditional treatment i.e. originating within a set of cultural beliefs, had been used by all. In a study from rural India where only 12% of children with epilepsy were on treatment, it was shown that 62% of these had sought help in the past from a qualified practitioner and 44% from traditional practitioners. Approximately one third had received help from both.

The stigma related to epilepsy emanates from the many myths and misconceptions perpetuated about the disease. Thus, people with epilepsy do not want to be identified as having epilepsy, and do not come forward to obtain treatment, even in the best of situations.

17. MANAGEMENT OF EPILEPSY

People with epilepsy want to live seizure-free lives and be free from the fear of future attacks. It is usually the fear of attacks which interferes with the day-to-day activities of affected people.

The first effective antiepileptic drug, phenobarbital, was discovered in 1912. This drug continues to be the mainstay of medical management of epilepsy in SEAR Member Countries. Several other drugs have entered the market in the last ten years and are advocated to be far superior to phenobarbital, but evidence-based reviews do not verify this.

The comprehensive management of epilepsy includes many aspects, such as:

- Essential information to be provided to patients and their families.
- Information about first-aid during a seizure which even the family can provide.
- Information for physicians treating epilepsy.

- Management of status epilepticus as a medical emergency.
- Ensuring compliance with treatment.
- Modes of treatment other than medicines.

17.1 Essential Information to be Provided to Patients and Their Families

Advice to care-givers about care for patients

- Although seizures look frightening, they are not directly dangerous to the patients who, often, will have no recollection of the episode.
- Seizures are generally self-limiting, i.e. they stop spontaneously.
- Every adult in the family should be aware of the first-aid measures which can be administered by them.
- Injury to the patient should be prevented.
- There should be no attempt to force open the patient's mouth if clenched. This may break the teeth.
- Until the patient has regained full consciousness, they should not be forced to drink anything.
- There is no need for an extra dose of antiepileptic drugs.
- The care-giver needs to stay with the patient and provide reassurance once the patient regains consciousness.
- If the seizure persists for more than 10 minutes or if it recurs, medical assistance should be sought.

Advice to patients about their lifestyle

If seizures are well controlled, patients are encouraged to lead as normal a life as possible, conducting activities of daily living, working and recreation. However, certain precautions must be taken.

- **Driving:** Driving a motor vehicle is an essential part of living and working in urban areas. Each country has its own law about people with epilepsy and driving. Even if the patient is within the law and has a valid driving licence, routine precautions, such as not driving when sleepy or avoiding driving for an extended period should be taken.
- **Working with heavy machines:** Although people with epilepsy are encouraged to work, working with heavy and dangerous machines should be avoided.
- **Daily activities:** Simple precautions should be taken while engaging in daily activities and doing chores around the house, such as cooking. These activities should be avoided when the patient is tired, has not had adequate sleep or when an aura occurs.
- **Rural areas:** Although life is simpler in rural areas compared to urban areas, there are other hazards, such as falling into a well, into an open fire or getting limbs cut while working with machines such as harvesters, threshers and tractors used in agriculture. Patients and families should take adequate precautions.

17.2 Information About First-aid During a Seizure Which Even the Family can Provide.

The first step in the management of any seizure is to stop it through specific first-aid measures.

Generalized tonic-clonic seizure

During this type of seizure, the patient may fall down and experience jerking of the limbs. Hence, first-aid measures should ensure that the patient is safe. Usually everyone around is in panic, wanting to help. Make sure nobody interferes with the patient. The following measures should be taken:

- Help the person into a lying position, preferably on the floor.
- Make the person lie down on the side, so that any secretions from the mouth can flow out freely.
- Loosen tight clothing, remove glasses.
- Clear the surrounding area of any objects that may harm the patient.
- Do not force anything into the patient's mouth. E.g. spoon, or your own finger.
- Do not hold the patient, as the seizures cannot be stopped by restraint.

Once the seizure stops, keep the patient lying on one side to allow saliva to drain out from the mouth. Do not offer any food or drink until the patient is fully alert.

Complex partial seizure

Care-givers and health personnel should be aware of the manifestations of this type of seizure

- Such a patient should not be restrained or agitated.
- The patient should be moved to a safe place.
- The patient should not be forced to eat or drink anything till fully alert.
- Be with the patient till the seizure ends.

17.3 Treatment of Epilepsy

One-drug treatment

About 75-80% of people with epilepsy can be managed easily with one drug. This is called monotherapy, and it prevents interaction between drugs, ensures good compliance and is also cost-effective. However, the remaining 20-25% of patients may require multiple drugs. Each type of epilepsy has a drug that usually proves to be most effective. The best drug for the specific type of epilepsy should be started in a low dose, once or twice daily, depending upon the nature of the drug. Dose escalation should always be under medical guidance and needs to be undertaken slowly during follow-up, until either the seizures are controlled or undesirable side-effects appear.

Selection of Antiepileptic Drugs (AEDs)

The pharmacological treatment of epilepsy has been extensively studied primarily in high-income countries. Many controlled clinical trials have tested the efficacy of the older AEDs (such as phenobarbital and phenytoin) and newer AEDs (such as carbamazepine and valproic acid) in controlling seizure frequency and their safety when prescribed in monotherapy or in combination.

However, there is a lack of definitive evidence on the differences between the older and newer medications.

Recently, some anticonvulsants (lamotrigine, topiramate, gabapentin) have been approved in many countries. Generally these are recommended as “add on” drugs for better seizure control in patients with refractory epilepsy who are already on anticonvulsants. Approximately 20% of these patients respond with 50% improvement in their condition (defined as “responder rate”). These medications are very expensive, and are practically impossible to access by populations in most developing countries. Long-term studies have shown a disappointing tendency of patients to abandon these AEDs: only 30% of patients continued on topiramate or lamotrigine (LTG), and 10% on gabapentin after three years, due to toxicity or lack of efficacy.

In many circumstances, particularly in low-income countries, even phenobarbital or phenytoin are not available, nor supplied by governments, and when they are, continuity of supply is irregular. Frequently, economic issues lead to the interruption of treatment.

Phenobarbital is a cost-effective drug in the management of epilepsy. Its benefits far exceed its side-effects, and relative to the newer anticonvulsants, it remains the drug of choice for large-scale, community-based programmes particularly in rural and remote areas. Unfortunately, its abuse potential and side-effects, both of which are minimal, have been given too much prominence because of which the drug has fallen into disrepute. Alternative but more expensive AEDs such as carbamazepine and valproic acid have become the first-line drugs of choice in developed countries due to the perceived lower risk of possible long-term side-effects, including cognitive impairment in children. Unfortunately, these are also being extensively promoted in developing countries. The Global Campaign Against Epilepsy, jointly sponsored by WHO, the International League Against Epilepsy and the International Bureau for Epilepsy advocates the use of phenobarbital for closing the currently high treatment gap (as much as 90%) in low-income countries. In resource-poor countries, low-cost AEDs such as phenobarbital can be provided for as little as US\$ 5-10 per annum for one patient.

Annex 1 describes the dose, frequency of administration, indications and toxicity of phenobarbital, valproic acid, phenytoin and carbamazepine.

Serum antiepileptic drug estimation

The dose of medicine required by each patient depends largely on the clinical response and is, therefore, based on success in controlling seizures or the appearance of side-effects. Only a few major hospitals in SEAR Member Countries offer a facility for serum antiepileptic drug estimation, but it is not necessary to refer all patients there. Serum antiepileptic drug levels need to be estimated only in certain conditions:

- To monitor compliance in patients with uncontrolled/refractory seizures;
- In patients with kidney or liver disorders;
- To assess antiepileptic drug dosage in pregnant women with epilepsy;
- In patients participating in controlled trials of antiepileptic drug safety;
- When the patient is on polytherapy and drug interaction is suspected.

Adverse effects of medication

A few patients experience adverse effects when antiepileptic drugs are administered. These are of four types:

- Acute dose-related effects
- Chronic toxic effects

- Idiosyncratic or allergic reactions
- Teratogenic effects (affecting the unborn child)

Acute dose-related side-effects are similar for most antiepileptic drugs. These include dizziness, gait imbalance, nausea, visual disturbances and excessive drowsiness. Once reported, these can be mitigated by reducing the dose of the drug or by starting with small doses of the drug and gradually building it up.

Chronic toxic effects develop gradually and can be observed during follow-up. The side-effects common to most antiepileptic drugs are drowsiness, lethargy, mental slowing, memory disturbance, irritability and aggression. In addition, there are specific toxic effects of each individual drug. (see Annex 1)

Idiosyncratic (allergic) side-effects are temporally related to the administration of a particular drug. These are not dose-related, and require a complete, immediate cessation of the drug.

Teratogenic effects (effects on the unborn child) may result if a pregnant woman is on antiepileptic drugs, especially if she is on multiple drugs. Teratogenic effects vary from drug to drug. Some effects noted include cleft lip or palate, congenital heart defects, mental retardation, deformities of the brain and small size of head.

Special needs of patients with epilepsy and other systemic disorders

Since people with epilepsy can also suffer from other diseases such as asthma, hypertension, diabetes, renal and liver disorders, it is essential that patients inform their treating physicians of their illness, so that those drugs which interact with antiepileptic drugs can be avoided. As certain kidney and liver disorders interfere with the excretion of some antiepileptic drugs, the doses of these antiepileptic drugs need to be adjusted and some drugs completely avoided.

Duration of treatment

Epilepsy is a chronic illness, as is hypertension or diabetes mellitus, and requires long-term treatment. In view of the stigma attached to this disorder and the requirement for long-term administration of medications, it is essential to confirm the diagnosis before treatment commences. Not all seizures require antiepileptic drugs. For example, a young housewife, whose general health, neurological examination and all tests are normal and who has suffered only one seizure, may not require antiepileptic drugs in the first instance. A child experiencing convulsions with only high fever is not started on long-term antiepileptic drug treatment.

Once commenced, antiepileptic drug treatment should be continued till the patient has been totally seizure-free for a minimum of three years. Before considering discontinuation, it is necessary to note the following:

- The patient has had no major or minor episodes in the last three years;
- The patient has normal mental development;
- The seizures are not due to a progressive brain disorder;
- Periodic EEGs have been normal, and EEG prior to tapering medicines is normal.

If the above-mentioned factors are not met, it is advisable to continue antiepileptic drug treatment for a longer period. However, the situation in some SEAR Member Countries is such that EEGs may not be available. In this, case the physician will have to decide.

After successful completion of the course of treatment, the drug should not be stopped abruptly; it should be withdrawn slowly over a period of several months. In the case of a patient taking more

than one drug, withdrawal of one drug should be complete before the dose of the other drug is reduced.

The risk of recurrence remains, even after a seizure-free two-year period on treatment and a gradual reduction and cessation of drug therapy. Patients should be informed about this. Long-term studies have indicated that the relapse rate over a period of time is about 1% per year for persons who have remained seizure-free for more than two years with adequate treatment. It is believed that patients with symptomatic seizures, associated mental handicaps and initial difficulty in achieving control have a higher susceptibility to recurrence. Risk of recurrence is highest soon after stopping the drug and gradually declines with time. It is essential that patients remain in contact with their doctors during this period.

Why does treatment fail?

Despite the best of efforts, some patients fail to respond to medication and continue to suffer from seizures. This is referred to as chronic epilepsy, difficult-to-treat epilepsy or refractory epilepsy. The following factors may be responsible:

- Poor drug compliance
- Inadequate dosage, i.e. not enough drug levels in the blood
- Patient cannot afford the medication
- Non-availability of drugs
- Inappropriate medication
- Wrong diagnosis
- Seizures secondary to an underlying cause

Most of these causes are controllable. In developing countries of SEAR, non-availability of the specified drugs and unaffordability play an important role in poor drug compliance. In some cases, patients continue to get seizures subsequent to eliminating the above factors and, thus, further investigations are essential to rule out an underlying cause.

18. STATUS EPILEPTICUS

Status epilepticus is a serious medical emergency. If a seizure is allowed to continue for a long duration, there is a great risk of permanent brain damage. It is not uncommon to find patients with seizures lasting for more than 24–48 hours in the emergency wards of hospitals in SEAR Member Countries. There are several reasons for this: ignorance among the general public, who usually practise locally available methods such as native medicines or tattooing, etc. before reaching the hospital; lack of proper hospital facilities and distant location of major hospitals and poor modes of transport in rural areas.

The most common causes of status epilepticus in developing countries are poor drug compliance and abrupt drug withdrawal. The latter could be caused by the non-availability of drugs, poverty or ignorance among patients or their caregivers. Other causes could be: (a) brain infections such as viral encephalitis, which is still common in SEAR Member Countries. (b) clotting of blood in veins of the brain due to restricting fluids to women just after delivery of a baby as practised among some rural populations.

It is essential that local physicians, paediatricians or family physicians be educated about the principles of management of status epilepticus. This expertise should be available at least in all district hospitals, so that delay in the proper institution of drug treatment can be prevented. More often than not, guidelines provided by the International League Against Epilepsy cannot be practised in these countries as patients reach hospitals very late. In SEAR Member Countries, future community programmes for epilepsy should emphasize the management of status epilepticus.

18.1 Management of Status Epilepticus

While making arrangements to set up an i.v. line, a few questions must be asked of the accompanying persons (a detailed history can be taken later).

1. *Questions*

- Is the patient known to suffer from epilepsy?
- Did he/she take anticonvulsants?
- Did he/she discontinue the intake?
- If so, when? – Is the patient known to use alcohol or other drugs? Did he/she discontinue to use this recently?
- Have any symptoms been noticed that might indicate a disorder apt to cause convulsions?
- When was the last meal taken?
- Were any traditional medicines, especially herbs, taken recently?

The answers to the last three questions above could indicate a hypoglycaemic state.

2. *Diagnostic procedures*

- If there is no laboratory, a blood glucose determination can be done with dextrostix.
- If there is a laboratory, blood to be taken for more investigations (blood glucose, calcium, electrolytes and urea).
- Lumbar puncture should be done when fever is present or the patient's immune system function is poor. (e.g. with HIV/AIDS)
- Other detailed investigations can be done after the seizures are under control.

3. *Treatment*

- start i.v. line with normal saline (5% glucose should NOT be used as IV phenytoin can precipitate in glucose)
- start monitoring pulse, respiration and blood pressure. Prevent aspiration, maintain clear airway. If possible intubate the patient.
- a schematic approach to management of the patient is given on the next page.

4. *Other therapy*

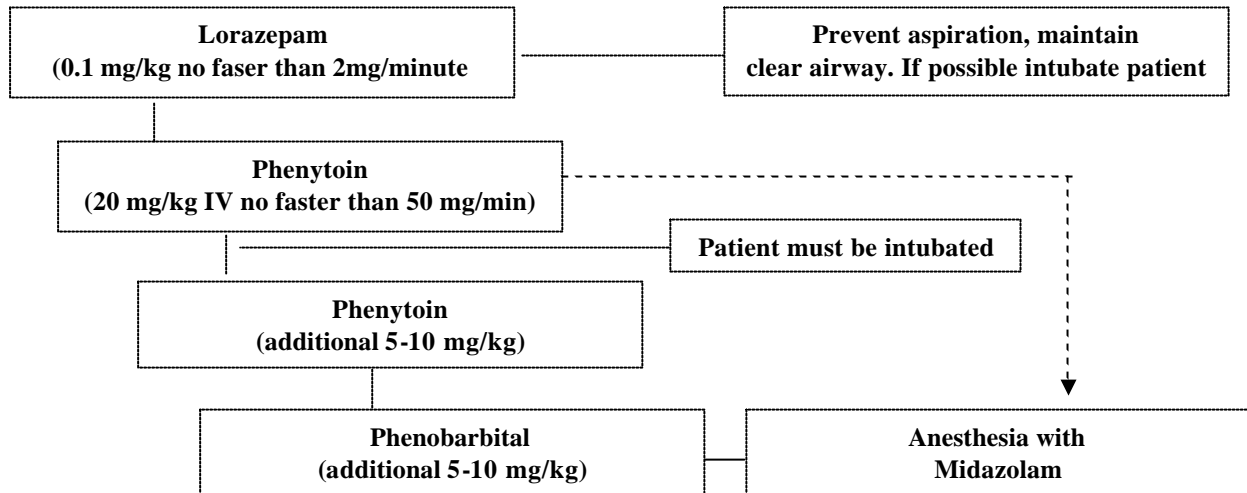
- Depends on the results of investigations (for instance, if meningitis, start i.v. antibiotics).

5. *Further diagnostic procedures*

- A status epilepticus might be the first sign of a brain tumour. Depending on facilities, an EEG, or CT /MRI scan should be done. If needed, the patient should be referred to a specialist.

The medical emergency is to stop status epilepticus; the appropriate special investigations can be done later once the seizures have been stopped.

Status Epilepticus: Treatment Guidelines



Source: Adapted from Lowenstein DH et. al. *N Engl J Med.* 1998;338:970-976

19. PROMOTING COMPLIANCE WITH TREATMENT

19.1 Follow-up Evaluation

Follow-up is an essential step in the management of epilepsy. The patient has to maintain a “seizure diary” where every seizure is recorded and reported to the treating physician periodically. The interval between follow-up varies, depending upon the frequency of seizures. The treating physician should evaluate the clinical response of the patient with respect to the dose of the drug being administered and any side-effects noted during follow-up visits. It is essential to note the effect of seizures on the patient’s day-to-day activities.

19.2 Need for Regular Use of Antiepileptic Drugs

AEDs must be taken daily as prescribed. Missing a dose or taking twice the dose are both undesirable. If the patient is unable to take the initiative to take the medicine daily, the family should help to ensure that the drugs are taken as prescribed.

Patients should be aware of “withdrawal seizures”, i.e. an abrupt discontinuation of AEDs may cause an increasing number of seizures. Patients also need to be informed about the necessity of good compliance, keeping an adequate stock of drugs with them and storing the daily quota in a small container so that no dose is missed.

Certain AEDs interact with commonly-used drugs such as some anti-asthmatic drugs, like theophylline or antibiotics such as erythromycin. Patients should inform their family physicians about the AEDs they are taking, so that drug interactions are avoided. Some drugs cause undesirable effects if the dose is increased too quickly, hence this should be avoided. If the first drug is not effective or not tolerated, a second drug from the commonly used drug list can be tried, and the previous drug withdrawn.

19.3 Compliance with Prescribed Treatment

The patient's adherence to any prescribed treatment will increase if the following points are considered. In the particular case of treatment with AEDs (before starting the treatment and during its entire duration) the patient has to be informed especially in a clear and understandable way to bear in mind the following:

- (1) the patient needs to accept his clinical condition (in this case, seizures) and not view it as a problem;
- (2) the patient should be convinced that the proposed treatment has a reasonable probability of improving his clinical condition (i.e., decreasing the magnitude of the problem);
- (3) that disappearance of seizures does not mean that treatment is no longer necessary;
- (4) some of the side-effects have to be tolerated;
- (5) the goal of the treatment is the reduction of seizures to a minimum possible not necessarily "guaranteed". For some patients this could represent no more seizures, but for others only less seizures;
- (6) the treatment may not have immediate effect; it can take upto one-two weeks before the drug reaches a protective blood level;
- (7) the prescribed dose should not be altered by the patient and his/her family, regardless of the degree of seizure control. Only the physician can modify the prescribed dose;
- (8) abrupt interruption of drug intake should be avoided at all costs as this may precipitate continuous seizures (status epilepticus). Provisions should be made for timely procurement of the drug.

The language, the terms and the contextual meaning must be those which the patient can understand. It is also important to enquire about the reasons for noncompliance and to deal appropriately with those reasons. The following procedures have successfully proven to help in promoting compliance with treatment:

- (1) The treatment procedures are easy to follow;
- (2) Use of family reminders;
- (3) Linking drug intake to specific daily activities; and
- (4) Increased home visits by health worker with repeated reemphasis of:
 - the necessity for continuous long-term treatment, and
 - possible side-effects.

20. OTHER MODES OF TREATMENT

20.1 Diet

There are no special dietary restrictions for epilepsy. The belief among some rural populations that consuming "cold" items of food such as ice cream or fruits such as banana will cause seizures is a misconception.

Special diets such as the high fat diet known as "ketogenic diet" has been of some help in children with intractable epilepsy. However, this is costly and extremely difficult to follow. Also, the patient may not like this diet.

20.2 Surgery for Epilepsy

In recent years selected centres in developed countries and some centres in developing countries have been performing surgery on patients with refractory epilepsy. About 50% of patients with refractory epilepsy have mesial temporal pathology on MRI. Some of these patients are potential candidates for epilepsy surgery. Resources needed for evaluation of such patients for surgery include: good outpatient EEG, good structural MRI, neuropsychological evaluation, the ability to conduct the Wada test (intracarotid injection of amobarbital to determine dominant hemisphere for speech) and a skilled neurosurgeon.

Surgery can be done if an EEG shows discharges ipsilateral to evidence of mesial temporal sclerosis or other mesial temporal pathology on MRI, and if the neuropsychological evaluation and Wada test are concurrent. About 50% of patients who undergo surgery will be totally seizure-free and another 25% have only 1-2 seizures per year after surgery, but they have to keep taking anti-epileptic drugs.

20.3 Psychotherapy

Psychotherapy cannot cure epilepsy. However, some patients who experience seizures whenever they are tense or emotionally upset can be helped, such as a child who has seizures at the beginning of the school year. Psychotherapy can help such patients to understand the problem, to have a positive attitude and to control stress. Often, parents of children with epilepsy are extremely worried and require psychotherapy themselves.

Annex

ANTIEPILEPTIC DRUGS

	Phenobarbital	Valproic acid (Valproate; dipro-pylacetic acid)	Phenytoin (diphenyl hydantoin)	Carbamazepine
Starting dose	Newborns: 15–20 mg/kg once only (loading dose) Children: 30 mg daily Adults: 60 mg daily.	Children: 15–20 mg/kg/day For e.g. 1-2 years: 150–200 mg daily 3–5 years: 200–300 mg daily 6–10 years: 300–400 mg daily 11–15 years: 450 mg daily Adults: 10–15 mg/kg/day	Children: 3 mg/kg/daily For e.g. 1–6 years: 50 mg daily 7–14 years: 100 mg daily Adults: 200 mg daily	(First week administer half the starting dose) Under 1 year: 100 mg daily 1–5 years : 150 mg daily 6–10 years: 200 mg daily 11–15 years: 200–300 mg daily Adults: 200–400 mg daily
Increments	30 mg every 4 weeks.	Children: 10 mg/kg daily every 4–7 days Adults: 200 mg daily every 4–7 days.	Children: 25 mg every 3–4 weeks Adults: 50 mg in every 3–4 weeks.	Children: 50 mg weekly Adults: 100 mg every 1–2 weeks.
Maintenance dose	Newborns: 3.5 mg/kg/day Children: 2–6 mg/kg/day Adults: 0.5–4 mg/kg/day, maximum 180 mg/day	10–30 mg/kg/day (Adults 600–2400 mg daily).	3–8 mg/kg/daily (max. 400 mg if serum levels are not available. If available, serum level to be kept below 20 µg/ml, but may exceed if toxicity is not a problem).	Children: 10-30 mg/kg/day Adults: 10–20 mg/kg/day (400–1400 mg).
Elimination half life	Newborns: ± 100 hours Children: 30–70 hours Adults: 60–150 hours	Approximately 16 hours.	From 9–140 hours.	Up to 36 hours after the first dose Decreasing to up to 12 hours when taken regularly

	Phenobarbital	Valproic acid (Valproate; dipro-pylacetic acid)	Phenytoin (diphenyl hydantoin)	Carbamazepine
Steady state	Reached after five times the half life. Children: 1 1/2 weeks after starting therapy Adults: 3-4 weeks after starting therapy	Reached in 3-4 days after starting therapy	Reached in 7-30 days after starting therapy	Reached in upto 8 days after starting therapy.
Dose frequency	Once daily	Three times daily	Children: twice daily Adults: once daily (unless gastrointestinal discomfort, then divide into two dosages)	2 times daily when it is the only drug 3 times daily when the dosage is high or in combination with other drugs.
Indications	First drug in: - Primary and secondary generalized tonic-clonic seizures - Febrile convulsions	- Absence-seizures - Myoclonic forms of generalized epilepsy - Febrile convulsions - All generalized tonic, clonic or tonic-clonic seizures - All varieties of partial seizures - Photosensitive epilepsy	As first drug in: - partial seizures with or without secondary generalization Also active in: - Primary generalized tonic-clonic seizures (beware of provocation of absence seizures) - Status epilepticus	- Benign childhood epilepsy with centrotemporal spikes - Childhood epilepsies with occipital paroxysms - Primary and secondary generalized tonic-clonic
Not indicated in	Absence seizures Seizures which occur mainly during sleep Children with hyperactive behaviour	Hepatic impairment; Infants with severe epilepsy	Absence and myoclonic seizures Febrile convulsions	Absence- and myoclonic seizures Febrile convulsions
Interactions	Phenobarbital decreases the serum levels of: - bilirubin, folate, cortisol, vitamin D and vitamin K	Valproate increases the serum level of: - phenobarbital, lamotrigine, phenothiazines and antidepressants	Phenytoin decreases the serum levels of: - folate, vitamin D, griseofulvin - carbamazepine, clonazepam	Carbamazepine decreases the serum levels of: - folates, warfarin, doxycycline and oral contraceptives

	Phenobarbital	Valproic acid (Valproate; dipro-pylacetic acid)	Phenytoin (diphenyl hydantoin)	Carbamazepine
	<ul style="list-style-type: none"> - carbamazepine - chloramphenicol in neonates, doxycycline - digitoxin, griseofulvin, warfarin, - contraceptive hormones Phenobarbital levels are increased by: <ul style="list-style-type: none"> - phenytoin, valproate - frusemide. 	Valproate levels are decreased by: <ul style="list-style-type: none"> - phenytoin and phenobarbital 	<ul style="list-style-type: none"> - contraceptive hormones - vitamin K in newborns Phenytoin sometimes increases the levels of: <ul style="list-style-type: none"> - phenobarbitone The phenytoin level may be increased by: <ul style="list-style-type: none"> - INH, rifampicin and ketoconazole. 	Carbamazepine serum levels are decreased by: <ul style="list-style-type: none"> - phenytoin and phenobarbitone Carbamazepine levels are increased by: <ul style="list-style-type: none"> - erythromycin and INH.
Toxicity: <i>Local effects</i>	Very rare	<ul style="list-style-type: none"> - Mild, like nausea, vomiting, diarrhoe mainly at the beginning of treatment - Decreased but also increased appetite with weight gain may occur - If the tablets are not enteric-coated gastric distress is frequent. 	<ul style="list-style-type: none"> - Slight upper abdominal discomfort, nausea, vomiting. 	<ul style="list-style-type: none"> - Occasionally anorexia, nausea or vomiting.
Toxicity: <i>Effects on the foetus and the new born</i>	<ul style="list-style-type: none"> - Congenital malformations are sometimes associated with phenobarbital therapy - Increased bleeding tendency due to decreased vitamin K levels in the newborn - Phenobarbital-withdrawal syndrome (hypotonia and irritability) in newborns born to mothers on phenobarbital treatment - may be prevented by breastfeeding. 	As other antiepileptic drugs, in particular spina bifida.	There is an increased occurrence of cleft lip and palate, and increased congenital heart malformations <ul style="list-style-type: none"> - in the newborn vitamin K deficiency with bleeding may occur 	Congenital malformations have been reported (spina bifida). Treatment with carbamazepine can be continued during pregnancy when given as monotherapy.

	Phenobarbital	Valproic acid (Valproate; dipro-pylacetic acid)	Phenytoin (diphenyl hydantoin)`	Carbamazepine
Toxicity: <i>Dose determined effects</i>	<ul style="list-style-type: none"> - During the first few days of treatment drowsiness may occur, but this disappears by itself without reducing the dosage - when increasing the dosage drowsiness may recur, now a sign of toxicity, and dosage should be reduced - hyperactivity and irritability occur in children but the condition of the children should be noted before treatment is started: the irritability and hyperactivity might be due to the organic brain damage rather than the phenobarbital - decline in scholastic performance - lethargy, hypoactivity, ataxia - confusion in the aged 	<ul style="list-style-type: none"> - Tremor, weakness, ataxia excitement, mental stimulation 	<ul style="list-style-type: none"> - Nystagmus, ataxia, diplopia, drowsiness, slurred speech - vomiting, choreiform movements - gingival hypertrophy, can be reduced by good dental hygiene (regular teeth brushing) - hirsutism, acne, coarse facies - re-occurrence of seizures - cerebellar syndrome. 	<ul style="list-style-type: none"> - Headache, dizziness, somnolence, ataxia - disturbed vision, diplopia - overdosage might give tremor, excitation and convulsions.
Toxicity: <i>Idiosyncratic side effects</i>	<ul style="list-style-type: none"> - Skin rash, exfoliative dermatitis, porphyrinuria; - agranulocytosis, aplastic anaemia, jaundice and hepatitis, but very rarely; - Dupuytren's contracture and frozen shoulder are more common 	<ul style="list-style-type: none"> - Thrombocytopenia and prolonged bleeding time - Acquired factor VIII deficiency (Von Willebrand disease) - Hair loss (temporary and reversible) - Impaired hepatic function, especially in children under two and on polytherapy (but an isolated increase in gamma GT in 	<ul style="list-style-type: none"> - Morbilliform rash rarely going into exfoliative dermatitis - Lymphadenopathy, fever, eosinophilia - Bone-marrow depression - Hepatitis 	<ul style="list-style-type: none"> - Hepatitis, jaundice, fever - Skin rashes (especially sunshine induced), generalized erythema, erythema - Multiforme exudativum (stevens-johnson syndrome), exfoliative dermatitis,

	Phenobarbital	Valproic acid (Valproate; dipro-pylacetic acid)	Phenytoin (diphenyl hydantoin)	Carbamazepine
		some cases is not a reason to lower the valproate dose) - polycystic ovaries - Pancreatitis		- Lymph-node swelling - Aplastic anaemia, leucopenia, neutropenia
Toxicity: <i>Breast milk</i>	Phenobarbital is present in breast milk, and sometimes produces drowsiness in infants when the mother is on a high dosage.	- Valproate passes into the breast milk - No reason to stop breastfeeding	- Phenytoin is present in breast milk but in amounts too small to be harmful - So continue breastfeeding	Carbamazepine passes into the breast milk, but not in sufficient amounts to stop breastfeeding

Source: Dekker, PA. Epilepsy: A manual for Medical and Clinical Officers in Africa, WHO, Geneva, 2002