Vol 2|Issue 1| 2012 |16-22.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

LITERATURE REVIEW AND PHARMACOLOGICAL SCREENING OF EPILEPSY

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ABSTRACT

The more common epilepsy conditions and will enable physicians to efficiently evaluate and manage these disorders. Salient aspects of the history and examination, together with electroencephalography, will usually determine the epilepsy syndrome (category), forming the basis for any further investigation and possible antiepileptic therapy. Imaging may be required in some circumstances. This review focused on type of epilepsy, pathophysiology, screening methods and clinical management of epilepsy.

Keywords: Epilepsy, Clinical Management, Pharmacological Screening.

INTRODUCTION

Epilepsy (Greek - to seize) is a common chronic neurological disorder characterized by seizures. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. People have seizures when the electrical signals in the brain misfire. The brain's normal electrical activity is disrupted by these overactive electrical discharges, causing a temporary communication problem between nerve cells. About 50 million people worldwide have epilepsy, and nearly two out of every three new cases are discovered in developing countries. Epilepsy is more likely to occur in young children or people over the age of 65 years; however, it can occur at any time. As a consequence of brain surgery, epileptic seizures may occur in recovering patients. Epilepsy is usually controlled, but cannot be cured with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are lifelong some forms are confined to particular stages of childhood. Epilepsy should not be understood asa single disorder, but rather as syndromic with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain [1,2].

SEIZURE TYPES

Based on source of the seizure within the brain they are classified as :
1)Partial or focal onset seizures - Localised
2)Generalised seizures - Distributed

1.Partial seizures

Partial seizures are further divided on the extent to which consciousness is affected.Majority of people with epilepsy have focal seizures. The various types of focal seizures are described by the area of the brain in which they originate. An individual may be said to suffer with a partial frontal lobe seizure if the problem has occurred in the part of the brain right behind the forehead. Psychomotor seizures are recurrent partial seizures and are referred to the interaction between the brain and the muscle. In such a seizure, a person may experience hallucinations and may also twitch or blink [3].
The main types of partial seizures may be classified as follows:

Simple partial/focal seizure

Typically the person does not lose his/her consciousness but experiences strange unrelated feelings of joy, anger, sadness or even nausea. Such people may also hear, see, smell or taste things that are unreal. However, such a seizure lasts only for a few seconds.

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Complex partial/focal seizure

Beginning with a blank stare indicating a short loss of consciousness, complex partial seizures may cause people to blink several times, twitch or even smack the lips repeatedly. Such repeated movement is called automatisms. Such people may seem to be drunk and may appear to be dreamy. They may also throw things around and may appear to be struggling against restraint. Most of these seizures occur in the temporal lobe of the brain, close to the ear and are thus called as temporal lobe seizures. However, these may also originate in the frontal lobes and last no more than two minutes.

Aura

Some people who have partial seizures experience unusual sensations that warn them of an impending seizure. A person may get a sinking feeling deep down in their stomach or a sense of the seizure itself. It could also appear to be a sound, something like an audible hallucination, forewarning them of the seizure. What is crucial is that when a person experiences an aura, one may not have lost his/her consciousness.

Secondarily generalized seizures

Many times, partial seizures also spread to the whole brain and the change is so rapid that most of the times, the partial seizure goes unnoticed [4,5].

2.Generalised seizures

Generalized seizures are divided according to the effect on the body but all involve loss of consciousness. These include

- Absence (petit mal)
- Myoclonic
- Tonic-Clonic (grand mal)
- Atonic seizures
- Status epilepticus

Absence seizures

Also referred to as petit mal meaning little sickness, these last less than thirty seconds and as they occur for such a brief period, in most cases, they go unnoticed. However, such a person may get almost 50 to 100 seizures in a day. A person may appear to be staring into an empty space or may even get a sudden jerk or experience twitching of muscles.

Tonic seizures

In such seizures, aperson may experience stiffening of the back, leg and arms muscles but no twitching is experienced. Such people may lose consciousness for not more than ten seconds.

Clonic seizures

This is a rare type of seizure and it is mostly the children who suffer with these types of seizures. Although the muscles do not stiffen, but the seizure causes repeated jerking movements on both sides of the body.

Myoclonic seizures

These may cause jerking movements or twitches of the upper body, arms or even legs.

Atonic seizures

These may be called as drop attacks as a person suffering with this seizure may suddenly lose consciousness and collapse. This could also affect the whole body or even single parts of the body. If it happens in the head, the head may just bend for a few seconds. These cause loss of normal muscle tone for about 10 seconds after which the person can stand up and walk. These must not be mistaken with fainting spells as fainting occurs slowly and could be avoided by lying down

Tonic-clonic seizures

Referred to as grand mal or huge sickness, these may begin with the tonic phase, where the muscles going rigid, pass on in the clonic phase. In some cases, people often lose their bladder and bowel control. As these seizures often last for about two to three minutes, the person may feel very confused and weak after a seizure [6,7].

Idiopathic Generalized Epilepsy

In idiopathic generalized epilepsy, there is often, but not always, a family history of epilepsy. Idiopathic generalized epilepsy tends to appear during childhood or adolescence, although it may not be diagnosed until adulthood. In this type of epilepsy, no nervous system (brain or spinal cord) abnormalities other than the seizures have been identified as of yet. The brain is structurally normal on a brain magnetic resonance imaging (MRI) scan.

People with idiopathic generalized epilepsy have normal intelligence and the results of the neurological exam and MRI are usually normal. The results of the electroencephalogram (EEG -- a test which measures electrical impulses in the brain) may show epileptic discharges affecting the entire brain (so called generalized discharges).

The types of seizures affecting patients with idiopathic generalized epilepsy may include:

- Myoclonic seizures (sudden and very short duration jerking of the extremities)
- Absence seizures (staring spells)
- Generalized tonic-clonic seizures (grand mal seizures)

Idiopathic generalized epilepsy is usually treated with medications. Some forms of this condition that may be outgrown, as is the case with childhood absence epilepsy and a large number of patients with juvenile myoclonic epilepsy.

Idiopathic Partial Epilepsy

Idiopathic partial epilepsy begins in childhood (between ages 5 and 8) and may have a family history. Also known as benign focal epilepsy of childhood (BFEC), this is considered one of the mildest types of

epilepsy. It is almost always outgrown by puberty and is never diagnosed in adults. Seizures tend to occur during sleep and are most often simple partial motor seizures that involve the face and secondarily generalized (grand mal) seizures. This type of epilepsy is usually diagnosed with an EEG.

Symptomatic Generalized Epilepsy

Symptomatic generalized epilepsy is caused by widespread brain damage. Injury during birth is the most common cause of symptomatic generalized epilepsy. In addition to seizures, these patients often have other neurological problems, such as mental retardation or cerebral palsy. Specific, inherited brain diseases, such as adrenoleukodystrophy (ADL) or brain infections (such as meningitis and encephalitis) can also cause symptomatic generalized epilepsy. When the cause of symptomatic general epilepsy cannot be identified, the disorder may be referred to as cryptogenic epilepsy. These epilepsies include different subtypes -- the most commonly known type is the Lenno-Gastaut syndrome. Multiple types of seizures (generalized tonic-clonic, tonic, myoclonic, tonic, atonic, and absence seizures) are common in these patients and can be difficult to control. Learn more about these seizure types [8,9].

Symptomatic Partial Epilepsy

Symptomatic partial (or focal) epilepsy is the most common type of epilepsy that begins in adulthood, but it does occur frequently in children. This type of epilepsy is caused by a localized abnormality of the brain, which can result from strokes, tumors, trauma, congenital (present at birth) brain abnormality, scarring or "sclerosis" of brain tissue, cysts, or infections. Sometimes these brain abnormalities can be seen on MRI scans, but often they cannot be identified, despite repeated attempts, because they are microscopic. This type of epilepsy may be successfully treated with surgery that is aimed to remove the abnormal brain area without compromising the function of the rest of the brain. Epilepsy surgery is very successful in a large number of epilepsy patients who failed multiple anticonvulsant medications (at least two or three drugs) and who have identifiable lesions. These patients undergo a pre surgical comprehensive epilepsy evaluation in dedicated and specialized epilepsy centers [10,11].

CAUSES

There are different causes of epilepsy that are common in certain age groups. Neonatal period and early infancy: Hypoxic-ischemic encephalopathy, CNS infections, Trauma, Congenital CNS abnormalities and Metabolic disorders. Late infancy and early childhood - febrile seizures are fairly common: CNS infections and Trauma. Adolescence and adulthood Secondary to any CNS lesion: Stress, Trauma, CNS infections, Brain tumors, illicit drug use and Alcohol withdrawal. Older adults: Cerebrovascular disease: CNS tumors, Head trauma and Degenerative diseases such as dementia [12].

Drug induced seizures

- Lignocaine at normal blood levels act as anticonvulsant but at levels more than 5 microgm, toxic effects are observed, generalized convulsions.
- Metronidazole potentiates leptazole induced seizures and also produces convulsions which used in very high doses.
- Penicillin, Benzyl penicillin and penicillin have lowered the threshold for electro convulsions. This is due to alternation in the storage or transport of GABA in CNS. Benzyl penicillin on administration for 8 days has produced seizures in mice [13].

PATHOPHYSIOLOGY

- Mutations in several genes have been linked to some types of epilepsy. Several genes that code for protein subunits of voltage-gated and ligand-gated ion channels have been associated with forms of generalized epilepsy and infantile seizure syndromes.
- Several ligand-gated ion channels have been linked to some types of frontal and generalized epilepsies. One speculated mechanism for some forms of inherited epilepsy are mutations of the genes that code for sodium channel proteins; these defective sodium channels stay open for too long, thus making the neuron hyper-excitable.
- Glutamate, an excitatory neurotransmitter, may, therefore, be released from these neurons in large amounts, which by binding with nearby glutamatergic neurons triggers excessive calcium (Ca^{2+}) release in these post-synaptic cells. Such excessive calcium release can be neurotoxic to the affected cell.
- The hippocampus, which contains a large volume of just such glutamanergic neurons (and NMDA receptors, which are permeable to Ca^{2+} entry after binding of both sodium and glutamate), is especially vulnerable to epileptic seizure, subsequent spread of excitation, and possible neuronal death.
- Another possible mechanism involves mutations leading to ineffective GABA (the brain's most common inhibitory neurotransmitter) action. Epilepsy related mutations in some non-ion channel genes have also been identified.
- Epileptogenesis is the process by which a normal brain develops epilepsy after trauma, such as a lesion on the brain. One interesting finding in animals is that repeated low-level electrical stimulation to some brain sites can lead to permanent increases in seizure susceptibility: in other words, a permanent decrease in seizure "threshold." This phenomenon, known as kindling (by analogy with the use of burning twigs to start a larger fire) was discovered by Dr. Graham Goddard in 1967.
- It is important to note that these "kindled" animals do not experience spontaneous seizures. Chemical stimulation can also induce seizures; repeated exposures to some pesticides have been shown to induce seizures in both humans and animals. One mechanism proposed for this is called excitotoxicity. The roles of kindling and excitotoxicity, if any, in human epilepsy are currently hotly debated.
- Other causes of epilepsy are brain lesions, where there is scar tissue or another abnormal mass of tissue in an area of the brain [14,15].

DIAGNOSIS

In order to make a correct epilepsy diagnosis, a detailed medical history of the patient is absolutely crucial, after which blood tests and brain mapping becomes important. It is important for the physician to know what kind of epilepsy a person suffers from and what kind of seizures are affecting the person. A person may also be experiencing a seizure due to a non-epileptic event.

Medical history and examination

A relative/friend could give a detailed medical history of a person, the timings of a seizure or the duration and the symptoms, and previous family history. Developmental, Neurological, and Behavioral Tests help the doctors in evaluating the case better.

CAT scan (Computed Tomography)

Also known as Computerized Axial Tomography, is a method which uses low radiation X-rays to create an image of the brain. This diagnostic test helps in revealing abnormalities in the brain such as a tumor, clots, or cysts in the brain. It gives the physician a clear idea from which part of the brain, the seizure is occurring.

EEG Monitoring

The problems in the brain's electrical activity can be easily monitored through an electroencephalogram (EEG). However, although it is a very useful test, but it may not be foolproof as sometimes people show normal brain wave patterns even after a seizure. It has been noted that many people who do not suffer with epilepsy may also show unusual electrical activity of the brain. Although it is a non-invasive method, but neurosurgeons may not rely on it [15].

Magnetic Source Imaging (MSI)

Magnetoencephalography helps in detecting the functioning of the brain. It helps the doctor to see how different parts of the brain are working together in interaction. Many times, this method is used in planning a surgery of the brain to treat epilepsy or even to map the brain effectively before the surgery.

Magnetic resonance imaging (MRI)

Radio waves and a strong magnetic field are used to produce image of the brain in full detail. A person must inform the doctor about any dental fillings or braces before hand as these may distort the image. A functional MRI (FMRI) can also be used to measure all possible metabolic changes that occur when a part of the brain is working. It helps in identifying the function of all parts of the brain and helps to doctor to decide whether a epilepsy surgery will be safe or not.

Positron emission tomography (PET)

This is a scanning method where radioactive material is injected to detect chemical and physiological changes related to the brain. Very little quantity of these radioactive materials is used and the test takes about 30 to 45 minutes. It is by way of measuring the blood flow in the brain and the general metabolism that a neurologist finds out the area of the brain where seizures originate.

Single-photon emission computerized tomography (SPECT)

It is crucial for a doctor to be sure about the area of the seizure. However, when the area is not clear even with an MRI or EEG, SPECT may be used. A person is tested twice, one during a seizure and one 24 hours later. Radioactive material is injected for both and then the result may be compared. It helps in finding out how well the various regions of the brain are working and also measures the blood flow in the brain. This information may help the neurosurgeon to evaluate the area from where the seizure is originating and thus may be useful for the surgery [16].

Blood Tests

Genetic or metabolic disorders in children may be tested with the help of taking a blood sample. Other infections or health problems may also be diagnosed through this method and may benefit the doctor in finding out the cause of the seizure which is crucial before beginning any treatment.

CLINICAL MANAGEMENT

Epilepsy is usually treated with medication prescribed by a physician; primary caregivers, neurologists, and neurosurgeons all frequently care for people with epilepsy. However, it has been stressed that accurate differentiation between generalized and partial seizures is especially important in determining the appropriate treatment. If a seizure lasts longer than 5 minutes, or if more than one seizure occurs without regaining consciousness emergency medical services should be contacted

Pharmacological treatment

The mainstay of treatment of epilepsy is anticonvulsant medications. Often, anticonvulsant medication treatment will be lifelong and can have major effects on quality of life. The choice among anticonvulsants and their effectiveness differs by epilepsy syndrome.

Currently there are 20 medications approved by the Food and Drug Administration(FDA) for the use of treatment of epileptic seizures : carbamazepine (Tegretol), clorazepate (Tranxene), clonazepam (Klonopin), ethosuximide (Zarontin), felbamate (Felbatol), fosphenytoin (Cerebyx), gabapentin (Neurontin), lacosamide (Vimpat), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), phenobarbital (Luminal), phenytoin (Dilantin), pregabalin (Lyrica), primidone (Mysoline), tiagabine (Gabitril), topiramate (Topamax), valproate semisodium (Depakote), valproic acid (Depakene), and zonisamide (Zonegran). Most of these appeared after 1990. Medications currently under clinical trial under the supervision of the FDA include retigabine, brivaracetam, and seletracetam. Other

drugs are commonly used to abort an active seizure or interrupt a seizure flurry; these include diazepam (Valium) and lorazepam (Ativan). Drugs used only in the treatment of refractory status epilepticus include paraldehyde (Paral), midazolam (Versed), and pentobarbital (Nembutal).

The most commonly used antiepileptic drugs used to treat epilepsy are

- Carbamazapine: It is the most effective while treating partial and tonic-clonic seizures. Its side-effects include headache, sleepiness, dizziness, double-vision, and an upset stomach. These usually go away within a week.
- Clonazepam: It's used to treat myoclonic and atonic seizures. People usually experience third problems with balance and may become irritated easily and may also feel drowsy. Children may become hyperactive.
- Ethosuximide: It treats absence seizures (petit mal). The side effects include dizziness, stomach problem, lethargy.
- Phenobarbital: It treats tonic-clonic and simple partial seizures. A person may experience behavioral changes, drowsiness and rash, learning problems.
- Phenytoin: It also treats simple and partial seizures along with tonic-clonic. High doses may cause drowsiness, nausea, growth of body hair and may cause the gums to shrink.
- Valproate: It is used to treat the generalized seizures. But it may cause problems of the liver, blood disorders, tremor, hair loss and stomach problems.

Some anticonvulsant medications do not have primary FDA-approved uses in epilepsy but are used in limited trials, remain in rare use in difficult cases, have limited "grandfather" status, are bound to particular severe epilepsies, or are under current investigation. These include acetazolamide (Diamox), progesterone, adrenocorticotropic hormone (ACTH), various corticotropic steroid hormones (prednisone), or bromide [15,17].

SCREENING METHODS

Motor Activity

The mice were divided into two groups of six mice each. Mice were first individually placed in the photoactometer and normal movement recorded. After five minutes, the counter was stopped and the reading noted. The animal was then removed and the counter reset to zero. The same procedure was repeated for all animals. Group 1 received 50 mg/kg BW of extract orally. The animals were then individually placed in the photoactometer at 0.5, 1, 2, 3, 4, and 5 hours and the readings were noted. The results were tabulated and converted into percentages for convenient calculations.

Pentylenetetrazol-Induced Convulsions in Rats

Albino rats of 150-200 g body weight were divided into five groups of six animals each. The first group, receiving saline orally, served as control whereas the second group received 4mg/kg of diazepam intraperitoneally (i.p); the third group received a sub protective dose of diazepam, i.e. 0.5 mg/kg i.p.; the fourth received 50 mg/kg of BM (p.o); and the fifth group received a sub protective dose of diazepam, i.e. 0.5 mg/kg and 50 mg/kg of BM. After an hour, all the animals were injected with 80 mg/kg pentylenetetrazol (Sigma, St. Louis, USA) intraperitoneally and presence or absence of clonic convulsions was noted for each animal. The % latencies of clonic convulsions were noted, and numerically transformed to a seizure score (S) calculated from the formula:

S = 1- (control Latency/ drug seizure Latency)

In the case of control animal; S = 0, whereas for animals that did not experience seizures latencies of infinity, S =1. This numerical transformation enabled inclusion of all animals in the statistical analysis, irrespective of whether they had a seizure or not. The mortality in the 24h following PTZ, in the different pretreatment groups was also recorded.

Maximal Electroshock (MES) - Induced Convulsion in Rats

Albino rats of 150-200 g body weight were divided into three groups of six animals each. The first group, which received saline orally, served as the control whilst the second group received 30 mg/kg of phenobarbitone sodium intraperitoneal (i.p), and third group received 50 mg/kg of BM (p.o). After an hour of treatment, convulsions were produced in rats using an "Inco" convulsiometer by delivering current of 150 mA through corneal electrodes for a period of 0.2 seconds. The severity of convulsions was assessed by the duration of flexion, extension, clonus, stupor and recovery phase for each animal. Inhibition of extensor phase was studied in this model.

Strychnine-Induced Convulsion in Rats

Eighteen albino rats each weighing 150-200 g were divided into three groups of six rats each. The first group received saline orally and served as the control, while the second received 4 mg/kg of diazepam (i.p), and third group received 50 mg/kg of BM orally. After an hour of treatment, 4 mg/kg of strychnine (CDH, Bombay) was administered intra peritoneally to control and drug treated animals, which produced powerful opisthotonus tonic convulsions of the body and limbs. The latency of convulsions and the % mortality was assessed for each animal.

Hypoxic Stress-Induced Convulsions in Mice

The albino mice each weighing 18-25 g, were divided into seven groups of six mice each. Group one was given saline orally and served as the control; group two received 4 mg/kg of diazepam (i.p), group three received 50 mg/kg BM orally, group four received 50 mg/kg adenosine (i.p), group five received 50 mg/kg of theophylline (i.p), group six received 50 mg/kg of BM orally followed by 50 mg/kg of adenosine (i.p), and group seven received 50 mg/kg of BM orally followed by 50 mg/kg of theophylline (i.p). The mice were put individually into a glass container of 370 ml

capacity for induction of convulsion. The container was air tight, so under these circumstances, the animal showed convulsions and then mortality due to hypoxia. The latency for convulsions and death was assessed for each animal.

Lithium-Pilocarpine-Induced Status Epilepticus

Eighteen albino rats each weighing between 150-200 g were divided into three groups of six rats each. The first control group received saline orally; the second group received 4 mg/kg of diazepam (i.p), and third group received 50 mg/kg of BM orally. Status epilepticus was induced by intra peritoneal injection of 3 meq/kg, (i.p) lithium chloride, followed by 30 mg/kg, (sc) pilocarpine 21 h later. The animals were observed for a period 90 minutes for behavioral seizures. Immobility, repetitive chewing, head nodding, vibrissial twitching, forelimb clonus with or without rearing and falling, characterized behavioral seizures evoked by LiCl/ pilocarpine. Seizure terminations were defined as the absence of forelimb clonus or falling, facial twitching and stop and stare activity. The onset was taken as the time of onset of forelimb clonus with rearing (FC+R). The extract was administered 2 hours prior to pilocarpine challenge, while diazepam was administered 30 minutes prior to pilocarpine challenge [15-17].

Statistical Analysis and Calculations

The % inhibition (or decrement) was calculated by using the formula:

% inhibition = (1-test reading/ Control reading) **x** 100

Student's t- test was performed for statistical analysis. $P<0.05$ was considered statistically significant.

LITERATURE REVIEW

- The importance of evaluating the currently available literature relative to the epileptic seizure disorders is apparent when current statistics are considered. Approximately 2 million Americans have epilepsy; of the 125,000 new cases that develop each year, up to 50% are in children and adolescents.
- The prevalence of epilepsy in persons younger than 18 years is estimated to be as high as 4.7 per 1000.1 Affecting approximately 2% of the US population, epilepsy is a chronic neurologic condition characterized by sudden, brief attacks of altered consciousness, motor activity, sensory phenomena, or inappropriate behavior caused by abnormal electric discharges in the brain.
- Schimp has provided a criterion by which seizure activity can be differentiated from other atypical sensory phenomena.
- Most people with epilepsy have only 1 type of seizure; approximately 30% have 2 or more types.
- Approximately 90% have generalized tonic-clonic (formerly called grand mal) seizures. Such a seizure typically begins with an outcry and continues with loss of consciousness and falling; this is followed by tonic, then clonic, contractions of the muscles of the extremities, trunk, and head. The seizure usually lasts 1 to 2 minutes.
- Absence (formerly called petit mal) seizures consist of brief, primarily generalized attacks manifested by a 10- to 30-second loss of consciousness and eyelid fluttering at a rate of 3 per second, with or without loss of axial muscle tone. Affected patients do not fall or convulse.

Table 1. Major types of epilepsy

Generalized idiopathic epilepsies	Benign Myoclonic epilepsy in infants Juvenile Myoclonic epilepsy Childhood absence epilepsy Juvenile absence epilepsy Epilepsy with generalized tonic clonic seizures in childhood
Generalized symptomatic epilepsies	Infantile spasms (West syndrome) Lennox-Gastaut syndrome Progressive myoclonus epilepsies
Partial epilepsies	Benign occipital epilepsy (Benign focal epilepsy with occipital paroxysms) Benign rolandic epilepsy (Benign focal epilepsy with centrotemporal spikes) Frontal lobe epilepsy Occipital lobe epilepsy Mesial temporal lobe epilepsy Parietal lobe epilepsy
Unclassified epilepsies	Febrile fits Epilepsy with continuous spike and waves in slow wave sleep (ESES)

CONCLUSION

Management of patients with epilepsy focuses on three main goals: controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. In selecting an antiepileptic drug that is most appropriate for the individual patient, it is important to consider: seizure type, side effects, patient profile (e.g., sex, age, and childbearing potential), ease of medication use, and cost. A balance between efficacy, tolerability, and safety must be obtained. Overall, up to 80 percent of patients can become seizure free on antiepileptic drug treatment. Epilepsy may be a lifetime diagnosis for some patients (e.g., mentally challenged, inoperable brain tumors, etc), but antiepileptic therapy is not necessarily lifelong.

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