A COMPARATIVE STUDY OF REMISSION OCCURRENCE IN THE MONO AND ADD ON THERAPIES DURING THE TREATMENT OF EPILEPTIC SEIZURES AND THE EVALUATION OF PATIENTS KNOWLEDGE ON FIRST AID IN TERTIARY CARE HOSPITAL

Dissertation submitted in partial fulfillment of the Requirement for the award of the degree of

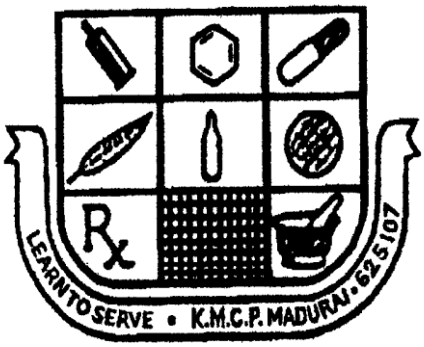
MASTER OF PHARMACY IN

PHARMACY PRACTICE

OF

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY,

CHENNAI



DEPARTMENT OF PHARMACY PRACTICE

K.M.COLLEGEOF PHARMACY

UTHANGUDI,

MADURAI-625107

APRIL 2016

CERTIFICATE

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It is a bonafide work carried out by him under my guidance and supervision during the academic year **APRIL-2016.** The dissertation partially or fully has not been submitted for any other degree or diploma of this university or other universities.

GUIDE
Mrs. K.Jeyasundari, M.Pharm.,
Assistant Professor,
Dept. of Pharmacy Practice,
K.M. College of Pharmacy,
Madurai-625107.

HEAD OF DEPARTMENT
Prof.K.Thirupathi,M.Pharm.,
Professor and HOD,
Dept. of Pharmacy Practice,
K.M. College of Pharmacy,
Madurai- 625107.

PRINCIPAL
Dr.S.Venkataraman, M.Pharm., Ph.D.,
Professor and HOD,
Dept. of Pharmaceutical Chemistry,
K.M. College of Pharmacy,
Madurai- 625107.

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Dept. of Pharmaceutical Chemistry,
K.M. College of Pharmacy,
Madurai- 625107.

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"Our Unknown future is secure in the hands of our all knowing God"

I humbly submit this work to the Lord Almighty, without whom it would have been unsuccessful.

"Optimism is the faith that leads to achievement. Nothing can be done without Hope, Confidence and Perseverance"

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"It's in your moments of decision that your destiny is shaped"

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ABBREVIATIONS

ACTH	-	Adrenocorticotropic hormone
ADCME	-	Autosomal dominant cortical myoclonus and epilepsy
ADNFLE	-	Autosomal dominant nocturnal frontal lobe epilepsy
AED	-	Anti-epileptic drug
ASE	-	Absence status epileptics
BID	-	Giving medication twice per day
CAE	-	Childhood absence epilepsy
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CT	-	Computed tomography
DDI	-	Drug–drug interaction
ECG	-	Electrocardiography/electrocardiogram
EEG	-	Electroencephalography/electroencephalogram
FS	-	Febrile seizures
GABA	-	Gamma-amino butyric acid
IGE	-	Idiopathic generalised epilepsy
LFTLE	-	Lateral familial temporal lobe epilepsy
MFTLE	-	Mesial familial temporal lobe epilepsy
MRI	-	Magnetic resonance imaging epilepsy
SUDEP	-	sudden unexpected death in epilepsy
TLE	-	Temporal lobe epilepsy
VNS	-	Vagal nerve stimulation

INTRODUCTION

While the Evaluation and treatment of patient with seizures (or) epilepsy, is often challenging. Modern therapy[1] provides many patient with seizure control. After a first seizure evaluation should focus on excluding an underling neurologic or medical condition assessing the relative risk of seizure reoccurrence & determining whether treatment is indicated. Successful management of patient with recurrent seizure[2] begins with the establishment of accurate diagnosis of epilepsy syndrome followed by treatment using an appropriate medication in a manner to optimize the efficacy. The goal of AED's therapy is to completely control seizures with producing Un acceptable medication [4] side effects.

Patients who do not achieve complete seizure control should refer to an epilepsy specialist. Since new medication and surgical treatment offers patients unprecedented options in seizure control.[9]

Newly diagnosed epileptic patients and principles of treatment in chronic epilepsy help in designing steps to improve the safety of drug use in the hospital working setup. Better health care practice could be ensured by applying this knowledge to individual patients.[18]

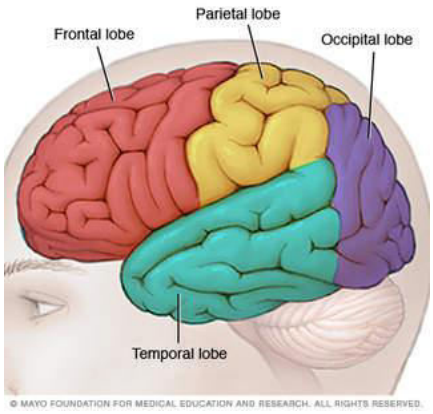
Present study was undertaken to understand the treatment outcome of AED's observed in neurology unit of a teaching hospital with regarding to demographics of patients, choice of prescribed AED's usual dosing regimens and faster routine incremental and decrimental rates, management of seizures & identify precipitating factors [21] of epilepsy.

2. SUBJECTIVE INTRODUCTION

2.1 DEFINITION

Epilepsy is the tendency to have seizures that start in the brain. The brain uses electrical signals to pass messages between brain cells. If these signals are disrupted, this can lead to a seizure.

Epilepsy is usually diagnosed when someone has more than one seizure. Seizures can vary a lot. They can affect your feelings, awareness or movement. Different types of seizures involve different things. These may include confusion, strange feelings, repetitive movements, 'blank' moments muscle jerks, sudden falls, or convulsions.



Seizures are caused by disturbances in the electrical activity of the brain.

- 65 MILLION: Number of people around the world who have epilepsy.
- NEARLY 3 MILLION: Number of people in the United States who have epilepsy.
- 1 IN 26 people in the United States will develop epilepsy at some point in their lifetime.
- BETWEEN 4 AND 10 OUT OF 1,000: Number of people on earth who live with active seizures at any one time.
- 150,000: Number of new cases of epilepsy diagnosed in the United States each year
- ONE-THIRD: Number of people with epilepsy who live with uncontrollable seizures because no available treatment works for them.
- 6 OUT OF 10: Number of people with epilepsy where the cause is unknown.

Epilepsy is thought to be one of the oldest medical conditions and may be as old as humankind itself. Some of the earliest medical texts describe events that likely were seizures. Jackson defined a seizure as "an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles."

Epilepsy is a group of neurological diseases characterized by epileptic seizures. Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking. In epilepsy, seizures tend to recur, and have no immediate underlying cause [35] while seizures that occur due to a specific cause are not deemed to represent epilepsy.[37]

The cause of most cases of epilepsy is unknown, although some people develop epilepsy as the result of brain injury, stroke, brain tumors, and substance use disorders. Known genetic mutations are directly linked to only a small proportion of cases.[38] Epileptic seizures are the result of excessive and abnormal cortical nerve cell activity in the brain. The diagnosis typically involves ruling out other conditions that might cause similar symptoms such as fainting. Additionally, making the diagnosis involves determining if any other cause of seizures is present such as alcohol withdrawal or electrolyte problems. This may be done by imaging the brain and performing blood tests. Epilepsy can often be confirmed with an electroencephalogram (EEG), but a normal test does not rule out the condition.

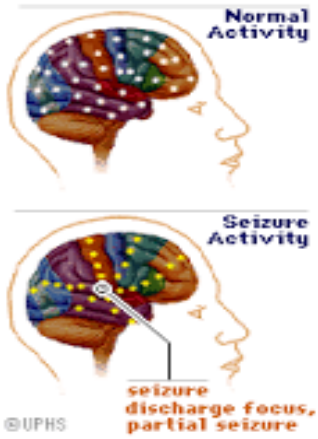
Seizures are controllable with medication in about 70% of cases.[39] In those whose seizures do not respond to medication, then surgery, neurostimulation, or dietary changes may be considered. Not all cases of epilepsy are lifelong, and some people improve to the point that treatment is no longer needed.

About 1% of people worldwide (65 million) have epilepsy, and nearly 80% of cases occur in developing countries. In 2013 it resulted in 116,000 deaths up from 112,000 deaths in 1990. Epilepsy becomes more common as people age.[43] In the developed world, onset of new cases occurs most frequently in infants and the elderly; in the developing world this is in older children and young adults, due to differences in the frequency of the underlying causes. About 5–10% of all people will have an unprovoked seizure by the age of 80, and the chance of experiencing a second seizure

is between 40 and 50%. In many areas of the world those with epilepsy either have restrictions placed on their ability to drive or are not permitted to drive, butmost are able to return to driving after a period of time without seizures.

Seizure

A seizure is a short episode of symptoms caused by a burst of abnormal electrical activity in the brain. Typically, a seizure lasts from a few seconds to a few minutes. (Older words for seizures include convulsions and fits.)



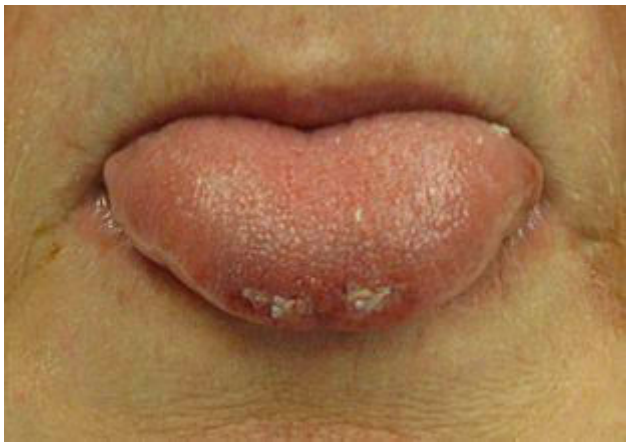
The brain contains millions of nerve cells (neurons). Normally, the nerve cells are constantly sending tiny electrical messages down nerves to all parts of the body. Different parts of the brain control different parts and functions of the body. Therefore, the symptoms that occur during a seizure depend on where the abnormal burst of electrical activity occurs. Symptoms that may occur during a seizure can affect your muscles, sensations, behaviour, emotions, consciousness or a combination of these. The different types of seizures are discussed below.

The most common type (60%) of seizures are convulsive. Of these, one-third begin as generalized seizures from the start, affecting both hemispheres of the brain. Two-thirds begin as partial seizures (which affect one hemisphere of the brain) which may then progress to generalized seizures. The remaining 40% of seizures are non-convulsive. An example of this type is the absence seizure, which presents as a decreased level of consciousness and usually lasts about 10 seconds

Partial seizures are often preceded by certain experiences, known as auras. They include sensory (visual, hearing, or smell), psychic, autonomic, and motor

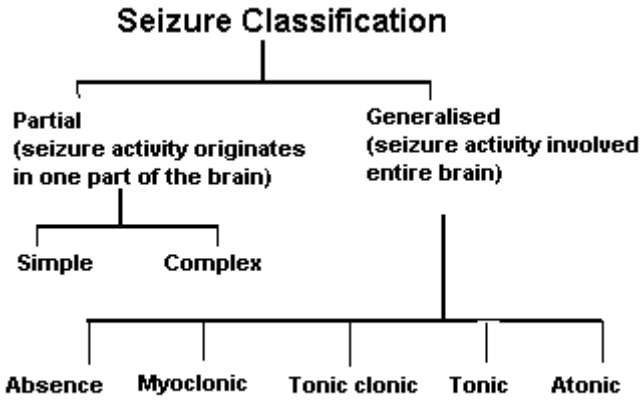
phenomena. Jerking activity may start in a specific muscle group and spread to surrounding muscle groups in which case it is known as a Jacksonian march. Automatisms may occur, which are non-consciously-generated activities and mostly simple repetitive movements like smacking of the lips or more complex activities such as attempts to pick up something.

A person is considered to have epilepsy if they meet any of the following conditions.



1. At least two unprovoked (or reflex) seizures occurring greater than 24 hours apart.
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
3. Diagnosis of an epilepsy syndrome
4. Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

2.2 Different types of epilepsy and seizures



Seizures are divided into two main types - generalised and focal (used to be called partial). (There are also other uncommon types of seizure.) If you have epilepsy you usually have recurrences of the same type of seizure. However, some people have different types of seizures at different times.

Generalised seizures

These occur if the abnormal electrical activity affects all or most of the brain. The symptoms tend to be general and involve much of your body.

There are various types of generalised seizure:

- **A tonic-clonic seizure** is the most common type of generalised seizure. With this type of seizure your whole body stiffens, you lose consciousness and then your body shakes (convulses) due to uncontrollable muscle contractions.
- **Absence seizure** is another type of generalised seizure. With this type of seizure you have a brief loss of consciousness or awareness. There is no convulsion, you do not fall over and it usually lasts only seconds. Absence seizures mainly occur in children.
- **A myoclonic seizure** is caused by a sudden contraction of the muscles, which causes a jerk. These can affect the whole body but often occur in just one or both arms.
- **A tonic seizure** causes a brief loss of consciousness and you may become stiff and fall to the ground.

- **An atonic seizure** causes you to become limp and to collapse, often with only a brief loss of consciousness

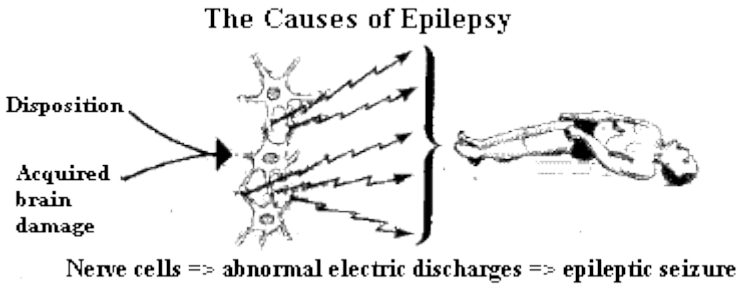
Focal seizures

In focal seizures the burst of electrical activity starts in, and stays in, one part of the brain. Therefore, you tend to have localised (focal) symptoms. Different parts of the brain control different functions and so symptoms depend on which part of the brain is affected:

- **Simple focal seizures** are one type. You may have muscular jerks or strange sensations in one arm or leg. You may develop an odd taste, or pins and needles in one part of your body. You do not lose consciousness or awareness.
- **Complex focal seizures** are another type. These commonly arise from a part of the brain (called a temporal lobe) but may start in any part of the brain. Therefore, this type is sometimes called temporal lobe epilepsy. Depending on the part of the brain affected, you may behave strangely for a few seconds or minutes. For example, you may fiddle with an object, or mumble, or wander aimlessly. In addition, you may have odd emotions, fears, feelings, visions or sensations. These differ from simple focal seizures in that your consciousness is affected. You may not remember having a seizure.

Sometimes a focal seizure develops into a generalised seizure. This is called a secondary generalised seizure.

2.3 Causes of epilepsy



Unknown cause (idiopathic epilepsy)

In many cases, no cause for the seizures can be found. The abnormal bursts of electrical activity in the brain occur for no known reason. It is unclear why they start, or continue to occur. Hereditary (genetic) factors may play a part in some cases.

People with idiopathic epilepsy usually have no other brain (neurological) condition. Medication to control seizures usually works very well.

Symptomatic epilepsy

In some cases, an underlying brain condition or brain damage causes epilepsy. Some conditions are present at birth. Some conditions develop later in life. There are many such conditions - for example:

- A patch of scar tissue in a part of the brain.
- A head injury.
- A stroke.
- Cerebral palsy.
- Some genetic syndromes.
- Growths or tumours of the brain.
- Previous infections of the brain such as meningitis and encephalitis.

The condition may irritate the surrounding brain cells and trigger seizures.

Some underlying conditions may cause no other problems apart from seizures. In other cases, the underlying condition may cause other problems or disabilities in addition to the seizures.

These days, with modern scans and tests, a cause can be found for some cases previously thought to be of unknown cause. For example, a small piece of scar tissue in the brain or a small anomaly of some blood vessels inside the brain. These may now be found by modern brain scanning equipment which is more sophisticated than in the past.

Triggers a seizure

There is often no apparent reason why a seizure occurs at one time and not at another. However, some people with epilepsy find that certain triggers make a seizure more likely. These are not the **cause** of epilepsy but may trigger a seizure on some occasions.

Possible triggers may include:

- Stress or anxiety.
- Some medicines such as antidepressants, antipsychotic medication (these lower the seizure threshold in the brain).

- Lack of sleep, or tiredness.
- Irregular meals (or skipping meals) which may cause a low blood sugar level.
- Heavy alcohol intake or using street drugs.
- Flickering lights such as from strobe lighting or video games.
- Periods (menstruation).
- Illnesses which cause high temperature (fever) such as flu or other infections.

Postictal

After the active portion of a seizure, there is typically a period of confusion referred to as the postictal period before a normal level of consciousness returns. It usually lasts 3 to 15 minutes[43] but may last for hours. Other common symptoms include feeling tired, headache, difficulty in speaking, and abnormal behaviour. Psychosis after a seizure is relatively common, occurring in 6–10% of people. Often people do not remember what happened during this time. Localized weakness, known as Todd's paralysis, may also occur after a partial seizure. When it occurs it typically lasts for seconds to minutes but may rarely last for a day or two.

Psychosocial

Epilepsy can have adverse effects on social and psychological well-being. These effects may include social isolation, stigmatization, or disability. They may result in lower educational achievement and worse employment outcomes. Learning disabilities are common in those with the condition, and especially among children with epilepsy. The stigma of epilepsy can also affect the families of those with the disorder.

Certain disorders occur more often in people with epilepsy, depending partly on the epilepsy syndrome present. These include depression, anxiety, obsessive–compulsive disorder (OCD), and migraine. Attention deficit hyperactivity disorder affects three to five times more children with epilepsy than children in the general population. ADHD and epilepsy have significant consequences on a child's behavioral, learning, and social development. Epilepsy is also more common in children with autism.

2.4 EPIDEMIOLOGY

EPILEPSY is a disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. Epilepsy is the second most common chronic neurological condition seen by neurologists. It is estimated that there are 55,00,000 persons with epilepsy in India, 20,00,000 in USA and 3,00,000 in UK. Three to five per cent of the population have a seizure sometime in their life and half to one per cent of the population have 'active epilepsy'.

Incidence, prevalence and mortality studies provide crucial measures of the frequency and therefore the burden of the disease and allow the planning of services. The applications of epidemiological techniques in the field of epilepsy have extended beyond the usual concept of prevalence and incidence. The objectives of epidemiological studies also include

(1) Identification of risk factors for epilepsy and to estimate the effect of potential interventions;

(2) To determine overall prognosis for seizure control and the identification of factors which may modify this prognosis;

(3)To assess the risk for other conditions in both the patient as well as in relatives

(4)To evaluate interventions, including drug trials.

If you have epilepsy, it means that you have had repeated seizures.

Epilepsy can affect anyone at any age. Around 456,000 people in the UK have epilepsy. Epileptic seizures arise from within the brain. A seizure can also be caused by external factors which may affect the brain. For example, a high temperature (fever) may cause a febrile convulsion. Other causes of seizures include lack of oxygen, a low blood sugar level, poisons and a lot of alcohol. Seizures caused by these external factors are not classed as epilepsy likely to occur, they also spread more readily than in a fully developed brain. The rise in the incidence of epilepsy in adults as they age is due to changes in the brain caused by tumors and strokes and other brain abnormalities. This understanding of seizures and epilepsy, the oldest anticonvulsant drug still in common use, was developed in 1912; the ketogenic diet was first put into use in 1920. From the twentieth century on there has been a

steady stream of new epilepsy treatments and breakthroughs in medical understanding.

Alongside medical advances, significant progress has been made in reducing the social stigma and discrimination sometimes associated with epilepsy. This effort has been led by organizations such as the Epilepsy Foundation of America, founded in 1968, and legislation such as the Americans with Disabilities Act of 1990.

Today medical researchers are actively pursuing better treatments for epilepsy and ultimately a cure. At the same time, local, regional, national, and international epilepsy organizations are working to educate people about the disorder in an effort to eliminate stigma and discrimination.

Epilepsy affects between 1 and 3 percent of the population. In the United States alone, approximately 180,000 new cases of epilepsy are diagnosed each year, and in 2004, 2.7 million Americans were living with the disorder.

Epilepsy affects people of all ages, both sexes, and all ethnic groups. Children under the age of 2 and adults over 65 are more likely to develop epilepsy than any other age group. This is explained in part by changes that occur in the brains of people early and late in life. During childhood brain development, for example, seizures are not only more Approximately 300,000 American children under the age of 14 have epilepsy, with approximately 45,000 diagnosed each year. Males have a slightly higher incidence than females, and socioeconomically disadvantaged populations may also be at higher risk for the disorder.

In approximately 70 percent of cases, no cause can be determined. Of the known causes of epilepsy, some of the most common are brain injury, abnormal brain development prior to birth, lack of oxygen during or following birth, infection of the brain or surrounding tissues, and abnormal structures such as tumors in the brain. Although genetics likely to play a role in many cases of epilepsy, in most cases it is impossible to determine a clear pattern of inheritance from one family member to another.

Anticonvulsant medications are the first line of treatment for epilepsy. In approximately half of all cases, seizures are controlled or eliminated with a single

medication—often the first medication prescribed—and these success rates have improved as new drugs have been developed. Approximately one-third of childhood epilepsy cases are said to be intractable, meaning that two or more medications have failed to control the child's seizures. In these cases, physicians typically pursue other treatment options, including dietary therapies, surgery, or vagus nerve stimulation.

Finding an effective treatment sometimes takes time. However, due to the variety of options available, many children with epilepsy can expect their seizures to be fully controlled and can look forward to living full, happy, productive lives.

2.5 ETIOLOGY

Epilepsy can have both genetic and acquired causes, with interaction of these factors in many cases. Established acquired causes include serious brain trauma, stroke, tumours and problems in the brain as a result of a previous infection. In about 60% of cases the cause is unknown. Epilepsies caused by genetic, congenital, or developmental conditions are more common among younger people, while brain tumors and strokes are more likely in older people. Seizures may also occur as a consequence of other health problems; if they occur right around a specific cause, such as a stroke, head injury, toxic ingestion or metabolic problem, they are known as acute symptomatic seizures and are in the broader classification of seizure-related disorders rather than epilepsy itself.

1. Genetics

Genetics is believed to be involved in the majority of cases, either directly or indirectly. Some epilepsies are due to a single gene defect (1–2%); most are due to the interaction of multiple genes and environmental factors. Each of the single gene defects is rare, with more than 200 in all described. Most genes involved affect ion channels, either directly or indirectly. These include genes for ion channels themselves, enzymes, GABA, and G protein-coupled receptors.

In identical twins, if one is affected there is a 50–60% chance that the other will also be affected.[38] In non-identical twins the risk is 15%.These risks are greater in those with generalized rather than partial seizures. If both twins are affected, most of the time they have the same epileptic syndrome (70–90%). Other close relatives of a

person with epilepsy have a risk five times that of the general population. Between 1 and 10% of those with Down syndrome and 90% of those with Angel man syndrome have epilepsy.

2. Acquired

Epilepsy may occur as a result of a number of other conditions including tumors, strokes, head trauma, previous infections of the central nervous system, genetic abnormalities, and as a result of brain damage around the time of birth. Of those with brain tumors, almost 30% have epilepsy, making them the cause of about 4% of cases. The risk is greatest for tumors in the temporal lobe and those that grow slowly. Other mass lesions such as cerebral cavernous malformations and arterio venous malformations have risks as high as 40–60%. Of those who have had a stroke, 2–4% develop epilepsy.

3. Risk Factors

Risk factors are factors that increase the possibility of getting a condition. The risk factors for epilepsy are:

- Malnutrition
- Injury to the brain
- Head injury (trauma) / birth injury
- Cerebral malformation
- Stroke
- Vasculitis – e.g. Systemic Lupus erythmetosis
- Tumour (Primary or metastatic)
- Conditions that might deprive the brain of oxygen – for example near drowning.
- Infective causes: e.g. – meningitis, encephalitis, febrile convulsions etc.
- Coeliac disease.
- Metabolic conditions like hypoxia, low blood sugar, low or high salt, low magnesium or calcium etc.

4. Other factors:

- Exposure to lead, carbon mono oxide or other environmental toxins
- Overdose or withdrawal or certain medications
- Alcoholism

2.6 Pathophysiology

At the cellular level, the two hallmark features of epileptic form activity are neuronal hyperexcitabilityAnd neuronal hyper synchrony. *Hyper excitability* refers to the heightened response of a neuron to Stimulation, so that a cell might fire multiple action potentials rather than single ones in response to a Synaptic input. *Hyper synchrony* reflects increased neuron firing within a small or large region of cortex, with cells firing in close temporal and spatialproximity.While there are differences in the mechanisms that underlie focal versus generalized seizures, at a simplistic level it is still useful to view any seizure activity as a perturbation in the normal balance between inhibition and excitation in a localized region, in multiple discrete areas (seizure "foci"), or throughout the whole brain (Figure 1.2).

This imbalance likely involves a combination of increased excitation and decreased inhibition (Table 1.1).In addition to the traditional concept of excitation/inhibition imbalance, novel pathophysiological mechanisms for the epilepsies are also being discovered. For example, in febrile seizures, release of inflammatory mediator's such as cytokines could contribute to neuronal hyper excitability, an observation that might open new avenues of treatment.

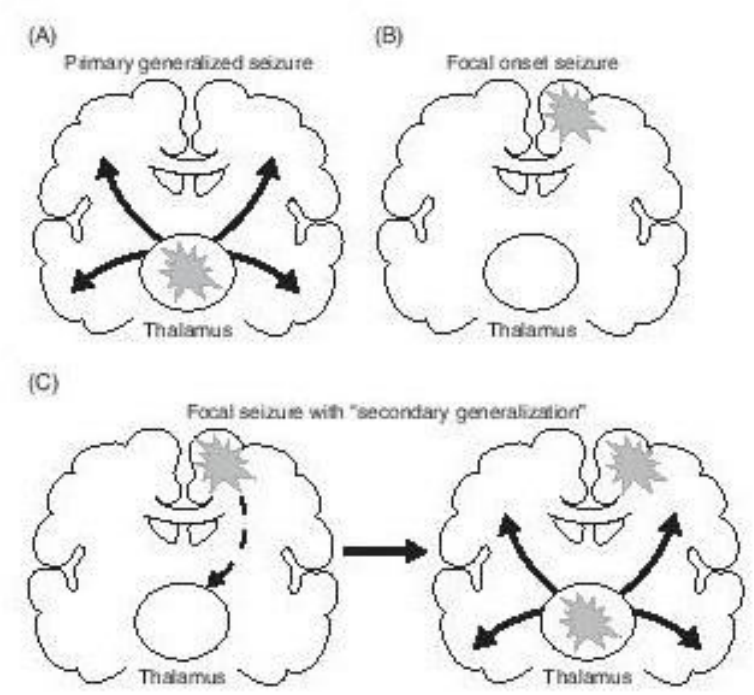


Figure 1.1.

Coronal sections of the brain indicating patterns of seizure origination and spread. (A) Primary Generalized seizure begins deep in brain (thalamus) with spread to superficial cortical regions (arrows). (B) Focal onset seizure begins in one area of the brain (star) and may spread to nearby or distant brain regions. (C) A focal onset seizure "secondarily generalizes" by spreading first to thalamus (left panel) then to widespread cortical regions (right panel).

Pathophysiology

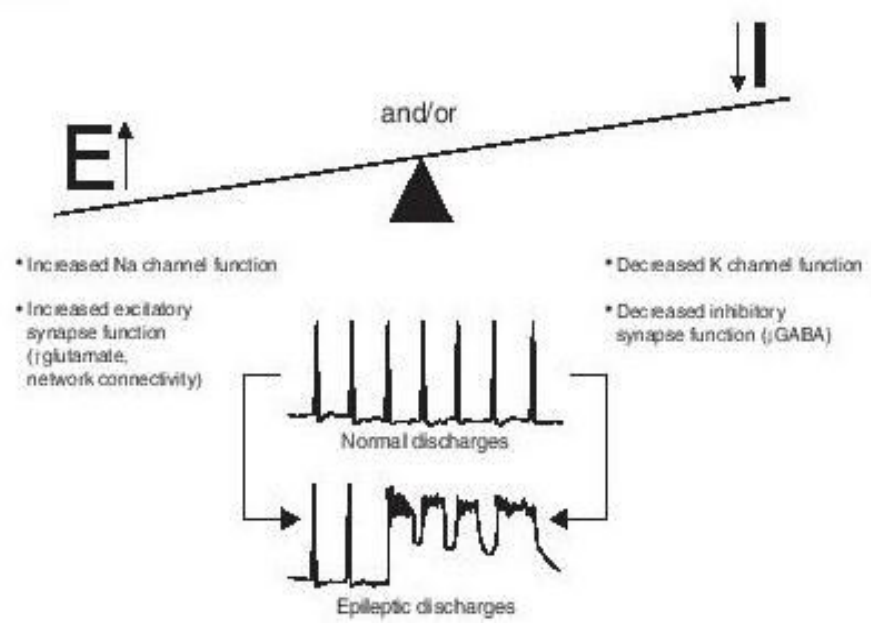


Figure 1.2. Simplified scheme indicating that seizure generation results from increased excitation (E), decreased inhibition (I), or both. Examples of intracellular recordings from normal and epileptic neurons are drawn next.

The normal brain contains billions of neurons activated at different time, i.e., asynchronous firing. The inhibitory feedback mechanisms in the normal brain regulate the frequency of firing of individual neurons and prevent synchronization. When inhibitory feedback defective, large number of cells in a given area of the brain fire at the same time and produce a self – regenerative electrical focus, such area is called 'epileptic focus'.

Such foci may be cortical or sub – cortical and their spread to normal brain tissue is inhibited by inhibitory mechanisms. Factors which themselves can not initiate seizures may trigger off the abnormal focus or permit the spread of activity to the normal brain Such factors, rapid blinking of eyes or other rhythmic photic

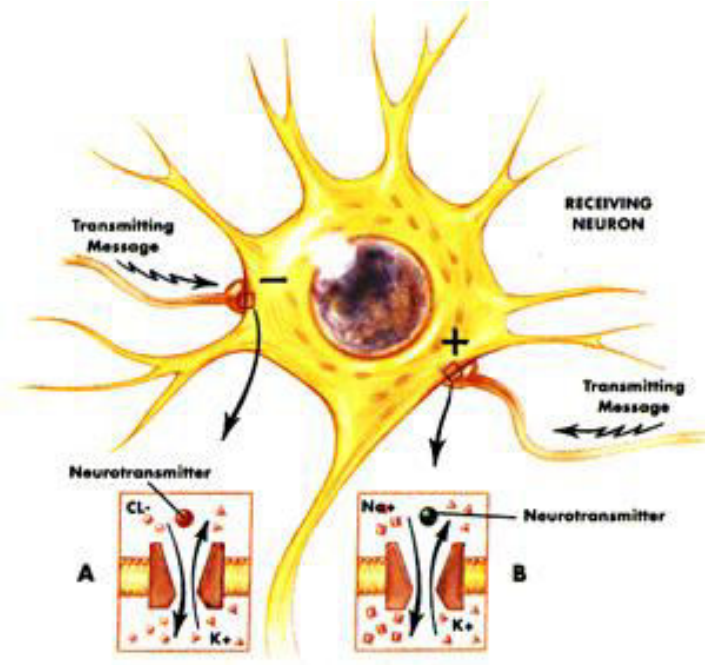
stimulation, spread of the abnormal electrical activity to the normal brain tissue causes generalized seizures.

- A seizure is traceable to an unstable cell membrane or its Surrounding cells.
- An abnormality of potassium conductance, a defect in the voltage-sensitive calcium channels or a deficiency in the membrane ATPase result in seizure.
- Normal neuronal activity depends on normal functioning of excitatory and inhibitory neurotransmitters. Also based on adequate supply of oxygen, glucose, sodium, potassium, chloride, calcium and amino acids.

Examples :

Excitatory : Glutamate, aspartate, acetyl choline, histamine-releasing factor, purines, peptids, cytokines and steroid hormones.

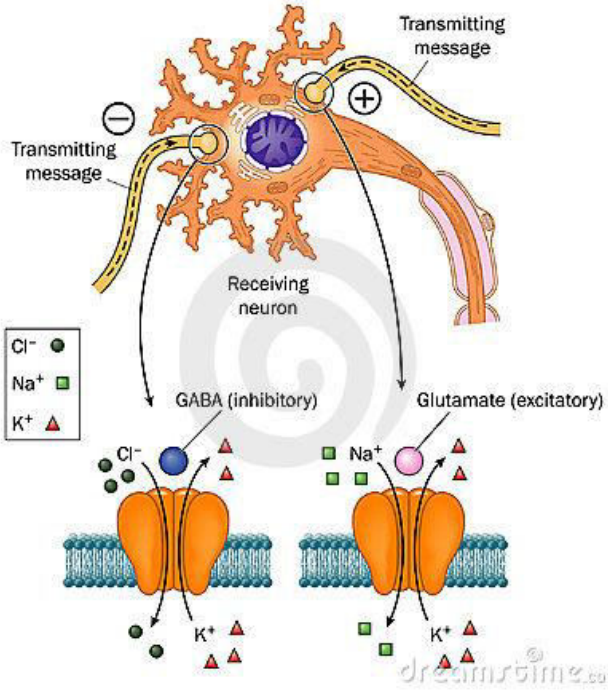
Inhibitory : Dopamine, Gamma amino butyric acid.



Neurons are interconnected in complex network in which each individual neurone is linked through synapses with hundreds of others. A small electrical current is discharged by neurons to release neurotransmitters at synaptic levels to permit communication with each other. Neurotransmitters fall into two basic categories: inhibitory or excitatory. Therefore, a neurone discharging can either excite or inhibit neurons connected to it. An excited neurons will activate the next neurone whereas an

inhibited neurone will not. In this manner, information is conveyed, transmitted and processed throughout the central nervous system.

A normal neurone discharges repetitively at a low baseline frequency, and it is the integrated electrical activity generated by the neurons of the superficial layers of the cortex that is recorded in a normal EEG. If neurons are damaged, injured or suffer a chemical or metabolic insult, a change in the discharge pattern may develop. In the case of epilepsy, regular low – frequency discharges are replaced by bursts of high – frequency discharges usually followed by periods of inactivity.



Mutations in several genes have been linked to some type of epilepsy. Several genes that code for protein subunits of voltages – gated and ligand –gated ion channels have been associated with generalized epilepsy and infantile seizure syndromes.

Several ligand – gated ion channels have been linked to some types of frontal and generalized epilepsies. Epilepsy – related mutations in some non – ion channel genes have also been identified.

Table 1.1. Examples of pathophysiological processes leading to epilepsy.

Level of dysfunction	Disorder	Pathophysiological mechanism
Ion channels	Benign familial neonatal convulsions Dravet syndrome	Potassium channel mutations: impaired repolarization Sodium channel mutations: enhanced excitability
Synapse development	Neonatal seizures	Depolarizing action of GABA early in development
Neurotransmitter receptors Excitatory	Nonketotic hyperglycinemia	Excess glycine leads to over-activation of NMDA receptors
Inhibitory	Angelman syndrome	Abnormal GABA receptor subunits
Neurotransmitter synthesis	Pyridoxine (vitamin B6) dependency	Decreased GABA synthesis; B6 is a cofactor of GAD
Neuron structure	Down syndrome and other disorders with intellectual impairment and seizures	Abnormal structure of dendrites and dendritic spines: altered current flow in neuron
Neuronal network	Cerebral dysgenesis; post-traumatic scar; mesial temporal sclerosis (in TLE)	Altered neuronal circuits: formation of aberrant excitatory connections (sprouting)

GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; NMDA, N-methyl-d-aspartate; TLE, temporal lobe epilepsy.

Table 1.2. Some common seizure mimics.

Seizure mimic	Underlying pathophysiology	Representative treatment
Benign paroxysmal positional vertigo	Labyrinth dysfunction	Head repositioning procedures
Breath-holding spells	Vasovagal	Reduce precipitant, reassurance
Migraine	Spreading cortical depression, neurogenic inflammation	Serotonin receptor agonists
Paroxysmal movement disorders	Multiple types and genetic basis; most are channelopathies	AEDs (e.g., carbamazepine)
Psychogenic seizure	Unknown; unresolved psychological conflicts	Counseling, behavior therapy
Sleep disorders	Multiple defects in regulation of arousal	Depends on type: e.g., reassurance for night terrors, arousal-promoting drugs for narcolepsy
Syncope	Vasovagal	Avoidance of triggers
Tics	Basal ganglia dysfunction	Dopamine receptor blockade

AED, antiepileptic drug.

Trips and tricks

The best practice is to use a single agent (monotherapy) to avoid side effects due to multiple AEDs. If it is necessary to treat apatient with more than one AED, drugs with *differing* mechanisms of action should be chosen to minimize adverse effects andDrug–drug interactions

2.7 Signs and symptoms

Epilepsy is characterized by a long-term risk of recurrent seizures. These seizures may present in several ways depending on the part of the brain involved and the person's age

Symptoms of Simple Partial Seizures

Symptoms may be motor, sensory, psychic (states of consciousness), and/or autonomic (involuntary activity controlled by the autonomic nervous system). There is no impairment of consciousness in simple partial seizures. While there is a wide range of potential signs and symptoms, for most patients symptoms are stereotypical.

- Alternating contraction and relaxation of muscle groups
- Eye movements and turning of the head to the same side
- Asymmetrical posturing of the limbs
- Speech arrest, vocalization

Sensory symptoms include the following:

- Seeing flashes of lights or colors, illusions and hallucinations
- Hearing humming, buzzing, hissing noises
- Experiencing unpleasant odors and tastes
- Dizziness, light headedness

Autonomic signs and symptoms include the following

- Borborygmi (rumbling noises produced by gas in the intestines)
- Flushing
- Incontinence
- Nausea, vomiting
- Piloerection (goose bumps)
- Pupillary dilation

- Sweating
- Tachycardia (rapid heart rate)

Psychic symptoms include the following:

- Detachment, depersonalization
- Dreamy state
- Memory distortion: flashback, deja vu (feeling that one has seen something before), dejaentendu (feeling that one has heard something before), jamais vu (feeling that one has never seen something that is familiar), jamaisentendu (feeling that one has never heard something that is familiar), panoramic vision (rapid recall of past events)
- Time distortion
- Unprovoked emotion: fear, pleasure, displeasure, depression, anger, elation, ereoticism

2.8 Diagnosis of Epilepsy

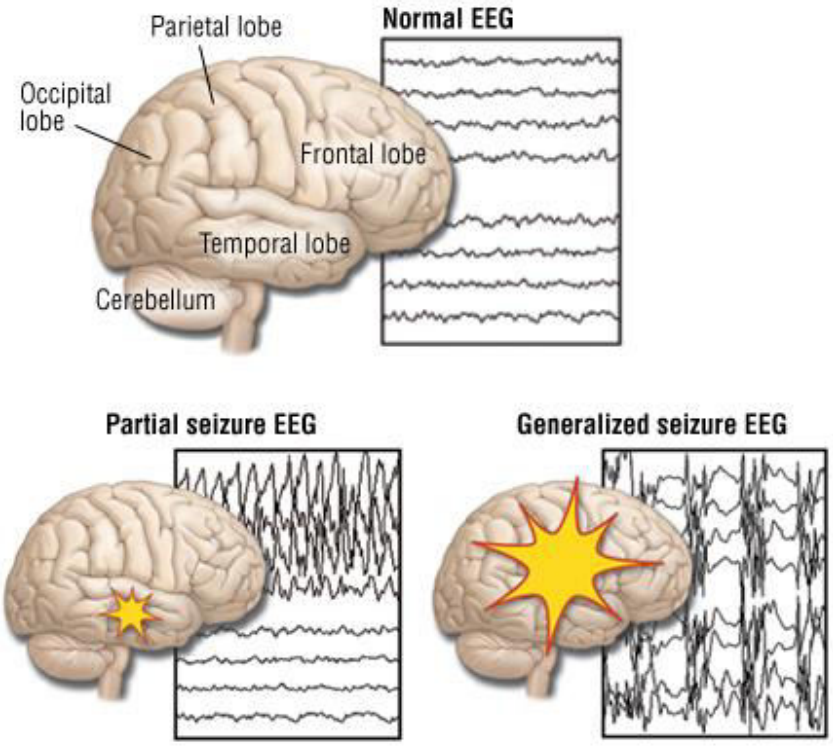
You should see a doctor if you have had a possible seizure or similar event. Sometimes it is difficult for a doctor to confirm that you have had a seizure. The most important part of confirming the diagnosis is the description of what happened. Other conditions can look like seizures - for example, faints, panic attacks, collapses due to heart problems, breath-holding attacks in children.

Therefore, it is important that a doctor should have a clear description of what happened during the event. It may be that a person who witnessed your seizure may be able to give a more accurate description of what happened during your seizure.

There is no one test to confirm a diagnosis of epilepsy. However, tests such as brain scans, an electroencephalogram (EEG - brainwave recordings) and blood tests may help to make a diagnosis.

- **A brain scan** - usually a magnetic resonance imaging (MRI) scan or computed tomography (CT) scan - shows the structure of different parts of the brain. This may be performed in some people.

- **Electroencephalograph (EEG)**.



This test records the electrical activity of the brain. Special stickers are placed on various parts of the scalp. They are connected to the EEG machine. This amplifies the tiny electrical messages given off by the brain and records their pattern on paper or computer. The test is painless. Some types of seizure produce typical EEG patterns. However, a normal recording does not rule out epilepsy and not all EEG abnormalities are related to epilepsy.

- **Blood tests** and other tests may be advised to check on your general well-being. They may also look for other possible causes of the event.

  Although helpful, tests are not foolproof. It is possible to have epilepsy with normal test results. Also, if an abnormality is found on a brain scan, it does not prove that it causes seizures.

- Video EEGS also demonstrates what patient was doing when the seizure occurred and how the seizure changed his behaviour.

Other diagnosis:

1. Magnetic resonance imaging (MRI)
2. Positron emission tomography (PET)
3. Single photon emission tomography (SPECT)

2.9 MANAGEMENT AND TREATMENTS FOR EPILEPSY

NON PHARMACOLOGICAL

First aid

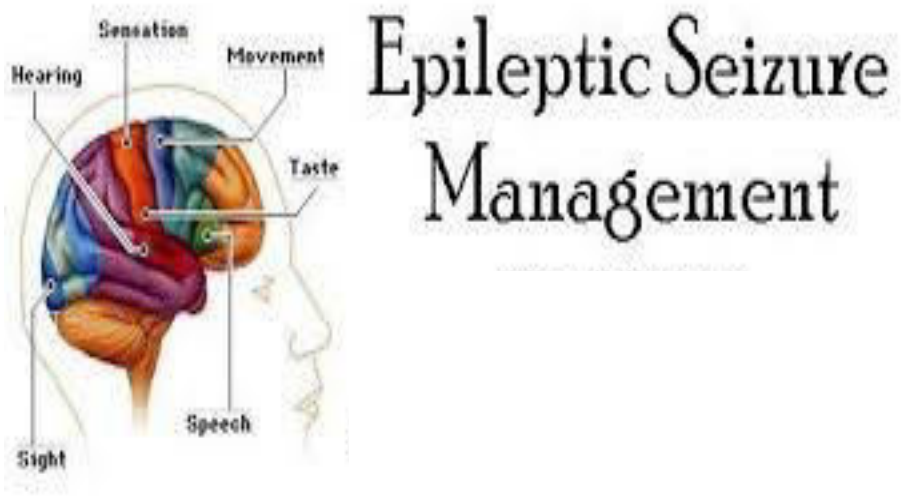
- Rolling a person with an active tonic-clonic seizure onto their side and into the recovery position helps prevent fluids from getting into the lungs.[46]
- Putting fingers, a bite block or tongue depressor in the mouth is not recommended as it might make the person vomit or result in the rescuer being bitten.
- Efforts should be taken to prevent further self-injury. Spinal precautions are generally not needed.
- If a seizure lasts longer than 5 minutes or if there are more than two seizures in an hour without a return to a normal level of consciousness between them, it is considered a medical emergency known as status epilepticus. This may require medical help to keep the airway open and protected; a nasopharyngeal airway may be useful for this.
- At home the recommended initial medication for seizure of a long duration is midazolam placed in the mouth. Diazepam may also be used rectally.

- In hospital, intravenous lorazepam is preferred. If two doses of benzodiazepines are not effective, other medications such as phenytoin are recommended.
- Convulsive status epilepticus that does not respond to initial treatment typically requires admission to the intensive care unit and treatment with stronger agents such as thiopentone or propofol.

Prevention

While many cases are not preventable, efforts to reduce head injuries, provide good care around the time of birth, and reduce environmental parasites such as the pork tapeworm may be effective. Efforts in one part of Central America to decrease rates of pork tapeworm resulted in a 50% decrease in new cases of epilepsy.

Management



Epilepsy is usually treated with daily medication once a second seizure has occurred,but for those at high risk, medication may be started after the first seizure. In some cases, a special diet, the implantation of a neurostimulator, or neurosurgery may be required.

PHARMACOLOGICAL

Medication

Epilepsy cannot be cured with medication. However, with the right type and strength of medication, the majority of people with epilepsy do not have seizures. The

medicines work by stabilising the electrical activity of the brain. You need to take medication every day to prevent seizures.

One medicine can prevent seizures in most cases. A low dose is usually started at first. The dose may be increased if this fails to prevent seizures. In some cases two medicines are needed to prevent seizures.

- The decision **when** to start medication may be difficult. A first seizure may not mean that you have epilepsy, as a second seizure may never happen or may occur years later. The decision to start medication should be made by weighing up all the pros and cons of starting, or not starting, the medicine. It is unusual to start treatment after a first seizure. A common option is to wait and see after a first seizure. If you have a second seizure within a few months, more are likely.

- Medication is commonly started after a second seizure that occurs within 12 months of the first. However, there are no definite rules and the decision to start medication should be made after a full discussion with your doctor. The type of treatment you will be given often depends on the type of seizures you have and also if you are taking any other medication.

- The mainstay treatment of epilepsy is anticonvulsant medications, possibly for the person's entire life. The choice of anticonvulsant is based on seizure type, epilepsy syndrome, other medications used, other health problems, and the person's age and lifestyle. A single medication is recommended initially; if this is not effective, switching to a single other medication is recommended. Two medications at once is recommended only if a single medication does not work. In about half, the first agent is effective; a second single agent helps in about 13% and a third or two agents at the same time may help an additional 4%.About 30% of people continue to have seizures despite anticonvulsant treatment.[39]

- There are a number of medications available. Phenytoin, carbamazepine and valproate appear to be equally effective in both partial and generalized seizures.[47] Controlled release carbamazepine appears to work as well as immediate release carbamazepine, and may have fewer side effects. In the United Kingdom, carbamazepine or lamotrigine are recommended as first-line treatment for partial

seizures, with levetiracetam and valproate as second-line due to issues of cost and side effects. Valproate is recommended first-line for generalized seizures with lamotrigine being second-line. In those with absence seizures, ethosuximide or valproate are recommended; valproate is particularly effective in myoclonic seizures and tonic or atonic seizures. If seizures are well-controlled on a particular treatment, it is not usually necessary to routinely check the medication levels in the blood. The least expensive anticonvulsant is phenobarbital at around $5 USD a year. The World Health Organization gives it a first-line recommendation in the developing world and it is commonly used there. Access however may be difficult as some countries label it as a controlled drug.[41]

List of anti-epileptic drugs

Anti-epileptic drugs (AEDs) are the main form of treatment for people with epilepsy. And up to 70% (7 in 10) people with epilepsy could have their seizures completely controlled with AEDs. There are around 26 AEDs used to treat seizures, and different AEDs work for different seizures. Here we explain what the different AEDs are, what type of seizures or epilepsy they are used for, as well as some essential information about average doses and common side effects.

There are three ways you can search for information about AEDs:

- **By the generic name of the AED**
- **By the brand name of the particular type of AED** or
- **By the type of seizure or seizures you have.**

Generic names

- Acetazolamide
- Carbamazepine
- Clobazam
- Clonazepam
- Eslicarbazepine acetate
- Ethosuximide
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Nitrazepam
- Oxcarbazepine
- Perampanel
- Piracetam

- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- Retigabine
- Rufinamide
- Sodium valproate
- Stiripentol
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

Brand names (available as):

- Carbogen modified release
- Convulex
- Desitrend
- Diacomit
- Diamox SR
- Emeside
- Epanutin
- Epilim
- Epilim Chrono
- Epilim Chronosphere
- Episenta (prolonged release)
- Epival
- Frisium
- Fycompa
- Gabitril
- Inovelon
- Keppra
- Lamictal
- Lyrica
- Neurontin
- Nootropil
- Phenytoin Sodium Flynn
- Rivotril
- Sabril
- Tapclob
- Tegretol
- Tegretol Prolonged Release
- Topamax
- Trileptal
- Trobalt
- Vimpat
- Zarontin
- Zebinix
- Zonegran

Seizure types

- **Absence seizures (including typical and atypical absences):**
  Acetazolamide | Clonazepam | Ethosuximide | Lamotrigine | Sodium valproate
- **Atonic seizures:**
  Phenobarbital | Phenytoin | Primidone | Sodium valproate
- **Catamenial seizures (menstrual-related):**
  Acetazolamide | Clobazam
- **Cluster seizures:**
  Clobazam
- **Episodic disorders:**
  Acetazolamide
- **Dravet syndrome (severe myoclonic epilepsy in infancy or SMEI):**
  Stiripentol
- **Focal (partial) seizures:**
  Acetazolamide | Carbamazepine | Clobazam | Clonazepam | Eslicarbazepine acetate | Gabapentin | Lacosamide | Lamotrigine | Levetiracetam | Oxcarbazepine | Perampanel | Phenobarbital | Phenytoin | Pregabalin | Primidone | Retigabine | Sodium valproate | Tiagabine | Topiramate | Vigabatrin | Zonisamide

Focal (partial) seizures with secondary generalisation:

Gabapentin | Lacosamide | Levetiracetam | Perampanel | Phenobarbital | Phenytoin | Pregabalin | Primidone | Retigabine | Sodium valproate | Tiagabine |Topiramate | Vigabatrin| Zonisamide

Focal seizures with secondary generalised tonic clonic seizures:

Carbamazepine | Eslicarbazepine acetate | Lamotrigine | Oxcarbazepine

Infantile spasms:

Nitrazepam | Sodium valproate | Vigabatrin

Juvenile Myoclonic Epilepsy (seizures related to):

Levetiracetam

Lennox-Gastaut syndrome (seizures related to):
Lamotrigine | Rufinamide | Topiramate

Menstrual-related (catamenial seizures):

- **Myoclonic seizures:**
  Clonazepam | Ethosuximide | Phenobarbital | Phenytoin | Primidone | Piracetam | Sodium valproate
- **Myoclonic seizures in Juvenile Myoclonic Epilepsy:**

Tonic seizures:

Phenobarbital | Phenytoin | Primidone | Sodium valproate

Tonic clonic seizures:

Acetazolamide | Carbamazepine | Clobazam | Clonazepam | Eslicarbazepine acetate | Lamotrigine | Phenobarbital | Phenytoin | Primidone | Sodium valproate | Topiramate

Tonic clonic seizures in severe myoclonic epilepsy in infancy (SMEI or Dravet syndrome):

West Syndrome with Tuberous Sclerosis: Vigabatrin

Adverse effect

- Mood changes
- Sleepiness
- Unsteadiness
- Rashes,
- Liver toxicity
- Suppression Of The Bone Marrow

Slowly stopping medications may be reasonable in some people who do not have a seizure for two to four years; however, around a third of people have a recurrence, most often during the first six months. Stopping is possible in about 70% of children and 60% of adults

Some points about medication for epilepsy include the following:

- Ask your doctor how long treatment is likely to be advised. This will vary from case to case. If you have not had seizures for several years, you may wish to try stopping medication. However, this depends on your particular type of epilepsy, as some types will need medication for life. Your life circumstances may influence the decision about stopping medication. For example, if you have recently regained your driving licence, the risk of losing it again for a year if a seizure occurs may affect your decision. However, if you are a teenager who has been free of seizures for some years, you may be happy to take the risk.
- Although the list of **possible** side-effects for each medicine seems long, in practice, most people have few or no side-effects, or just minor ones. Ask your doctor which side-effects are important to look out for. If you develop a troublesome side-effect it may be dose-related, or may diminish in time. Alternatively, a switch to another medicine may be advised.
- Medicines which are used for other conditions may interfere with medication for epilepsy. If you are prescribed **or buy** another medicine, remind your doctor or pharmacist that you take medication for epilepsy. Even things like indigestion medicines may interact with your epilepsy medication, which may increase your chance of having a seizure.
- Some medicines for epilepsy interfere with the contraceptive pill. A higher-dose pill or an alternative method of contraception may be needed.
- Tell your doctor if you intend to become pregnant. Pre-conception counselling is important for women with epilepsy.
- If you have epilepsy and take medication, you are exempt from prescription charges for all your prescriptions. You need an exemption certificate. You can get this from your pharmacist.

OTHER TREATMENTS FOR EPILEPSY

- **Surgery** to remove a small part of the brain which is the underlying cause of the epilepsy. This is only a suitable option if your seizures start in one small area of your brain (this means it is only possible for a minority of people with epilepsy). It may be considered when medication fails to prevent seizures. However, there are risks from operations. Only a small number of people with epilepsy are suitable for surgery and, even for those who are, there are no guarantees of success.

Surgical techniques continue to improve and surgery may become an option for more and more people in the future.

- **Vagal nerve stimulation** is a treatment for epilepsy, where a small generator is implanted under the skin below the left collarbone. The vagus nerve is stimulated to reduce the frequency and intensity of seizures. This can be suitable for some people with seizures that are difficult to control with medication.
- **The ketogenic diet** is a diet very high in fat, low in protein and almost carbohydrate-free which can be effective in the treatment of difficult-to-control seizures in children.
- **Complementary therapies** such as aromatherapy may help with relaxation and relieve stress; however, they have no proven effect on preventing seizures.

2.10 PROGNOSIS

The success in preventing seizures by medication varies depending on your type of epilepsy. For example, if no underlying cause can be found for your seizures (idiopathic epilepsy), you have a very good chance that medication can fully control your seizures. Seizures caused by **some** underlying brain problems may be more difficult to control.

The overall outlook is better than many people realise. The following figures are based on studies of people with epilepsy, which looked back over a five-year period. These figures are based on grouping people with all types of epilepsy together, which gives an overall picture:

- About 5 in 10 people with epilepsy will have no seizures at all over a five-year period. Many of these people will be taking medication to stop seizures. Some will have stopped treatment having had two or more years without a seizure while taking medication.
- About 3 in 10 people with epilepsy will have some seizures in this five-year period but far fewer than if they had not taken medication.
- So, in total, with medication, about 8 in 10 people with epilepsy are well controlled with either no, or few, seizures.
- The remaining 2 in 10 people experience seizures, despite medication.
- A very small number of people with epilepsy have sudden unexplained death. The exact cause of this is unknown. However, it may be related to a change in the

breathing pattern or to abnormal heart rhythms during a seizure. This is rare and the vast majority of people with epilepsy fully recover following each seizure.

A trial without medication may be an option if you have not had any seizures over 2-3 years. If a decision to stop treatment is made, a gradual reduction of the dose of medication is usually advised over several months. You should never stop taking medication without discussing it with a doctor.

2.11 INVESTIGATIONS

- Drug Therapy

Two Type of drug therapy is followed

1. Mono Therapy
2. Add on Therapy

1. MONOTHERAPHY

Antiepileptic Drug Monotherapy

- Antiepileptic drug (AED) mono therapy is the preferred initial management approach in epilepsy care, since most patients may be successfully managed with the first or second mono therapy utilized.
- The rationale and evidence supporting preferential use of mono therapy when possible and guidelines for initiating and successfully employing AED mono therapy. Suggested approaches to consider when patients fail mono therapy include substituting a new AED mono therapy, initiating chronic maintenance AED poly therapy, or pursuit of non-pharmacologic treatments such as epilepsy surgery or vagus nerve stimulation.
- Reducing AED poly therapy to mono therapy frequently reduces the burden of adverse effects and may also improve seizure control. AED mono therapy remains the optimal approach for managing most patients with epilepsy.[59]

Introduction

Epileptic seizures have been observed since antiquity . Treatment preferences generally favoured poly therapy prior to the evolution of modern antiepileptic drugs (AEDs). In the early 1900s, phenobarbital and the ketogenic diet were used to manage epilepsy. Throughout the earlier 20th century, the standard AEDs (phenytoin, phenobarbital, primidone, valproic acid, carbamazepine, and ethosuximide) were

often combined in poly therapy use, due to the pervasive belief that polytherapy was more efficacious than mono therapy. However, during the 1970s, several studies suggested that mono therapy was equally efficacious, less toxic, and more tolerable than poly therapy[60]. Since then, most epilepsy experts have advocated mono therapy as the preferred approach in epilepsy, although poly therapy is sometimes still necessary. The evidences favoring initial mono therapy and suggests methods to maintain mono therapy or reduce poly therapy to mono therapy when possible.

THE RATIONALE FAVORING MONOTHERAPY

Since the early 1990s, the second-generation AEDs, felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and pregabalin, have become available. Recently, the seemingly ever increasing armamentarium of AEDs has seen two additional newer ("third-generation") AEDs released, lacosamide and rufinamide. Advantages of most newer AEDs include a more desirable safety profile and fewer adverse effects and drug interactions than their predecessors. Recent pivotal clinical trials have provided evidence to support monotherapy use of second-generation AEDs[64]. Current treatment guidelines recommend monotherapy in most cases because data indicate similar efficacy and better patient tolerability compared to polytherapy[68]. Polytherapy may only minimally increase seizure control and can substantially increase AED toxicity,drug interactions, seizure aggravation[71], comorbid depression, risk of sudden unexplained death in epilepsy patients (SUDEP), noncompliance, and cost. Polytherapy and seizure burden were the two main causes of quality of life impairment in one recent survey of epilepsy patients.

WHO BENEFITS MOST FROM MONOTHERAPY

While mono therapy is preferable for most patients with epilepsy, mono therapy is particularly desirable for certain special patient populations, including women, elderly, and patients with co-morbid conditions (who are at increased risk for AED toxicity and drug interactions)[68]. Compared to poly therapy, mono therapy reduces the potential for adverse drug interactions. Hepatic and renal dysfunction significantly impacts the metabolism and elimination of many AEDs, which may reduce tolerability and safety of continued use. Pregnant women taking two or more

AEDs are at substantially increased risk of fetal malformations (3% versus 15%) than mothers receiving mono therapy .

EVIDENCE SUPPORTING PREFERENTIAL MONOTHERAPY IN EPILEPSY

The majority of patients with epilepsy respond to treatment with mono therapy; 47% of patients become seizure-free with the first AED tried, and another 13% achieve freedom from seizures with the second mono therapy trial.

While available evidence is central in determining whether an AED is effective for mono therapy usage, FDA approval and indication generally guide how an AED will be prescribed. First-generation AEDs were "grandfathered" by the FDA, receiving approval for mono therapy for a particular seizure type without requirement to satisfy current rigorous approval requirements. The majority of second-generation AEDs are approved only as adjunctive therapies. Since few comparator studies are funded by industry, government agencies should become involved in conducting additional comparative clinical trial studies, and independent groups should be persuaded to collect data from historically treated and control patients.

Currently, four second-generation AEDs are FDA approved for use as mono therapy, with some limitations; these are oxcarbazepine, lamotrigine, topiramate, and felbamate. In four randomized, controlled, blinded trials, oxcarbazepine demonstrated efficacy as mono therapy in patients with partial seizures. Lamotrigine is currently approved as mono therapy when converting from an enzyme-inducing AED or valproate but not for de novo or initial mono therapy . However, lamotrigine should be used with caution in persons under the age of 16 due to a higher incidence of a potentially life-threatening rash in pediatric patients, and patients receiving concurrent valproic acid or who receive inappropriately fast initial titration of lamotrigine are also at heightened risk of serious rash. Topiramate is indicated as initial mono therapy in adults and children aged 10 years and older with partial onset or primary generalized seizures; efficacy was established in both a large, double-blind, dose-controlled study and a second large trial comparing two doses of topiramate with standard comparators carbamazepine and valproate[72]. Felbamate also has evidence for monotherapy use in partial-onset seizures; however, severe idiosyncratic toxicities

limit its use. Additionally, gabapentin possesses adequate evidence for confident use as monotherapy in treatment of partial-onset seizures, although it lacks formal FDA approval for this indication.

Among the second-generation AEDs approved for monotherapy use, few comparator trials have been conducted. Gabapentin and lamotrigine have been shown to be comparably effective and tolerable in two large prospective trials, and were more tolerable than carbamazepine in elderly with newly diagnosed epilepsy. A large, naturalistic, unblinded controlled trial recently demonstrated superior efficacy of lamotrigine as compared to carbamazepine, oxcarbazepine, and topiramate.

The other second-generation and third-generation AEDs have not been FDA approved for monotherapy use since most lack an adequate level of evidence for this indication. However, the efficacy and tolerability of levetiracetam monotherapy for treatment of partial-onset seizures has been confirmed in a recent large, prospective, comparator trial against carbamazepine.

GUIDELINES FOR AED MONOTHERAPY

Given the complexity and expansive body of evidence concerning AED therapy in the medical literature and limitations in practical application of this literature to actual patients, practice guidelines and expert surveys are valuable tools to assist clinicians in applying evidence based practice for patients with epilepsy. Practice guidelines are available to assist practitioners in the management of new-onset and refractory epilepsy and epilepsy in women. The American Academy of Neurology/American Epilepsy Society (AAN/AES) Practice Guidelines for the treatment of new-onset epilepsy identified gabapentin, lamotrigine, oxcarbazepine, and topiramate as possessing Class I evidence (prospective study, blinding, statistical population-based sample, and patients studied concurrently and early in the course of therapy) for use as monotherapy in the treatment of new-onset partial or mixed seizures. In the treatment of epilepsy in women state that in women with epilepsy (WWE), monotherapy is recommended during the reproductive years to reduce the risk of teratogenicity seen with polytherapy .

A recent survey of epilepsy experts found that lamotrigine, levetiracetam, and valproic acid are preferred AED choices for monotherapy in the treatment of

generalized tonic-clonic, absence, and myoclonic seizures . Previous survey results were compared to the current survey, and, overall, valproic acid is still the drug of choice for each of these seizure types, except for absence seizures, where ethosuximide remains the preferred AED. Many practitioners chose lamotrigine and topiramate as first-line treatment for generalized tonic-clonic seizures.

HOW TO INITIATE MONOTHERAPY

Practical tenets for achieving successful monotherapy in new-onset epilepsy management include the following:

1. Select an efficacious AED for the specific seizure type;
2. Choose an AED with a tolerable adverse effect and toxicity profile.
3. Titrate the AED slowly to the desired dose, taking into account the patient's response to treatment.

If the first AED monotherapy is ineffective, adding a second AED, then tapering and discontinuing the ineffective AED, is the preferred approach. When switching AEDs, selecting an agent with a different MOA may increase the likelihood of a successful treatment response. If the second sequential AED monotherapy is ineffective, an adjunctive AED with a different and potentially complementary MOA should be considered for use in adjunctive polytherapy. Since approximately 35% of patients with epilepsy will not respond to monotherapy, most refractory patients become candidates for polytherapy. Polytherapy with lower or moderate dosages of two AEDs may also sometimes be preferred for management of refractory patients who have dose-limiting neurotoxic adverse effects with high-dose monotherapy.

Before initiating treatment, patients with epilepsy should undergo a thorough medical evaluation to determine seizure type and consider baseline patient characteristics that may influence the decision of whether treatment is necessary and, if so, which AED may be the most logical choice. Evaluation to determine the patient's epilepsy syndrome begins with a thorough clinical history, including a detailed description of the seizure semiology, an awake and asleep electroencephalogram (EEG), and a brain magnetic resonance image (MRI). A standard brain MRI is adequate in newly diagnosed epilepsy where the priority is to exclude underlying serious symptomatic pathologies, such as arteriovenous

malformations or neoplasms. However, when feasible, available, and of reasonable cost, it is advantageous to consider obtaining brain MRI with a volumetric seizure-protocol study in patients with suspected partial-onset seizures, given better identification of subtle mesial temporal lobe pathologies such as hippocampal sclerosis or malformations of cortical development that may impact on prognosis for drug responsiveness, as well as future decisions regarding surgical triage if the patient becomes refractory to AEDs.

Educating the patient about epilepsy, AED compliance, and seizure first-aid is important for ensuring successful therapy. AED selection is determined by seizure type, patient medical history, and concurrent medications. For partial epilepsy, any approved AED could be considered for use (except ethosuximide, which is ineffective for partial-onset seizure treatment). In idiopathic or symptomatic generalized epilepsies, as well as for ambiguous or unknown epilepsy syndromes, a broad-spectrum AED should be preferentially utilized given the potential to treat other potentially associated generalized seizure-types in generalized epilepsies (i.e., absence and myoclonic seizures in idiopathic generalized epilepsies, or tonic seizures in symptomatic generalized epilepsy).

After AED selection has been made, starting with a low dose and gradually titrating to a moderate and presumably effective dose is a reasonable strategy, since titration to higher doses. A more rapid titration may be necessary in selected patients who have had multiple recent seizures. Maximizing the dose is only recommended in patients who do not respond to moderate doses. At each patient visit, it is necessary to conduct a detailed assessment of AED therapy, including adverse effects and compliance. Utilizing a quantitative survey of patient's perceived adverse effects such as the adverse events profile (AEP) has been prepared alter antiepileptic drug therapies to for improving quality of life.

WHY ARE SOME PATIENTS REFRACTORY TO MONOTHERAPY

The efficacy of currently available AEDs is limited to reduction of seizure frequency, and no AED has yet been proven to impact the pathophysiology of epilepsy itself. Currently, there is no convincing evidence that any of the available AEDs are anti-epileptogenic, nor has any AED been shown to favorably impact the

long-term outcome of epilepsy Yet, prescribing an AED after a second or third seizure event is the accepted practice standard, based on logic derived in part from epidemiologic studies of the natural history of new onset unprovoked seizures that confirm a greatly increased risk for further seizure recurrence following the occurrence of a second unprovoked seizure. The desired short-term outcomes of epilepsy management are seizure freedom, seizure control when complete seizure freedom is not possible, and maximizing patient quality of life, given that the complications of untreated seizure activity are increased risk of injury and mortality, cognitive and behavioral abnormalities, and social disadvantage. Currently, there is no AED for the treatment of epilepsy that is completely effective, without adverse effects, and efficacious for all patients. Of the older AEDs, carbamazepine was shown to be the most effective and tolerable AED in two pivotal clinical trials; thus, it became the standard to which developing AEDs have been compared, although carbamazepine itself has never been compared to placebo or demonstrated efficacy in an active control-designed study. Most studies have shown that newer AEDs have equivalent efficacy to that of carbamazepine, but several newer AEDs have superior tolerability including lamotrigine and gabapentin[72]. However, recently published comparator trials of newer AEDs against a sustained release form of carbamazepine have shown relatively equivalent tolerability, suggesting that immediate release forms of carbamazepine may be less tolerable and sustained release forms of carbamazepine are equally tolerable to newer AEDs

Monotherapy is preferred when treating epilepsy, although previous reports indicate that polytherapy was sometimes the standard of care and given routinely as initial treatment.1 Polytherapy began to be questioned shortly after studies showed that 50% to 75% of patients who started on monotherapy remained seizure free for at least 1 year and that monotherapy is equally or more effective, better tolerated, and associated with fewer drug interactions compared with polytherapy. Other advantages of monotherapy include better compliance, lower costs, and improved quality of life.

The efficacy of conventional antiepileptic drugs (AEDs), including phenytoin, carbamazepine, phenobarbital, and valproate, as monotherapy is accepted, but efficacy of monotherapy with some of the newer AEDs has been established in well-controlled trials. To protect patients from the potential dangers of a noneffective agent

used as monotherapy, many newer medications were initially studied as adjunctive therapy in refractory patients, and when efficacy and tolerability as adjunctive treatments were established, newer medications were then studied as monotherapy.

There is a long tradition of treating epilepsy patients with two or more AEDs. However, in the past decade monotherapy has emerged as the ultimate treatment strategy for both newly-diagnosed and long-term patients because of fewer side effects, better compliance, less teratogencity and lower cost. Furthermore, the evidence does not exist that additional drugs improve seizure control in most patients. Obtaining FDA approval for monotherapy use is particularly important for the advantages of better tolerability, improved safety, less teratogenicity, and simpler pharmacokinetics than the older drugs.

Considering the ethical issues of placebo-controlled trials and the benefits of monotherapy treatment, however, there was considerable support at the workshop for consideration of active-control equivalence trials for monotherapy approval of AEDs. This resulted in substantial debates between participants and representatives from the FDA as to this approach. The FDA did indicate willingness to considering experiences from historical controls, if the data exist to support them. These data would have to be based on previous trials of active control vs. placebo under similar conditions with respect to study population, endpoints, dose of active control and other important design features.

The workshop ended with the draft of a brief consensus statement. A task force will be set up to look at the issue of historical control and to see what data exist. Most participants indicated that the workshop had been a good start in addressing the monotherapy issue.

EVALUATING MONOTHERAPY CLINICAL TRIALS

The long-term, randomized, double-blind, placebo-controlled clinical trial of monotherapy in epilepsy is generally untenable for new AEDs because of possible harm arising from withholding active treatment. Randomized active-control trials comparing monotherapy with a test medication and monotherapy with a reference medication in newly diagnosed patients allowing assessment of efficacy and tolerability under conditions approximating clinical use. Because a new drug would

not be expected to surpass the high (70%-80%) seizure remission rates achieved with established agents, demonstration of comparable efficacy of the test and reference medications is interpreted as evidence of the test medication's efficacy.

Several alternative study designs compare test medication with a suboptimal treatment, which may be a nontherapeutic dose of the same drug, a different drug, or a placebo. Presurgical trials compare high doses of a test AED with placebo in patients with refractory seizures who need to discontinue their current therapy for evaluation before epilepsy surgery. These trials are of short duration because of the risks patients are exposed to in the placebo arm (ie, no AED treatment). This trial design compares the seizure frequency between the study drug and placebo, just as in other placebo-controlled trials. In open-label substitution trials, a high dosage of the test medication is compared with a suboptimal dosage of the same drug or with either a suboptimal drug or an effective dosage of a different one.11 When ethically feasible, a placebo group sometimes takes the place of the active comparator in substitution trials.

These alternative study designs require relatively few patients to demonstrate statistically significant effects of treatment. However, because of short duration and lack of flexibility for titrating doses to optimum levels, the practical relevance of data derived from these studies is limited.

2. ADD ON THERAPY

Adequate control of partial-onset epilepsy often requires polypharmacy, either due the to less than ideal efficacy of one antiepileptic drug (AED) or due to side effects caused by the initial AED . Up to one-third of patients with partial-onset epilepsy will require treatment with more than one AED.

The ideal medical management of epilepsy is based on tailoring each patient's regimen to his or her seizure type, comorbidities, lifestyle, and history of medication side effects. Therefore, a greater number of potential treatments offers greater options for any given patient to be treated with the best combination of medications. In recent years, many new AEDs have become available for add-on therapy for partial-onset epilepsy of the newer AEDs, those that are US Food and Drug Administration (FDA)-approved for the adjunctive treatment of partial-onset epilepsy include

felbamatetigabine, lamotrigine, pregabalin, gabapentin, topiramate, oxcarbazapine, zonisamide, and levetiracetam. An add-on AED should ideally have a clean pharmodynamic and phamcokinetic profile to minimize drug interactions and side effect profile. The newer AEDs are generally safer than the first-generation AEDs and, with the exception of Felbamate, do not require routine blood monitoring. All of the newer AEDs are category C in terms of use in females who want to have children, although a patient who is planning a pregnancy should aim for the lowest number of AEDs given at the lowest dose.

The physician's armamentarium to treat epilepsy has been significantly improved by the increasing number of new AEDs, all of which can be used as add-on therapy. In treating a patient, one must consider not only efficacy, but also comorbidities, potential adverse effects, and dosing schedules. The real-world dosing of AEDs as add-on therapy does not need to follow the package insert dosing recommendation derived from clinical trial titration schedule because the mantra of starting with a lower dose and slowly increasing it will lead to better tolerability and higher retention in most cases, especially in the elderly. With a greater understanding of the strengths and weaknesses of each AED, physicians can use each medication optimally for each patient.

Levetiracetam

Levetiracetam is approved as adjunctive therapy in the treatment of partial-onset seizures, myoclonic seizures in juvenile myoclonic epilepsy, and primary generalized tonic-clonic seizures in adults and children ≥6 years of age. There is now an intravenous form of leveitracetam available. Levetiracetam binds a brain-specific binding site presynatpic vesicle protein SV2A, and has been shown to inhibit Ca^{2+} release and other possible neurotransmitters[73].

Levetiracetam has no known significant drug interactions. It is an AED that is generally well tolerated. The most significant adverse effects are somnolence, asthenia, and dizziness. A drug-specific adverse effect is irritability, which seems to be more common in patients with underlying behavioral issues and may be doserelated. No serious acute idiosyncratic reactions were reported.

CLOBAZAM

Clobazam (CLB) is in use for almost four decades since its introduction in 1975. Its use has expanded from anxiety to epilepsy including Lennox-Gastaut syndrome (LGS) This broad spectrum antiepileptic prevents recurrence of febrile seizures also. According to a Canadian study, more than 10 per cent treatment refractory patients achieved seizure freedom with clobazam over a period of seven years. Despite being a benzodiazepine, clobazam has lower sedative effects. Adverse effects associated with clobazam, generally transient and dose-related, include somnolence, dizziness, mood changes, irritability, depression and aggression.

Efficacy and safety of a drug are established through rigorous randomized controlled trials. Which especially play an important role in the pharmacotherapy of epilepsy. Though studies in Indian population have demonstrated the efficacy of CLB as monotherapy in adult patients and in refractory childhood epilepsy, data regarding the usage pattern, efficacy and safety of clobazam in different treatment regimens are limited.

CONVERTING FROM POLYTHERAPY TO MONOTHERAPY

Patients may begin receiving polytherapy while transitioning from one trial of monotherapy to another (transitional monotherapy), or because of two failed attempts with monotherapy (chronic polytherapy). In the first situation, eventual monotherapy is likely to result once the original AED is tapered off. However, in the latter case, patients may continue on multiple AEDs indefinitely. While receiving multiple AEDs, some patients may go into seizure remission, while other patients will continue to require sequential trials of additional AEDs). Patients who are appropriate candidates for tapering one or more AEDs are those who have been seizure free for 2 years or longer. For these patients, a slow taper is recommended, with dose reductions occurring weekly or every other week. Additionally, patients receiving unsuccessful polytherapy should be considered for a further trial of monotherapy or additional AED sequencing.[55]

RATING SCALES

1)Clinical Global Impressions (CGI) Scale is use to epilepsy treatment

CLINICAL GLOBAL IMPRESSIONS (CGI) SCALE

CGI is a three item scale used to assess treatment response in epileptic patients. They are.

- **Severity of Illness**

  It is rated on a seven – point scale (1=normal to 7=extremely ill)

- **Global Improvement**

  It is a rated on a seven – point scale (1=very much improved to 7=very much worse)

- **Efficiency Index**

  It is a four – point scale (from 'none' to 'outweighs therapeutic effect')

The Severity of Illness item requires the clinician to rate the severity of the patients illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating according to: normal borderline ill; mildly ill; moderately ill; markedly ill; severely ill; or extremely ill.

The global improvement item requires the clinician to rate how much the patient's illness has improved are worsened relative to a baseline state. Compared to condition at baseline, a patient's illness is compared to change over time, and related according to: very much improved; much improved; moderately improved; minimally improved; no change; minimally worse; moderately worse; much worse; or very much worse.

CGI SCALE BENEFITS

- Robust – CGI has proved to be a robust measure of efficacy in drug treatment trials
- Simplicity – the scale is clinically understandable
- Sensitive to change

CGI SCALE CHALLENGES

- Subjective – to a certain degree, severity of illness as rated on the CGI scale is based on the rater's subjective views of symptom severity, which can vary between raters and make consistent interpretation of CGI scores problematic in practice.
- Lack of structure – the CGI scale is administered at initial patient assessment and at least once when treatment / change in treatment has been initiated. Additional assessments are conducted at the discretion of the clinician. Again, this implies a certain degree of subjectivity in terms of the timing and frequency of CGI assessment which may make retrospective interpretation difficult.
- In – depth knowledge required – although the CGI scale is quickly administered, particularly for the global improvement scale it is paramount for the rater to know the patient. If a clinical history is not available, then the tool cannot be utilised.

3.1 PHENYTOIN [76_80]

Phenytoin, sold under the brand name **Dilantin** among others, is an anti-seizure medication. It is useful for the prevention of tonic-clonic seizures, partial seizures, but not absence seizures. The intravenous form is used for status epilepticus that does not improve with benzodiazepines. It may also be used for certain heart arrhythmias or neuropathic pain. It can be taken intravenously or by mouth. The intravenous form generally begins working within 30 minutes and is effective for 24 hours. Blood levels can be measured to determine the proper dose. Phenytoin was first made in 1908 and found useful in seizures in 1936. It is on the World Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.

Brand names

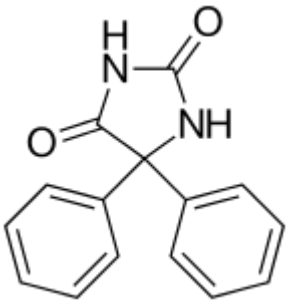
Dilantin, Phenytoin Sodium, Phenytoin Sodium, Extended Release, Phenytek

Drug class(es): **group I antiarrhythmics**, **hydantoin anticonvulsants**.

PHARMACOLOGICAL CLASSIFICATIONS: Anticonvulsants
DESCRIPTION

Chemical IUPAC Name: 5,5-diphenylimidazolidine-2,4-dione

STRUCTURE



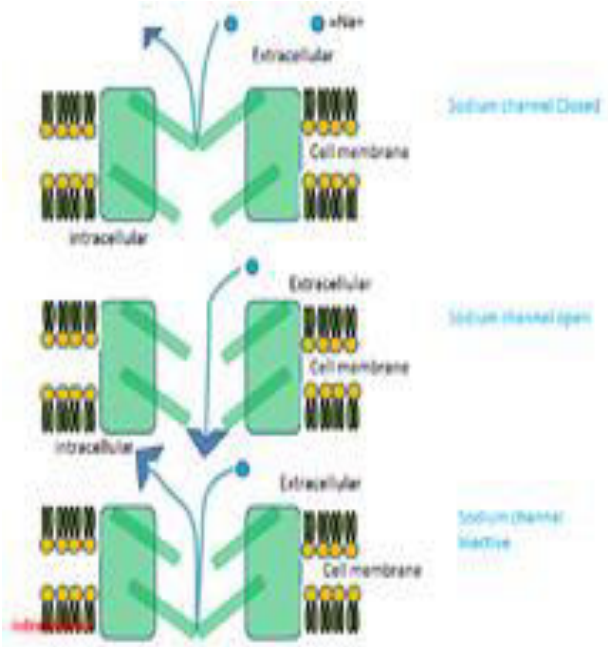
Chemical Formula: $C_{15}H_{12}N_2O_2$

INDICATIONS:

Phenytoin systemic is used in the treatment of:

- **Anxiety**
- **Arrhythmia**
- **Cluster-Tic Syndrome**
- **Epilepsy**
- **MyotoniaCongenita**
- **Neurosurgery**
- **Peripheral Neuropathy**
- **Rheumatoid Arthritis**
- **Seizures**
- **Status Epilepticus**
- **Trigeminal Neuralgia**

Mechanism of action



Phenytoin is believed to protect against seizures by causing voltage-dependent block of voltage gated sodium channels. This blocks sustained high frequency repetitive firing of action potentials. This is accomplished by reducing the amplitude of sodium-dependent action potentials through enhancing steady state inactivation. Sodium channels exist in three main conformations: the resting state, the open state, and the inactive state.

Phenytoin binds preferentially to the inactive form of the sodium channel. Because it takes time for the bound drug to dissociate from the inactive channel, there is a time dependent block of the channel. Since the fraction of inactive channels is increased by membrane depolarization as well as by repetitive firing, the binding to the inactive state by phenytoin sodium can produce voltage-dependent, use-dependent and time-dependent block of sodium-dependent action potentials.

The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. Possibly by promoting sodium efflux from neurons, phenytoin tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post-tetanic potentiation at synapses which prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of generalized tonic-clonic seizures

Clinical Pharmacology

Phenytoin is an anticonvulsant with a primary site of action in the motor cortex. Environmental changes or excessive stimulation can cause a reduction in membrane sodium gradient. Phenytoin causes an efflux of sodium from neurons and therefore stabilises the threshold against over-activity in those brain stem centres responsible for the tonic phase of grand mal seizures [9]. Absorption from gastrointestinal tract and intramuscular injection sites erratic. Phenytoin has high binding (85-90%) to plasma protein. Bilirubin displaces phenytoin from albumin binding sites resulting in higher percentage of unbound drug in plasma. Elimination via the kidney. Pharmacokinetics are dose-dependent over the therapeutic range and

unpredictable in the neonate. Relatively small margin between full therapeutic effect and a minimally toxic dose of phenytoin.

Pharmacokinetic data	
Bioavailability	70-100% oral, 24.4% for rectal and intravenous administration
Protein binding	95%[1]
Metabolism	liver
Onset of action	10 to 30 min (IV)[2]
Biological half-life	10–22 hours[1]
Duration of action	24 hr[2]
Excretion	Primarily through the bile, urinary

Dose and Administration

1. **Loading dose**: 20 mg/kg by slow IV infusion over 60 minutes [5].
2. **Maintenance dose**: 2-4 mg/kg/dose twice a day by slow IV infusion, or PO [6].
   Administer at a rate not faster than **1.0 mg/kg/minute** [6].
   The maintenance dose needs to be monitored and adjusted according to blood levels.

Contraindications

1. Sinus rhythm bradycardia, sinoatrial or atrioventricular block.

Precautions

1. Known hypersensitivity to phenytoin.
2. Neonates with jaundice, respiratory failure, hypotension or heart failure.
3. Preterm infants, especially extreme immaturity.
4. Neonates and infants with hepatic or renal impairment.

Drug Interactions

Phenytoin may increase the levels of:	Phenobarbitone.
Phenytoin may decrease the levels or activity of:	Paracetamol, caffeine, corticosteroids, diazoxide, digoxin, dopamine, fentanyl, furosemide, theophylline.
Phenytoin levels may be decreased by:	Phenobarbitone, rifampicin, theophylline.
Phenytoin levels may be increased by:	Fluconazole, ranitidine.
Phenytoin levels may be altered by:	Chlorpromazine, benzodiazepines.
Phenytoin levels may be altered by:	Interfere with thyroid function tests, and produce lower than normal values for metyrapone suppression tests.

Possible Adverse Effects

1. Injection is very alkaline –therefore may result in venous irritation and phlebitis. Avoid extravasation.
2. Observe diluted solution, for crystal formation.
3. Rapid administration may result in hypotension, CNS depression, cardiac arrhythmias, and impaired cardiac conduction.
4. Gastrointestinal disturbances (nausea, vomiting, constipation).
5. Overdosage may result in hypotension, coma, respiratory depression. Nystagmus may be an indication of toxicity.
6. Possible interference of Vitamin D and folate metabolism. Megaloblastic anaemia.
7. Hypersensitivity reactions eg. skin rashes. Bullous or purpuric rashes are indicators to withdraw therapy as they may be symptoms of rare but severe reactions eg. toxic epidermal necrolysis.
8. Hyperglycaemia.

3.2 Carbamazepine:[81-84]

Carbamazepine (**CBZ**), sold under the tradename **Tegretol** among others, is a medication used primarily in the treatment ofepilepsy and neuropathic pain. For seizures it works as well as phenytoin and valproate. It is not effective for seizures or myoclonic seizures. It may be used in schizophrenia along with other medications and as a second line agent in bipolar disorder. It is taken two to four times per day.

Brand Name:

Brandnames: **Tegretol, Carbatrol, Tegretol,XR, Epitol**

Drug class(es): **dibenzazepine anticonvulsants**

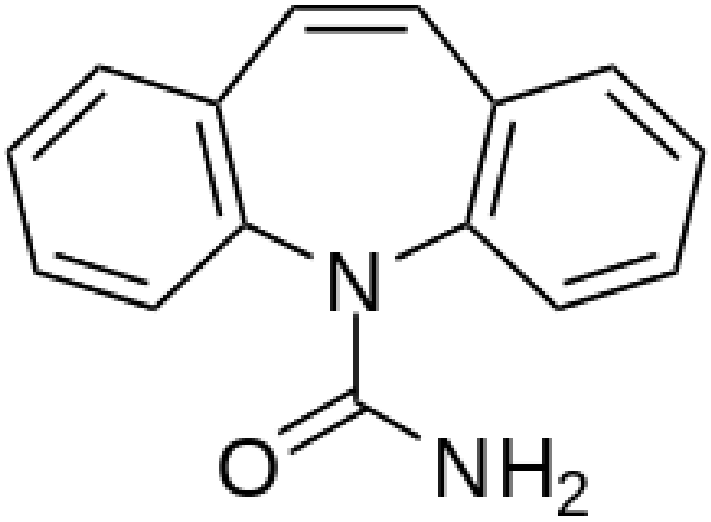
PHARMACOLOGICAL CLASSIFICATION: Anticonvulsants

DESCRIPTION:

Chemical IUPAC Name: 5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

Chemical Formula: $C_{15}H_{12}N_2O$

STRUCTURE



INDICATIONS:

Carbamazepine systemic is used in the treatment of:

- **Bipolar Disorder**
- **Cluster-Tic Syndrome**
- **Cyclothymic Disorder**
- **Diabetic Peripheral Neuropathy**
- **Dystonia**
- **Epilepsy**
- **Occipital Neuralgia**
- **Peripheral Neuropathy**
- **Reflex Sympathetic Dystrophy Syndrome**
- **Schizoaffective Disorder**
- **Trigeminal Neuralgia**
- **Vulvodynia**

MECHANISM OF ACTION

The mechanism of action of carbamazepine and its derivatives is relatively well understood. Carbamazepine stabilizes the inactivated state of voltage-gated sodium channels, making fewer of these channels available to subsequently open. This leaves the affected cells less excitable until the drug dissociates. Carbamazepine is also a GABA receptor agonist, as it has also been shown to potentiate GABA receptors made up of alpha1, beta2, and gamma2 subunits. This mechanism may contribute to its efficacy in neuropathic pain and manic-depressive illness. Laboratory research has further demonstrated that carbamazepine is a serotonin releasing agent and possibly even aserotonin reuptake inhibitor.

PHARMACOLOGY:

Carbamazepine is chemically related to imipramine. In addition to anticonvulsant properties it also has psychotropic, antidiuretic and anti neuralgic effects reduces polysynaptic reactions.

Pharmacokinetics

Pharmacokinetic data	
Bioavailability	~100%[1]
Protein binding	70-80%[1]
Metabolism	Hepatic—by CYP3A4, to active epoxide form (carbamazepine-10,11 epoxide)[1]
Biological half-life	36 hours (single dose), 16-24 hours (repeated dosing)[1]
Excretion	Urine (72%), faeces (28%)[1]

Bioavailability		**Peak plasma level**	**Plasma half-life**	**Active metabolites**	**Elimination**
variable	60-80% (tablets)	6 to 12 hours	initially, 30 to 50 hours* later, 12 to 17 hours*	important**	predominantly extrarenal

**Carbamazepine induces its own metabolism, plasma half-life therefore decreases.*
***The active metabolite carbamazepine-10,11-epoxide has a half-life of 6 hours.*

Dose

Indication	Administration	Initial loading dose		Maintenance dose	
		Dose	Interval	Dose	Interval
major tonic-clonic seizure	oral	100-200 mg	12 hours	200-400 mg	8 to 12 hours*
trigeminal neuralgia	oral	100 mg	12 hours	200-400 mg	12 hours

Adverse effects

In the US, the label for carbamazepine contains warnings concerning:

- Effects on the body's production of red blood cells, white blood cells, and platelets: rarely, there are major effects of aplastic anaemia and agranulocytosis reported and more commonly, there are minor changes such as decreased white blood cell or platelet counts that do not progress to more serious problems
- increased risks of suicide
- risk of seizures, if the person stops taking the drug abruptly
- Risks to the fetus in women who are pregnant, specifically congenital malformations like spina bifida, and developmental disorders.

Common adverse effects may include drowsiness, dizziness, headaches and migraine, motor coordination impairment, nausea, vomiting, and/or constipation. Alcohol use while taking carbamazepine may lead to enhanced depression of the central nervous system.[1] Less common side effects may include increased risk of seizures in people with mixed seizure disorders, abnormal heart rhythms, blurry or double vision. Also, rare case reports of an auditory side effect have been made, whereby patients perceive sounds about a semitone lower than previously; this unusual side effect is usually not noticed by most people, and disappears after the person stops taking carbamazepine.

INTERACTIONS

Carbamazepine has a potential for drug interactions; caution should be used in combining other medicines with it, including other antiepileptics and mood stabilizers.[12] Lower levels of carbamazepine are seen when administrated with phenobarbital, phenytoin (Dilantin), or primidone (Mysoline), which can result in breakthrough seizure activity. Carbamazepine, as a CYP450 inducer, may increase clearance of many drugs, decreasing their concentration in the blood to subtherapeutic levels and reducing their desired effects. Drugs that are more rapidly metabolized with carbamazepine include warfarin, lamotrigine, phenytoin, theophylline, and valproic acid Drugs that decrease the metabolism of carbamazepine or otherwise increase its levels include erythromycin, cimetidine, propoxyphene, and calcium channel blockers. Carbamazepine also increases the metabolism of the hormones in birth control pills and can reduce their effectiveness, potentially leading to unexpected pregnancies. As a drug that induces cytochrome P450 enzymes, it accelerates elimination of many benzodiazepines and decreases their action.

Valproic acid and valnoctamide both inhibit microsomal epoxide hydrolase (MEH), the enzyme responsible for the breakdown of carbamazepine-10,11 epoxide into inactive metabolites. By inhibiting MEH, valproic acid and valnoctamide cause a build-up of the active metabolite, prolonging the effects of carbamazepine and delaying its excretion.

Grapefruit juice raises the bioavailability of carbamazepine by inhibiting CYP3A4 enzymes in the gut wall and in the liver.

3.3 VALPROATE:[85-90]

Valproate (**VPA**), also known **valproic acid**, **sodium valproate**, and **divalproex sodium**, is a medication primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches. It is useful for the prevention of seizures in those with absence seizures, partial seizures, and generalized seizures. It can be given intravenously or by mouth. Long acting formulations exist.

BRAND NAME:-Convulex, Depakote, Epilim, Stavzor, Vilapro, Valparin

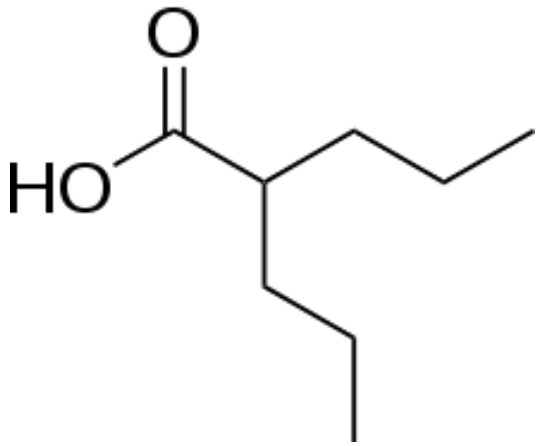
PHARMACOLOGICAL CLASSIFICATION: Anticonvulsant

DESCRIPTION

Chemical IUPAC Name: 2-propylpentanoic acid

Chemical Formula:$C_8H_{16}O_2$

STRUCTURE



INDICATIONS:

Its primary use to treatment epilepsy and bipolar disorder. It is also used to prevent migraine headaches

- Epilepsy
- Psychiatric disorders
- Migraines
- Other

The medication has been tested in the treatment of AIDS and cancer, owing to its histone deacetylase-inhibiting effects.

MECHANISM OF ACTION

Although the mechanism of action of valproate is blockade of voltage-dependent sodium channels and increased brain levels of gamma-aminobutyric acid (GABA). The GABAergic effect is also believed to contribute towards the anti-manic properties of valproate.[38] In animals, sodium valproate raises cerebral and cerebellar levels of the inhibitory synaptic neurotransmitter, GABA, possibly by inhibiting GABA degradative enzymes, such asGABA transaminase, succinate-semialdehyde dehydrogenase and by inhibiting the re-uptake of GABA by neuronal cells. It also possesses histone deacetylase-inhibiting effects. The inhibition of histone deacetylase, by promoting more transcriptionally active chromatin structures, likely presents the epigenetic mechanism for regulation of many of the neuroprotective effects attributed to valproic acid. Intermediate molecules mediating these effects include VEGF, BDNF, and GDNF.

Valproic acid has been found to be an antagonist of the androgen and progesterone receptors, and hence a non-steroidal antiandrogen and antiprogestogen, at concentrations much lower than therapeutic serum levels. It was concluded that these actions are likely to be involved in the reproductive endocrine disturbances seen with valproic acid treatment.

PHARMACOLOGY

Valproate has been in clinical use for nearly 40 years for the treatment of a variety of neuropsychiatric illnesses, including bipolar disorder and epilepsy. Early reports linked its biochemical mechanism of action to alterations in gamma-aminobutyric acid (GABA)-ergic function. The definitive mechanism(s) mediating the clinical efficacy of this relatively simple molecule remain obscure. Although valproate does not directly interact with postsynaptic GABA receptors, it does increase regional neuronal concentrations of GABA by both inhibiting its metabolism and increasing its synthesis.

PHARMACOKINETICS

Pharmacokinetic data	
Bioavailability	Rapid absorption
Protein binding	80-90%[1]
Metabolism	Hepatic—glucuronide conjugation 30–50%,mitochondrial β-oxidationover 40%
Biological half-life	9–16 hours
Excretion	Urine (30-50%)

Adult: Initial dose: 10 to 15 mg/kg orally or intravenously per day as an IV infusion in divided doses, increased by 5 to 10 mg/kg per week if necessary according to clinical response
Maintenance dose: 10 to 60 mg/kg per day in divided doses
Maximum dose: 60 mg/kg per day

Child (6 – 12 Yrs): Initial dose: 10 to 15 mg/kg orally or intravenously per day as an IV infusion in divided doses, increased by 5 to 10 mg/kg per week if necessary according to clinical response
Maintenance dose: 10 to 60 mg/kg per day in divided doses

Maximum dose: 60 mg/kg per day

CONTRAINDICATION

Contraindications include:

- Pregnancy
- Pre-existing acute or chronic liver dysfunction or family history of severe liver inflammation (hepatitis), particularly medicine related.
- Known hypersensitivity to valproate or any of the ingredients used in the preparation
- Urea cycle disorders
- Hepatic porphyria
- Hepatotoxicity
- Mitochondrial disease
- Pancreatitis
- Porphyria

INTERACTIONS

Valproate inhibits CYP2C9, glucuronyltransferase, and epoxide hydrolase and is highly protein bound and hence may interact with drugs that are substrates for any of these enzymes or are highly protein bound themselves.[38] It may also potentiate the CNS depressant effects of alcohol. It should not be given in conjunction with other antiepileptics due to the potential for reduced clearance of other antiepileptics (including carbamazepine, lamotrigine, phenytoin and phenobarbitone) and itself. It may also interact with:

- Aspirin: may increase valproate concentrations. May also interfere with valproate's metabolism.
- Benzodiazepines: may cause CNS depression and there are possible pharmacokinetic interactions.
- Carbapenem antibiotics: reduces valproate levels, potentially leading to seizures.

- Cimetidine: inhibits valproate's metabolism in the liver, leading to increased valproate concentrations.
- Erythromycin: inhibits valproate's metabolism in the liver, leading to increased valproate concentrations.
- Ethosuximide: may increase ethosuximide concentrations and lead to toxicity.
- Felbamate: may increase plasma concentrations of valproate.
- Mefloquine: may increase valproate metabolism combined with the direct epileptogenic effects of mefloquine.
- Oral contraceptives: may reduce plasma concentrations of valproate.
- Primidone: may decrease pyrimidone clearance leading to toxicity.
- Rifampin: increases the clearance of valproate, leading to decreased valproate concentrations
- Warfarin: may increase warfarin concentration and prolong bleeding time.
- Zidovudine: may increase zidovudine serum concentration and lead to toxicity.

OVERDOSE AND TOXICITY

Excessive amounts of valproic acid can result in sleepiness, tremor, stupor, respiratory depression, coma, metabolic acidosis, and death. In general, serum or plasma valproic acid concentrations are in a range of 20–100 mg/l during controlled therapy, but may reach 150–1500 mg/l following acute poisoning. Monitoring of the serum level is often accomplished using commercial immunoassay techniques, although some laboratories employ gas or liquid chromatography.[43] In contrast to other antiepileptic drugs, at present there is little favorable evidence for salivary therapeutic drug monitoring. Salivary levels of valproic acid correlate poorly with serum levels, partly due to valproate's weak acid property (p*K*a of 4.9).[44]

In severe intoxication, hemoperfusion or hemofiltration can be an effective means of hastening elimination of the drug from the body.[46] Supportive therapy should be given to all patients experiencing an overdose and urine output should be monitored. Supplemental L-carnitine is indicated in patients having an acute overdose[47]. And also prophylactically in high risk patients. Acetyl-L-carnitine lowers hyperammonemia less markedly[49] than L-carnitine.

Therapeutic range of valproic acid

Form	Lower limit	Upper limit	Unit
Total (including protein bound)	50[41]	125[41]	µg/mL or mg/l
	350[42]	700[42]	µmol/L
Free	6[41]	22[41]	µg/mL or mg/l
	35[42]	70[42]	µmol/L

- **Erik K St. Louis „ William E Rosenfeld„ Thomas Bramley et al.,** reported that Antiepileptic drug (AED) monotherapy is the preferred initial management approach in epilepsy care, since most patients may be successfully managed with the first or second monotherapy utilized. This article reviews the rationale and evidence supporting preferential use of monotherapy when possible and guidelines for initiating and successfully employing AED monotherapy. Suggested approaches to consider when patients fail monotherapy include substituting a new AED monotherapy, initiating chronic maintenance of AED polytherapy, or pursuit of non-pharmacologic treatments such as epilepsy surgery or vagus nerve stimulation. Reducing AED polytherapy to monotherapy frequently reduces the burden of adverse effects and may also improve seizure control. AED monotherapy remains the optimal approach for managing most patients with epilepsy.

- **Villanueva V, Serrano-Castro PJ. et al.,** reported that Zonisamide is an antiepileptic drug firstly approved in Europe as add-on therapy in adult patients with partial seizures and recently as monotherapy. It is a sulfonamide derivative that exerts its antiepileptic effect through different mechanisms, ion channels, neurotransmitters and free radicals. The efficacy of the drug was evaluated between 100 and 500 mg, showing a seizure reduction with respect to basal period between 24.7% (100 mg) and 52.5% (500 mg). The most frequent side effects were dizziness, fatigue, somnolence and weight loss. There is broad experience in conditions close to clinical practice in patients with partial epilepsy and different degree of refractoriness, paediatric population, monotherapy, generalized epilepsy and other special populations. Recently the results of a clinical trial in monotherapy have proved its efficacy in a no-inferiority design with carbamazepine. The seizure-free rate in the zonisamide group was 79.4%.

- **José Pimentel et al.,** reported that Approximately 64% of people with epilepsy (PWE) de novo are free of seizures with the first appropriate antiepileptic drug (AED) in monotherapy. The type of the first AED to use depends on the physician's personal choice provided that it is a first-line AED. There is a

tendency to prefer a substitution rather than a combination of a failed first AED when it was produced associated with an idiosyncratic reaction, was poorly tolerated at a moderate dose, or produced no improvement in seizure control. In contrast, there is some evidence to prefer secondary polytherapy whenever the PWE tolerate its first AED but with a suboptimal response. A very often used strategy is transitional polytherapy between two regimens of monotherapy.

- **Majid Ghaffarpour et al.,** reported that Seizure is a transient neurologic dysfunction caused by sudden abnormal firing of cerebral neurons. Epileptic syndrome is a complex of symptoms and signs that is characterized by not only the etiology but also the age at onset, seizure type, pattern of electroencephalography and prognosis. Treatment of the first seizures depends on their nature; some of them need no antiepileptic drugs (AED) therapy whereas the others should be treated appropriately. AEDs have long- and short-term adverse effects, interaction with other medications, and occupational and/or psychological consequences. Therefore, discontinuation of AEDs should be considered after a free-seizure period. Studies show that the rate of seizure recurrence after AEDs withdrawal is about two to three times more than those who continue therapy; thus, the most difficult decision facing a neurologist is when to start medication and when/how it should be discontinued.

- **Thorsten Gerstner et al.,** reported that Valproic acid (VPA) is considered to be a drug of first choice and one of the most frequently-prescribed antiepileptic drugs worldwide for the therapy of generalized and focal epilepsies, including special epileptic. It is a broad-spectrum antiepileptic drug and is usually well tolerated. Rarely, serious complications may occur in some patients, including hemorrhagic pancreatitis, coagulopathies, bone marrow suppression, VPA-induced hepatotoxicity and encephalopathy, but there is still a lack of knowledge about the incidence and occurrence of these special side effects. Additionally, the consequences for VPA therapy and indication are more or less unclear. By literature review and own data this review addresses some of the challenges of VPA therapy and its side effects, which are not unique to epilepsy in childhood.

- **L de Jong-van den Berg et al.,** reported that, eight cohort studies of 2680 pregnancies with carbamazepine monotherapy exposure, and the EUROCAT dataset included 98.075 registrations of malformations covering over 3.8 million births. Overall prevalence for a major congenital malformation after exposure to carbamazepine monotherapy in the first trimester. Odds ratios for malformations with exposure to carbamazepine among cases compared with two groups of controls: other non-chromosomal registrations of malformations and chromosomal syndromes.

- **Ettore Beghi et al.,** reported that Epilepsy is a chronic condition requiring long-term treatment with drugs that have intrinsic limitations. Antiepileptic drugs (AEDs) are effective in suppressing seizures but do not alter the disease process. They have a suboptimal tolerability profile and can be teratogenic. Second-generation compounds may be better tolerated but no more effective than traditional AEDs. The drug therapy is purely symptomatic, acute symptomatic seizures may require treatment only until recovery or stabilization of the injury. Treatment of the first unprovoked seizure may be considered in patients with abnormal EEG and imaging findings and in those in whom the relapse has severe social, emotional and personal implications. In these cases and in patients with epilepsy drugs for partial seizures supported by class I regulatory trials or pragmatic trials are oxcarbazepine in children, carbamazepine or lamotrigine in adults, and lamotrigine or gabapentin in the elderly. Pragmatic trials support use of valproate for generalized seizures, except for women of childbearing age for whom the drug should be tailored to the individual patient. The lowest maintenance dose should be chosen, based on the efficacy and tolerability of the assigned drug. If the first monotherapy fails, the safety profile of a drug is important when opting for another monotherapy or for an add-on therapy. The epilepsy syndrome and the social, psychological and emotional profile of the patient all contribute to the individualization of treatment discontinuation after long-term seizure remission.

- **BasselAbou-Khali et al.,** reported that Epilepsy is a common chronic disorder that requires long-term antiepileptic drug therapy. Approximately one half of patients fail the initial antiepileptic drug and about 35% are refractory to medical therapy, highlighting the continued need for more effective and better tolerated drugs. Its novel mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle protein SV2A in the brain. Its pharmacokinetic advantages include rapid and almost complete absorption, minimal insignificant binding to plasma protein, absence of enzyme induction, absence of interactions with other drugs, and partial metabolism outside the liver. The availability of an intravenous preparation is yet another advantage. It has been demonstrated effective as adjunctive therapy for refractory partial-onset seizures, primary generalized tonic-clonic seizures, and myoclonic seizures of juvenile myoclonic epilepsy. In addition, it was found equivalent to controlled release carbamazepine as first-line therapy for partial-onset seizures, both in efficacy and tolerability. Its main adverse effects in randomized adjunctive trials in adults have been somnolence, asthenia, infection, and dizziness. In children, the behavioral adverse effects of hostility and nervousness were also noted. Levetiracetam is an important addition to the treatment of epilepsy.
- **Xiao Y, Gan L, et al.,** reported that the efficacy and safety of vigabatrin (VGB) as an add-on therapy for refractory epilepsy have been well established. Five studies involving a total of 734 participants were eligible for inclusion. We assessed only one study as good quality and the other four as poor quality. However, it was difficult to perform a meta-analysis by extracting aggregate data to synthesise the results as originally planned, mainly because not all studies reported the same outcomes as those chosen for this review. No significant differences favoured VGB or CBZ in terms of time to treatment withdrawal and time to achieve six-month remission after dose stabilisation from randomisation, but results did show a disadvantage for VGB on time to first seizure after randomisation. Compared with CBZ, VGB was associated with more occurrences of weight gain and fewer occurrences of skin rash and drowsiness. No differences in visual field defects and visual disturbances were noted.

- **Steven Karceski, MD et al.,** reported that Epilepsy is the syndrome of two or more *unprovoked* seizures that occur more than 24 hours apart. Individuals who have had two or more unprovoked epileptic seizures are more likely to continue to have seizures. Seizures are disruptive in a patient's life and can cause injury. Epilepsy is associated with disability, adverse psychosocial outcomes, higher rates of psychiatric comorbidity, and an approximately threefold increased mortality. The management of patients with epilepsy is focused on three main goals: controlling seizures, avoiding or minimizing treatment side effects, and maintaining or restoring quality of life. The initial treatment of epilepsy is with a single antiseizure drug. With an ever-expanding list of available antiseizure drugs, and no single antiseizure drug that is clearly superior in terms of efficacy or tolerability, clinicians must individualize the choice of antiseizure drug for each patient. reported that Adverse effects of anti epileptic drugs (AEDs) can significantly affect the life of people with epilepsy. If polytherapy with AED has more adverse effects than monotherapy. We established a register for people with epilepsy. Participants were requested to complete the Liverpool Adverse Event Profile (LAEP) to quantify adverse effects. We also recorded type of epilepsy, seizure control and AED including drug doses. Five hundred and seventy six complete data sets were available, monotherapy (n=186), polytherapy (n=325) and control subjects not taking AED (n=65). The mean LAEP scores in polytherapy (45.56, confidence interval (CI)=44.36-46.76) were significantly higher than the mean LAEP scores in monotherapy (42.29, CI=40.65-44.02) and the mean LAEP scores in controls (33.25, CI=31.05-35.44). Tiredness, memory problems and difficulty concentrating were the most common symptoms in patients taking AED and were consistently higher in polytherapy than in monotherapy. Tiredness was reported as always or sometimes being a problem in (polytherapy/monotherapy/controls) 82.5%/75.6%/64.6%, memory problems in 76%/63.2%/29.2% and difficulty concentrating in 68%/63.9%/30.8%. The proportion of seizure-free patients was significantly lower in the polytherapy group (17%) than in the monotherapy group (55%). Depression rates between the monotherapy and polytherapy groups were similar. Drug dosages were higher in polytherapy, however this did not reach statistical significance.

Patients on polytherapy had significantly higher LAEP scores than patients on monotherapy. This should be carefully discussed with the patient before a second AED is added.

- **L M Specchio, L Tramacere, A La Neve, E Beghi et al.,** reported that recurrence rate of epilepsy attributable to discontinuation of treatment in seizure free patients and to identify the risk factors for recurrence. 330 patients referred to an epilepsy centre who were seizure free for at least 2 years while on stable monotherapy were the study population. Discontinuation of antiepileptic drugs (AEDs) was proposed to all eligible patients or to their carers after discussion of the risks and benefits. Depending on whether they accepted or refused treatment withdrawal, the patients were stratified into two cohorts and followed up until seizure relapse or 31 March 1999, whichever came first. For each patient, records were taken of the main demographic and clinical variables. The sample comprised 225 patients who entered the discontinuation programme and 105 who decided to continue treatment. Twenty nine patients (28%) continuing treatment had a relapse, compared with 113 (50%) of those entering the withdrawal programme. For patients continuing treatment, the probability of remission was 95% at 6 months, 91% at 12 months, 82% at 24 months, 80% at 36 months, and 68% at 60 months. The corresponding values for patients discontinuing treatment were 88%, 74%, 57%, 51%, and 48%. After adjusting for the principal prognostic factors, in patients discontinuing AEDs the risk of seizure relapse was 2.9 times that of patients continuing treatment. A relation was also found between relapse and duration of active disease, number of years of remission while on treatment, and abnormal psychiatric findings.

- **Steven C Schachter, MD et al.,** reported that management of patients with epilepsy is focused on three main goals: controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. Physicians should assist in empowering patients with epilepsy to lead lifestyles consistent with their capabilities.The optimal treatment plan is derived following an accurate diagnosis of the patient's seizure type(s), an objective measure of the intensity and frequency of the seizures, awareness of medication side effects,

and an evaluation of disease-related psychosocial problems. A working knowledge of available antiseizure drugs, including their mechanisms of action, pharmacokinetics, drug-drug interactions, and adverse effects is essential. It is usually appropriate to refer the patient to a neurologist, when establishing a diagnosis and formulating a course of treatment. Referral to an epilepsy specialist may be necessary if there is doubt about the diagnosis and/or if the patient continues to have seizures.

The overall approach to management of a patient with seizures is reviewed here. Evaluation of the patient who has had a first seizure and the pharmacology of specific antiseizure drugs are discussed separately.

- **Joy D Desai et al.,** reported that Epilepsy and cognition have a multi-tiered reciprocal relationship. Alteration in cognitive abilities and performance may occur in random with persistent seizures in a patient with epilepsy. Age at onset, type of seizures, frequency of seizures, types of underlying epilepsy syndrome, and the underlying pathological brain substrate driving epilepsy may all have variable and independent effects on cognition. Therapeutic intervention with anti-epileptic drugs (AEDs) variably modulates cognitive abilities in a patient with epilepsy. Pathological substrate specific effects can compound the potential negative effects of AEDs on cognition. In this review all these aspects are addressed with an analysis of relevant evidence from peer-reviewed publications.
- **Chaturbhuj Rathore, Ross Paterson et al.,** reported that Making a decision to withdraw antiepileptic drugs (AEDs) in patients with epilepsy in remission requires a careful assessment of many patient and disease related factors and the associated risks and benefits. Although unnecessary continuation of AEDs exposes the patients to unwarranted side-effects, a premature withdrawal with subsequent seizure recurrence may be distressing for the patient who otherwise considers himself as cured. Although the final decision needs to be individualized, there are certain guidelines which can help us in making evidence based decision. In this article, we intend to review the current evidence on this subject with an aim of providing a framework of the best clinical practice in this field.

- **SitaJayalakshmi et al.,** reported that To determine factors associated with lack of response to valproic acid (VPA) in juvenile myoclonic epilepsy (JME).Retrospective analysis of clinical and EEG data of 201 patients with JME who had at least 3 years follow up was performed. Psychiatric evaluation was performed using ICD-10 by structured clinical interview. Patients were divided into two groups: VPA responders (seizure free for 2 or more years) and those with lack of response to VPA. Effect size for non-response and correlations for variables significantly different between the groups was performed, the findings were confirmed by ROC curves.The mean duration of follow up was 7.75 (range 3–12) years; 55.2% were males. Focal semiologic features were noted is 16%. EEG was abnormal in 67%; focal EEG abnormalities were noted in 32.8%. Coexisting psychiatric disorders (PDs) were found in 33.3%. Lack of response to VPA was noted in 19%. Diagnosis of PDs and focal EEG abnormalities significantly increased the risk of VPA non-responsiveness by 5.54 (95% CI of 2.60–11.80; $p < 0.0001$) and 3.01 times respectively (95% CI of 1.40–6.47;$p < 0.008$). Diagnosis of PDs showed significant correlation ($r = 0.332$; $p < 0.0001$) and association (AUC 0.700; $p < 0.0001$) with lack of response to VPA. Though focal EEG abnormalities increased the chances, it did not correlate with lack of response to VPA.
- **SonuGoel, Navpreet Singh et al.,** reported that Knowledge about epilepsy and its management is not satisfactory among school students in developing countries. The present study was planned to ascertain the knowledge, attitude and practices (KAP) of students regarding first-aid management of epilepsy seizures in school setting. A total of 177 students of government schools of Chandigarh, a city of northern India, were taken. They were administered with a pre-tested semi-structured questionnaire (for knowledge and attitude assessment) and an observational checklist after role play (for practice assessment) on first-aid management of epilepsy. A scoring system was devised to quantify the knowledge and practices of students.Seventy-one percent of them had either heard or read about epilepsy. Half of the students believed epilepsy as a hindrance to education. Ayurvedic treatment was preferred by more than half of the students; however, many believed that visit

to religious places and exorcism as ways to cure epilepsy. Nearly 74% of students would call a doctor as first-aid measure for seizure in a person with epilepsy.

- **Ettore Beghi et al.,** reported that Epilepsy is a chronic condition requiring long-term treatment with drugs that have intrinsic limitations. Antiepileptic drugs (AEDs) are effective in suppressing seizures but do not alter the disease process. They have a suboptimal tolerability profile and can be teratogenic. Second-generation compounds may be better tolerated but no more effective than traditional AEDs. In this light, as drug therapy is purely symptomatic, acute symptomatic seizures (i.e. seizures occurring in close temporal relationship with acute CNS insults) may require treatment only until recovery or stabilization of the injury. Treatment of the first unprovoked seizure may be considered in patients with abnormal EEG and imaging findings and in those in whom the relapse has severe social, emotional and personal implications. In these cases and in patients with epilepsy (i.e. repeated unprovoked seizures), drugs for partial seizures supported by class I regulatory trials or pragmatic trials are oxcarbazepine in children, carbamazepine or lamotrigine in adults, and lamotrigine or gabapentin in the elderly. Pragmatic trials support use of valproate for generalized seizures, except for women of childbearing age for whom the drug should be tailored to the individual patient. The lowest maintenance dose should be chosen, based on the efficacy and tolerability of the assigned drug. If the first monotherapy fails, the safety profile of a drug is important when opting for another monotherapy or for an add-on therapy. The epilepsy syndrome and the social, psychological and emotional profile of the patient all contribute to the individualization of treatment discontinuation after long-term seizure remission.
- **Joseph I Sirven, et al.,** reported that Patients with epilepsy whose seizures do not successfully respond to antiseizure drug therapy are considered to have drug-resistant epilepsy (DRE). This condition is also referred to as intractable, medically refractory, or pharmacoresistant epilepsy. As many as 20 to 40 percent of patients with epilepsy (roughly 400,000 Americans) are likely to have refractory epilepsy. The annual cost for patients with epilepsy in the United States is estimated to be approximately 12.5 billion dollars (based on a

1995 survey); DRE contributes a substantive proportion of this cost. People with DRE have the greatest burden of epilepsy-related disabilities, further contributing to the scope of this problem.

- **HISAKO SHIMIZU et al., reported** that Clobazam (CLB) add-on therapy was attempted in 183 patients with intractable complex partial seizures in whom conventional benzodiazepines had been successfully discontinued before initiation of CLB. Although complete remission was initially achieved in 61, tolerance developed in almost half (49.2%) within the first 3 months, whereas 23 out of 31 patients (74.2%) who remained seizure free for the first 3 months continued to be so over the next 3 months. CLB add-on therapy proved to be significantly more effective when concurrent GTC occurred more often than yearly. In the current series, no frank psychotic episodes were elicited among the 61 patients who achieved complete suppression of long-standing complex partial seizures, which was in agreement with previous studies. From these results, we believe that CLB is an effective, safe, and inexpensive medication for add-on therapy it is difficult to treat focal epilepsies, especially without concurrent use of conventional benzodiazepine compounds.
- **Peter R. Camfield[*] and Carol S, reported et al.,** that in the first 5 years of epilepsy treatment as an average of at least one seizure every 2 months. For the longer term, we define intractable as at least one seizure per year. Population studies from Chicago, IL, U.S.A., Finland, and Nova Scotia, Canada indicate that with long follow-up, many children with intractable epilepsy eventually have remission of their seizure disorder. Epilepsy is no longer intractable when the seizures stop completely. How often does a new antiepileptic drug (AED) render a child seizure-free when one or more AEDs have failed? Literature on adults with epilepsy suggests that few with chronic epilepsy who have not achieved seizure control with several AEDs will achieve complete seizure control with additional AEDs. The Nova Scotia study suggests that if a child's seizure fails to be controlled with a first AED, there is an increased risk of intractable epilepsy. Nonetheless, the chance of eventual, complete remission of epilepsy (seizure-free without AED treatment) is approximately 40%. We conclude that intractability should not

be considered until there has been failure of at least three first-line AEDs. Intractable epilepsy is rare. Careful definition of the characteristics of children with intractable epilepsy who do respond completely to new AEDs will likely provide the only rational approach to treatment of children with three drug failures. Collaboration by multiple epilepsy centers will be required to gain this information.

- **U K Misra,J Kalita, C Rathore et al.,** reported that Cross reactivity between phenytoin, carbamazepine, and oxcarbazepine is reported. An 8 year old boy with partial seizures developed maculopapular rashes with itching on day 15 of carbamazepine therapy. After stopping carbamazepine, phenytoin 100 mg daily was prescribed two days later. On the 12th day of phenytoin therapy he developed cervical and axillary lymphadenopathy with fever. Lymph nodes revealed reactive hyperplasia. Oxcarbazepine 75 mg twice daily also resulted in oral and mucosa ulceration. The seizures were controlled without any side effects with sodium valproate 200 mg three times a day and gabapentin 300 mg twice a day. Due to the cross reactivity of aromatic anticonvulsants (phenytoin, carbamazepine, and oxcarbazepine), valproate or newer anticonvulsants should be used if a patient has sensitivity to these drugs.

  Phenytoin, phenobarbitone, and carbamazepine are first line antiepileptic drugs. Despite the availability of newer antiepileptic drugs, these first line drugs are commonly used because of their efficacy and low cost. These drugs have the limitation of a high toxicity, which involves the skin, liver, brain, kidney, and the gastrointestinal and haemopoetic systems, and these drugs result in both dose related toxicity and hypersensitivity reactions. The clinical spectrum of first line antiepileptic drugs is quite wide, ranging from a subtle skin rash to life threatening systemic toxicity and from benign lymphadenopathy to an association with malignant lymphoma.[1,2] An overlap between phenytoin and carbamazepine toxicity has also been reported,[3] which is not commonly appreciated by treating physicians. We recently managed a patient who had a skin reaction after carbamazepine and oxcarbazepine and lymphadenopathy after phenytoin treatment. We report this patient and highlight the problem of cross reactivity among first line antiepileptic drugs.

AIM AND OBJECTIVES

AIM:

To study the comparison between the remission occurrence while giving therapies (Mono/Add on) including AED's in the treatment of epileptic seizures & evaluate the patients access to medical care who were under the treatment of General Medicine Department of New Life Society, Bethesda Hospital, Tuticorin.

OBJECTIVES

- To identify the various precipitating factors & emotional symptoms, to assess the side effects caused by the drugs.
- To know about the choice of therapies (Mono/Add on) including AED's in treatment of Epileptic seizures.
- To evaluate the respondents access to medical care belongs to regional and urban population.
- To study the epidemiological factors and etiological factors of epilepsy.
- To develop guidelines for the first aid treatment of epilepsy.
- To develop guidelines for the management of epilepsy and seizures.
- To give effective patient counselling for epilepsy patient.
- To study the management of the adverse drug reaction and side effects.
- To find out the remission occurrence in the mono and add on therapy in epilepsy.

NEED FOR THE STUDY

While the evaluation and treatment of patient with seizures (or) epilepsy is often challenging. Modern Therapy provides many patients with seizure control. After a first seizure evaluation should focus on excluding an underlying neurologic or medical condition assessing the relative risk of seizure reoccurrence & determining whether treatment is indicated. Successful management of patient with recurrent seizure begins with the establishment of accurate diagnosis of epilepsy syndrome followed by treatment using an appropriate medication in a manner to optimize the efficacy. The goal of AED's therapy is to completely control seizures with producing an acceptable medication side effects.

Patients who do not achieve complete seizure control should refer to an epilepsy specialist since new medication and surgical treatment offers patients unprecedented options in seizure control Topics for information provision and counseling newly diagnosed epileptic patients and principle of treatment in chronic epilepsy help in designing steps to improve the safety of drug use in the hospital working set up. Better health care practice could be ensured by applying this knowledge to individual patients.

Present study was undertaken to understand the treatment outcome of AED's observed in neurology unit of a teaching hospital. With regarding to demography of patients choice of prescribed AED's usual dosing regimens and faster routine incremental and decremented rates, Management of seizure and identify precipitating factors of epilepsy. The holy grail of epilepsy an AED that is 100% effective but has no adverse effects or drug interactions.

METHODOLOGY

Study site: General Medicine department of New Life Society, Bethesda Hospital, Tuticorin.

Study Duration: 6 Month (August 2015 to January 2016)

Study Design: Monotherapy & Add on therapy with cohort study

Dosage

Carbamazepine (Tegritol): 200mg/day, twice a day

Phenytoin Sodium (Eptoin): 100mg/day, twice a day

Valproate (Depakine): 200mg/day, twicw a day

Phase 1:

- Discussion about the use of various types of epilepsy and seizures of different hospitals.
- Enquiring of the relevance of this study with Dr.J.Selvakumar,M.D., Consultant in General Medicine department.

Phase 2

- Designing of the methodology of the study was done.
- Case report forms were prepared and the different rating scales of epilepsy were collected.

Phase 3:

50 Patient having epilepsy and seizure during the study period 6 Month (August 2015 to January 2016) were independently evaluated by the epilepsy and seizures who initially did the clinical interview and arrived at a diagnosis using inclusion criteria & exclusion criteria.

Inclusion Criteria:

- Newly diagnosed & established patients in Neurology department for management of epileptic seizures.
- Age more than 14 years.

Exclusion Criteria:

- Patient referred to Neurology department for evaluation.
- Patients visiting on outpatient basis.

Phase: 4

- After AED selection has been made, starting with a low dose and gradually titrating to a moderate and presumably effective dose is a reasonable strategy, since titration to higher doses.
- A more rapid titration may be necessary in selected patients who have had multiple recent seizures. Maximizing the dose is only recommended in patients who do not respond to moderate doses.
- At each patient visit, it is necessary to conduct a detailed assessment of AED therapy, including adverse effects and compliance.
- Utilizing a quantitative survey of patient's perceived adverse effects such as the adverse events profile (AEP) has been prepared alter antiepileptic drug therapies to for improving quality of life.

Phase 5

Measurement of efficacy and safety

- A clinicians rating of "much improved" or "very much improved" on the clinical global impression of improvement.

Phase 6:

- Interpretations of the results are done and the efficiency and safety of each drug group is determined.
- Conclusions was made.

Ethical consideration:

- Before conducting the study an approval from the Dean of the Hospital were taken and an official permission were taken from the Director of the selected setting to conduct the study. An approval to participate in the study was taken from mothers during interview ensuring confidentiality and their right's to accept or refuse participation.

Method of collection of data:-

- Patient Interview.
- Hamilton rating scale for epilepsy.
- Clinical global impression scale.
- Patient case notes.
- Treatment chart.

The patients satisfying the inclusion criteria were assessed for the severity of the illness using.

1. Clinical global impression scale (CGI).

CLINICAL GLOBAL IMPRESSION SCALE (CGI-SCALE)

Patient Name: ----------

1. **SEVERITY OF ILLNESS**

   Considering the total clinical experience with this particular population, how mentally ill is the patient at this time?

0. = Not assessed
1. = Normal, not at all
2. = Border line ill
3. =Mildly ill
4. =Moderately ill
5. =Markedly ill
6. = Severely ill
7. =Among the most extremely ill.

2. **GLOBAL IMPROVEMENT**

   Rate total improvement whether are not in your judgement, it is a due to entirely to drug treatment.

   Compared to the patient's condition when first assessed, how much change has occurred?

0. = Not assessed
1. =Very much improved
2. =Very improved
3. =Minimally improved
4. =Minimally worse
5. =Much worse
6. =Very much worse
7. =No change

A suitable case report form was prepared which was used for the storage of data.

The data's collected were,

- The patient details
- The stage of the disease and duration of episode
- Concomitant diseases
- The signs and symptoms during examination
- CGI scores
- Details of medication
- Significant adverse drug reactions
- The data were collected for each visit of the patients

STATISTICAL ANALYSIS

Statistical Tools:

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of Graph Pad instate (GPI V3.0). Using these software mean, Standard Deviation (SD), Standard Error Mean (SEM) and p values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship. Data's were presented in mean, SD and percentage as applicable.

OBSERVATION AND RESULTS

PATIENT DEMOGRAPHIC CHARACTERISTICS

Table: 1 GENDER DISTRIBUTION

S.no	Gender	Number of patients	Percentage
1	Male	22	44%
2	Female	28	56%

Mean value = 25 Standard Value (SD) = 4.243

P value is 0.0760 considered not quite significant

t value 3.727 with 2 degrees of freedom

From the above table, Out of the 50 patients 22 (44%) were males and 28 (56%) were females. This shows that female patients were mostly affected by disorders than male patients.

FIGURE.1 GENDER DISTRIBUTION

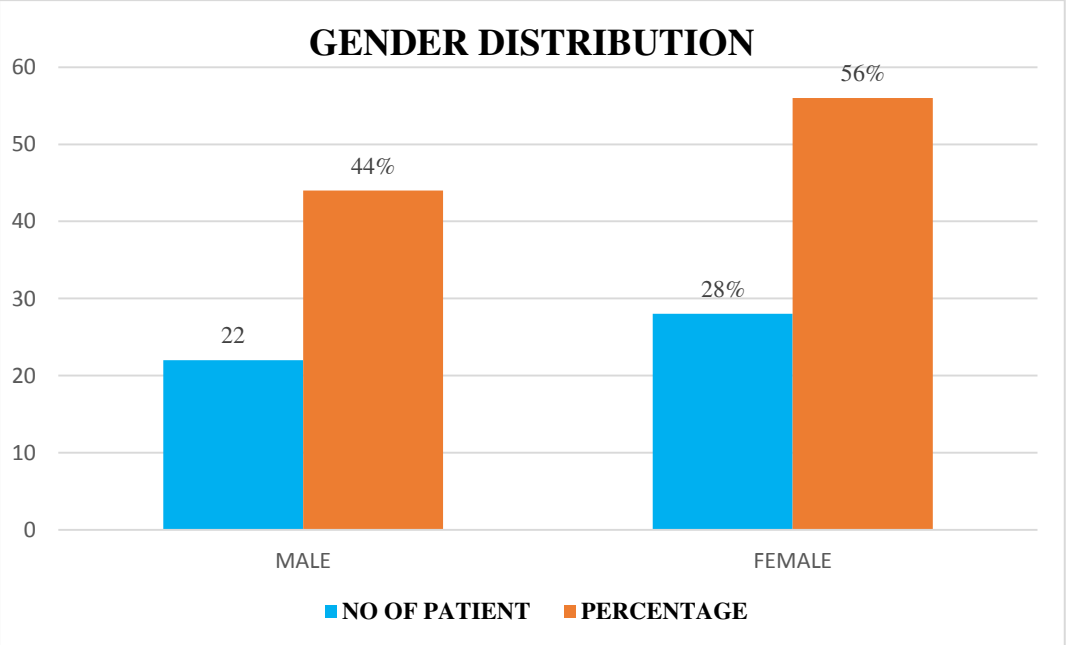


Table: 2 CLASSIFICATIONS OF PATIENTS BY AGE GROUP

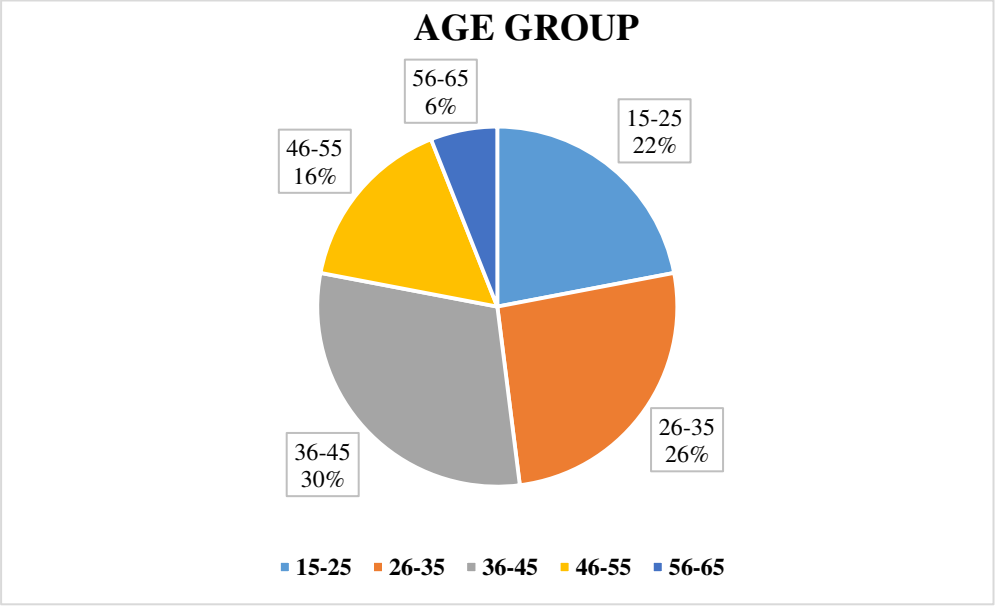
S.no	Age group(years)	Number of Patients	Percentage
1	15-25	11	22 %
2	26-35	13	26 %
3	36-45	15	30 %
4	46-55	8	16 %
5	56-65	3	06 %

Mean value = 10 SD value = 4.690

P value is 0.00089 considered very significant

t = 4.767 with 4 degrees of freedom

FIGURE.2 CLASSIFICATION OF PATIENTS BY AGE GROUP



Out of 50 patients11 patients were under the age group of 15 to 25, 13 patients were under the age group of 26 to 35, 15 patients were under the age group of 36 to 45, 8 patients were under the age group of 46 to 55, 3 patients were under the age group of 56 to 65.

TABLE: 3 CLASSIFICATION OF PATIENT'S ILLNESS

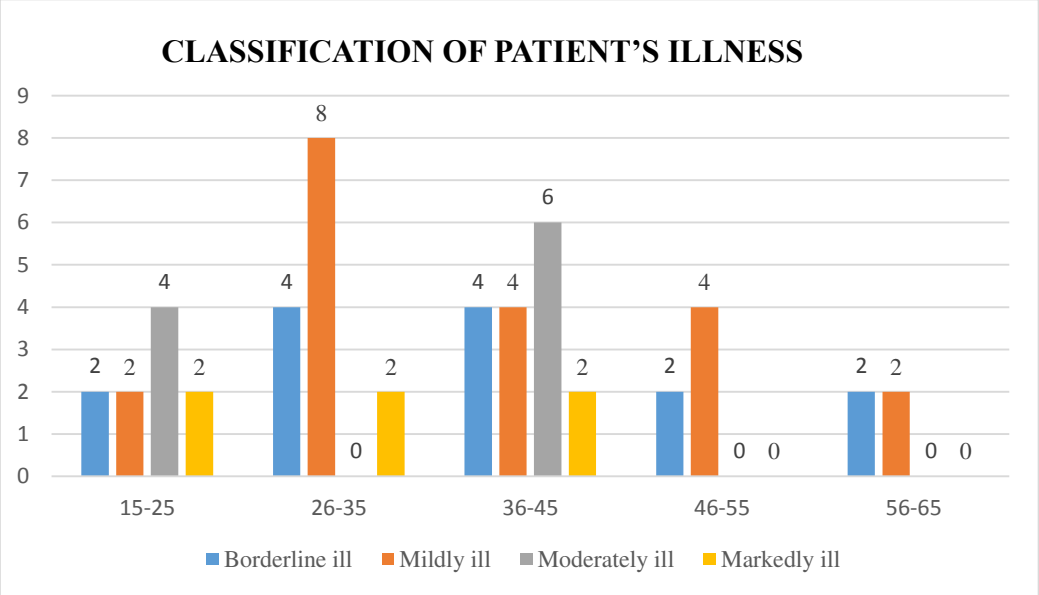
Age Group	Severity of illness				Total no of patients	Percentage
	Borderline ill	mildly ill	Moderately ill	Markedly ill		
15-25	2	2	4	2	10	20%
26-35	4	8	0	2	14	28%
36-45	4	4	6	2	16	32%
46-55	2	4	0	0	6	12%
56-65	2	2	0	0	4	8%

Mean value: 2.800, SD Value:1.095

P Value is 0.0046 considered very significant

t value 5.715 with 4 degrees of freedom

FIGUER-3 CLASSIFICATION OF PATIENT'S ILLNESS



Out of 50 patients 20% patients were under the age of 15-25, 28% patients were under the age group of 26-35, 32% patients were under the age of 36-45, 12% patients were under the age group of 46-55 and 8% patients were under the age group of 56-65. This shows that the maximum no of patients were under the age group of 36-45 were affected by moderate illness.

TABLE: 4 MARITAL STATUS

MARITAL STATUS	NO. OF PATIENTS	MALE	FEMALE	PERCENTAGE
MARRIED	39	14	25	78%
UNMARRIED	11	8	3	22%

Mean value:25 SD value:19.799

P Value is 0.3250 considered not significant

t value 1.786 with 1 degree of freedom

In this study out of 50 patients 39 were married and 11 were unmarried so we came to know married persons were affected by epilepsy and females were mostly affected by epilepsy and seizures.

FIGURE 4 MARITAL STATUS

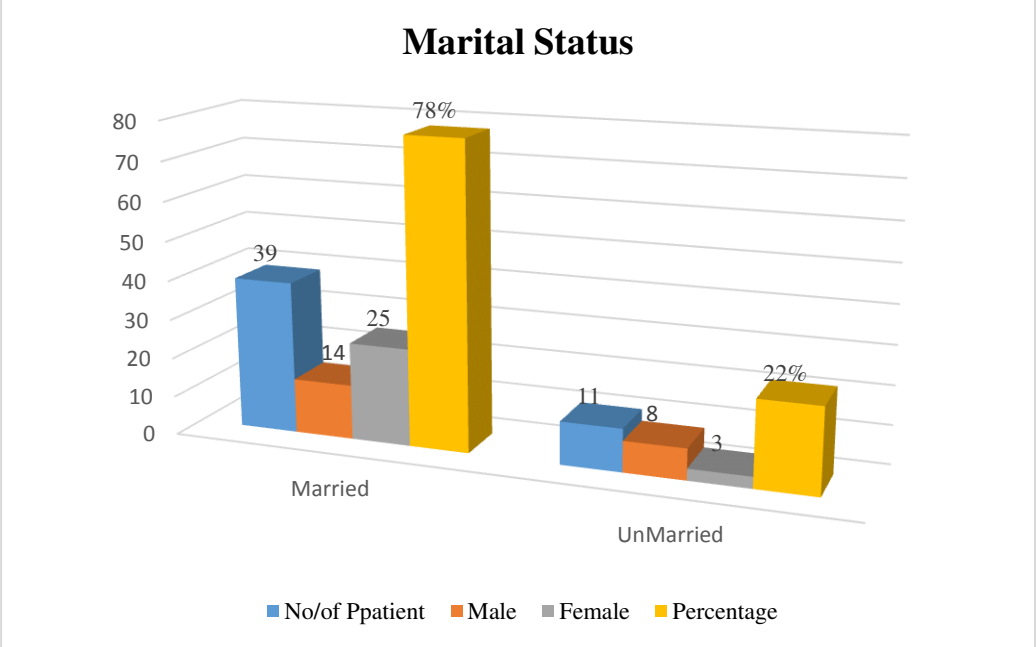


TABLE: 5 OCCUPATIONAL STATUS

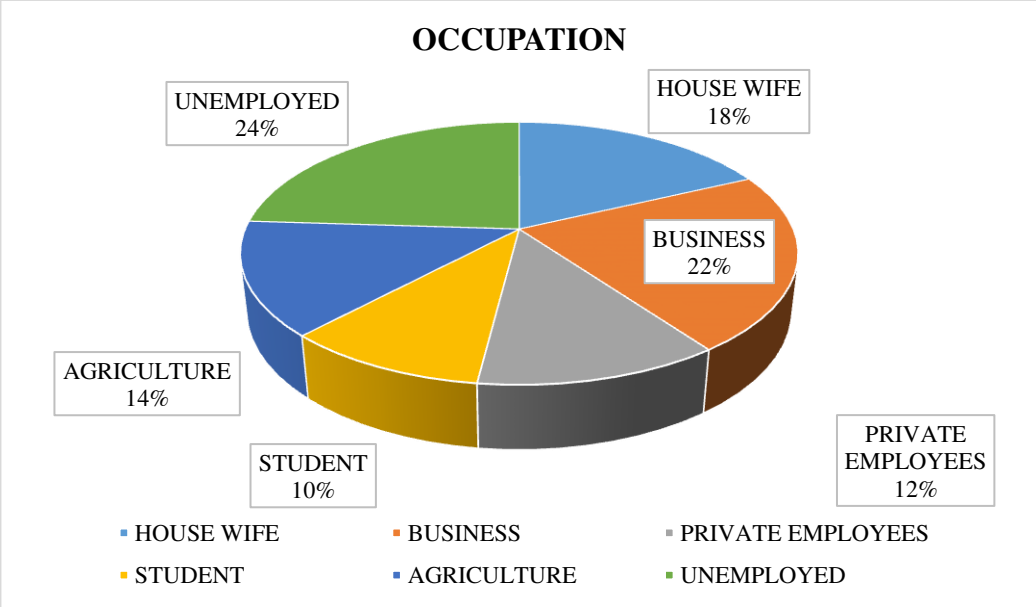
OCCUPATION	NO.OF PATIENTS	PERCENTAGE
HOUSE WIFE	9	18%
BUSINESS	11	22%
PRIVATE EMPLOYEES	06	12%
STUDENT	05	10%
AGRICULTURE	07	14%
UNEMPLOYED	12	24%

Mean value = 8.33 SD = 2.805

P value is 0.0008 considered very significant

t value 7.278 with 5 degrees of freedom

FIGURE 5 CLASSIFICATIONS OF PATIENTS BY THEIR OCCUPATION



Out of the 50patients, 9 patients were house wife, 11 patients were business man 6 patients were private employees 5 patients is student, 7 patients were agriculturist and 12 patients were unemployed. This data shows that the maximum number of epilepsy patients were unemployed.

TABLE: 6 ETIOLOGICAL FACTORS

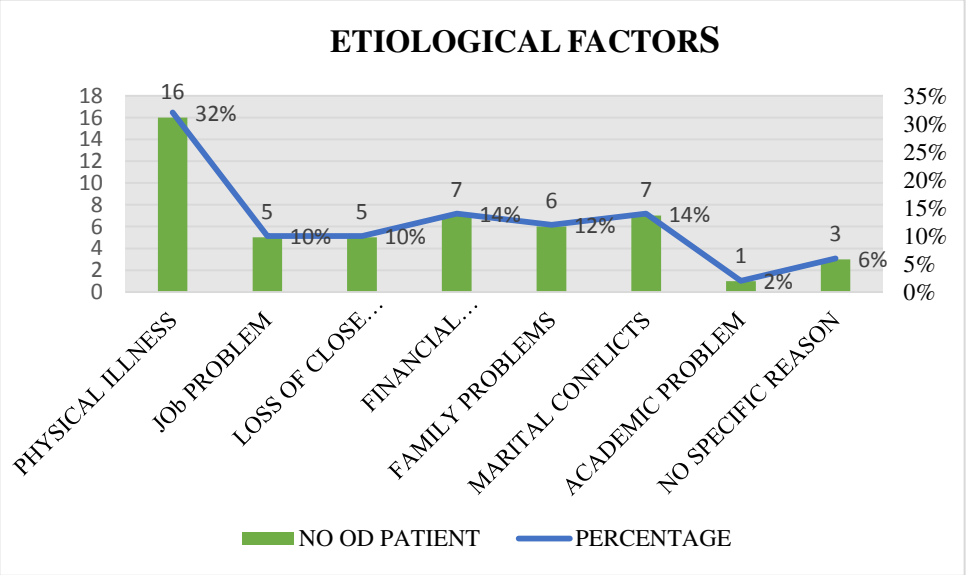
FACTORS	NO. OF PATIENTS	PERCENTAGE
PHYSICAL ILLNESS	16	32%
JOB PROBLEM	05	10%
LOSS OF CLOSE FAMILY MEMBERS	05	10%
FINANCIAL PROBLEMS	07	14%
FAMILY PROBLEMS	06	12%
MARITAL CONFLICTS	07	14%
ACADEMIC PROBLEM	01	02%
NO SPECIFIC REASON	03	06%

Mean value = 6.25 SD = 4.432

P value is 0.0053 considered very significant

t value 3.989 with 7 degrees of freedom

FIGURE 6 ETIOLOGICAL FACTORS



Out of the 50 patients, 16 patients had physical illness as the etiological factor for epilepsy 5 patients had job problems, 5 patients had a problem of loss of close family members, 7 patients had financial problems, 6 patients had family problems, 7 patients had marital conflict, 1 patient had academic problem and 3 patients had no specific reasons.

TABLE: 7 SOCIAL HABITS OF PATIENT

S.NO	SOCIAL HABITS	NUMBER OF PATIENTS	Percentage
1	Smoker	4	8%
2	Smoker & Alcoholic	3	6%
3	Non Smoker & alcoholic	43	86%

Mean value =18.33 SD = 21.572

P value is 0.2789 considered not significant

t value 1.472 with 2 degrees of freedom

Out of 50 patients, 4 patients are having smoking habits and 3 patients are alcoholic. 43 patients doesn't have habit of smoking and alcoholism.

FIGURE NO:7 SOCIAL HABITS OF PATIENT

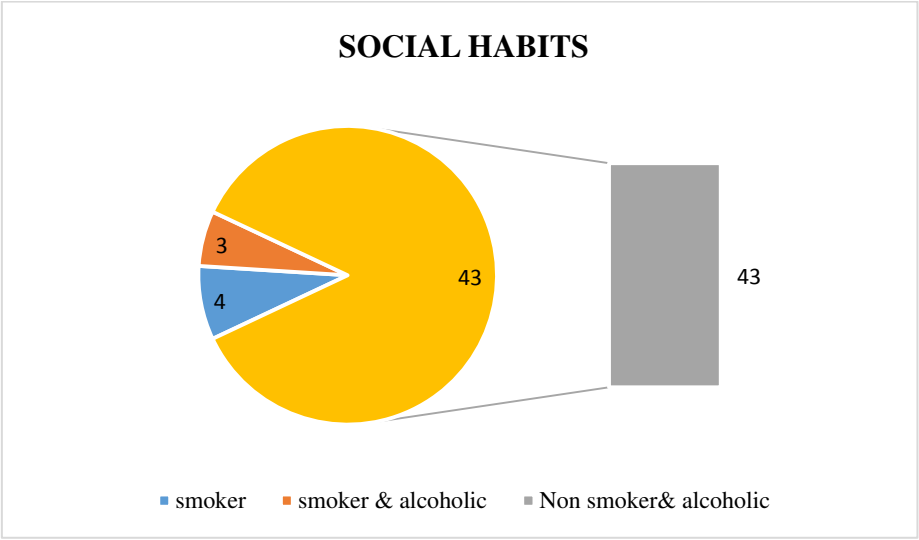


TABLE: 8 FAMILY HISTORY

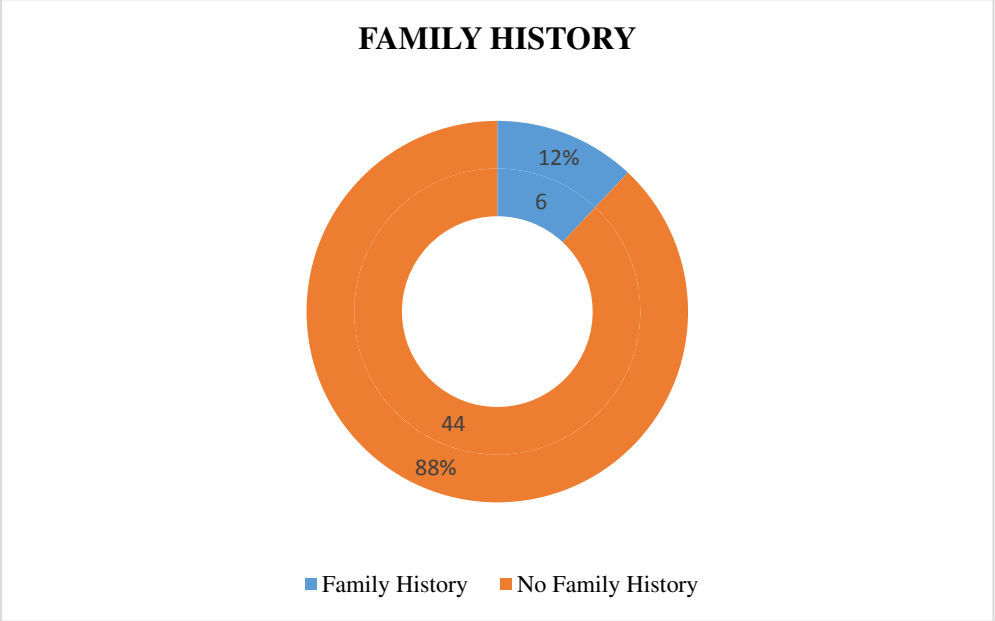
CATEGORY	NO. OF PATIENTS	PERCENTAGE
FAMILY HISTORY	6	12%
NO FAMILY HISTORY	44	88%

Mean value = 25 SD = 26.870

P value is 0.4137 considered not significant

t value 1.316 with 1 degree of freedom

FIGURE: 8 FAMILY HISTORY



Out of 50 patients 6 patients had a close relative with epilepsy whereas 44 patients had no Family history.

Table 9. ANTI EPILEPTIC DRUG PRESCRIPTION PATTERN (MONO-THERAPY)

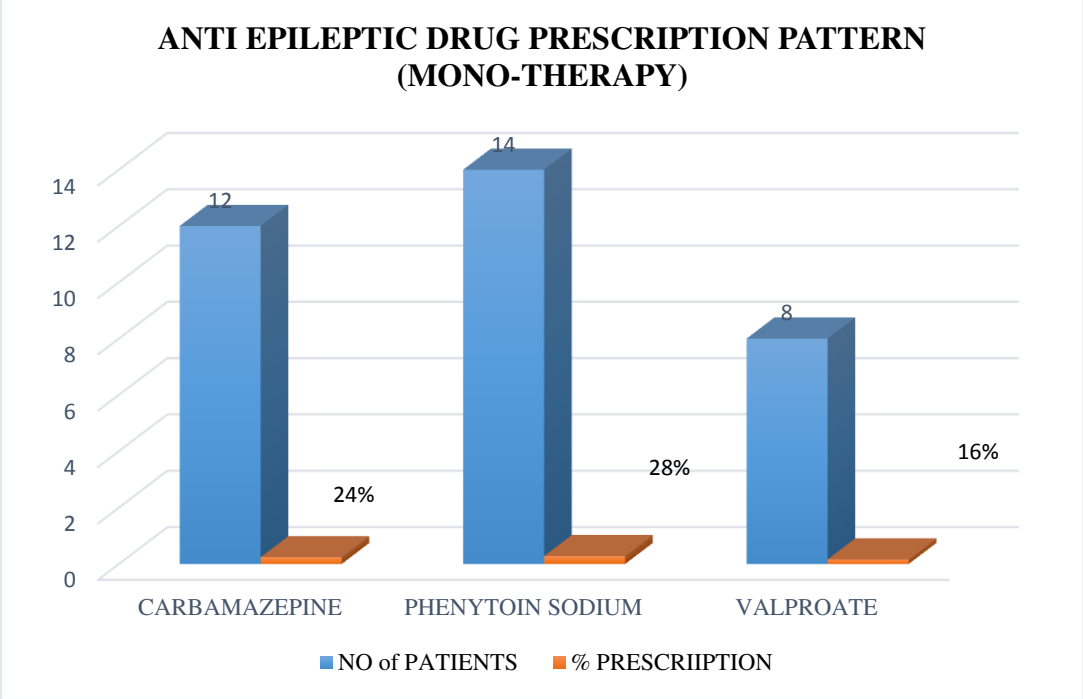
S.no	Prescribed AED's	No.of patients	% Prescription
1	CARBAMAZEPINE	12	24%
2	PHENYTOIN SODIUM	14	28%
3	VALPROATE	08	16%

Mean value = 11.33 SD = 3.055

P value is 0.0453 considered significant

t value 2.874 with 4 degrees of freedom

FIGURE 9. ANTI EPILEPTIC DRUG PRESCRIPTION PATTERN (MONO-THERAPY)



Out of 34 patients are treatment in mono therapy. 12 (24%) patient's prescription pattern in carbamazepine, 14 (28%) patient's prescription pattern in phenytoin sodium, 8 (16%) patients in prescription pattern in valproate.

TABLE 10. ANTI EPILEPTIC DRUG PRESCRIPTION PATTERN (ADD ON-THERAPY)

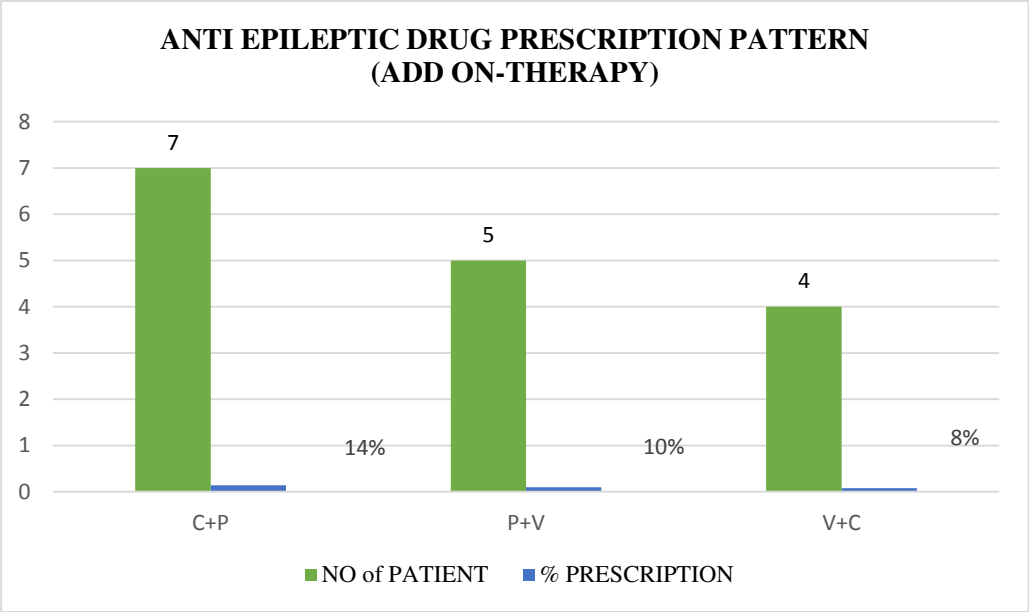
S.NO	Prescribed AED's	No. of patients	%of prescription
1	C+P	07	14%
2	P+V	05	10%
3	V+C	04	08%

Mean value = 5.33 SD = 1.528

P value is 0.0263 considered significant

t value 6.047 with 4 degrees of freedom

FIGURE 10. ANTI EPILEPTIC DRUG PRESCRIPTION PATTERN (ADD ON-THERAPY)



Out of 16 patients are treatment in add on therapy. 7 (14%) patients prescription pattern in C+P, 5(10%) patients prescription pattern in P+V. 4(8%) patients prescription pattern in V+C.

Table 11. RECURRENCE OF SEIZURE IN THE STUDY POPULATION

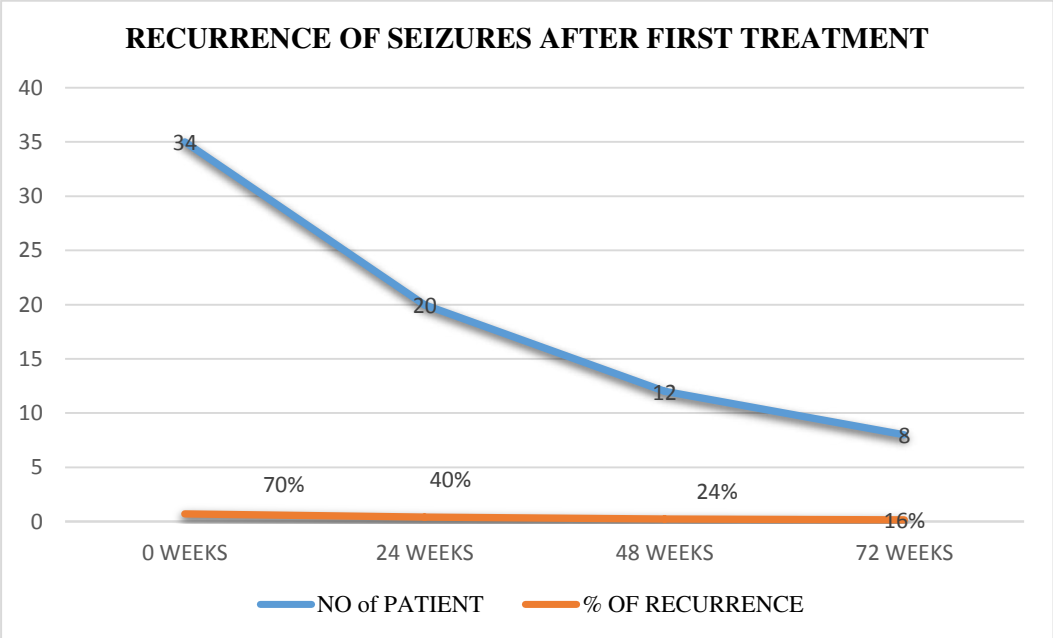
S.NO	Time from 1st seizure	No.of patients	%of recurrence
1	0 weeks	34	68%
2	24weeks	20	40%
3	48weeks	12	24%
4	72weeks	08	16%

Mean value = 18.5 SD = 11.475

P value is 0.0484 considered significant

t value 3.225 with 3 degrees of freedom

FIGURE11. RECURRENCE OF SEIZURE IN THE STUDY POPULATION



Recurrence of seizure after first treatment in 0 weeks 34(68%) patients, 24 weeks 20(40%), patients, 48 weeks 12(24%) patients, 72 weeks 8(16%) patients.

TABLE 12. OUTCOME OF EMOTIONAL SYMPTOMS

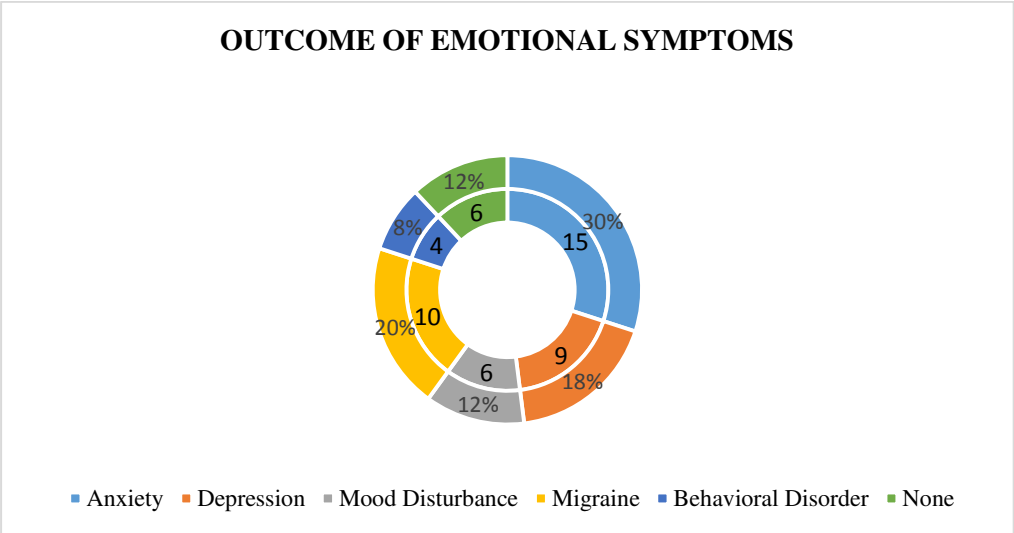
S.No	Emotional symptoms	No.of patients	%of Emotional symptoms
1	Anxiety	15	30%
2	Depression	09	18%
3	Mood disturbance	06	12%
4	Migraine	10	20%
5	Behavioral disorder	04	08%
6	None	06	12%

Mean value = 8.33 SD = 3.933

P value is 0.0035 considered very significant

t value 5.190 with 5 degrees of freedom

FIGURE 12 OUTCOME OF EMOTIONAL SYMPTOMS



Out of 50 patients outcome emotional symptoms in, anxiety patients 15(30%) depression patients 9(18%), mood disturbance patients 6(12%), migraine patients 10(20%), behavior disorder patients 4(8%), None patients 6(12%) were occur.

TABLE: 13 KNOWLEDGE OF FIRST AID IN THE STUDY POPULATION

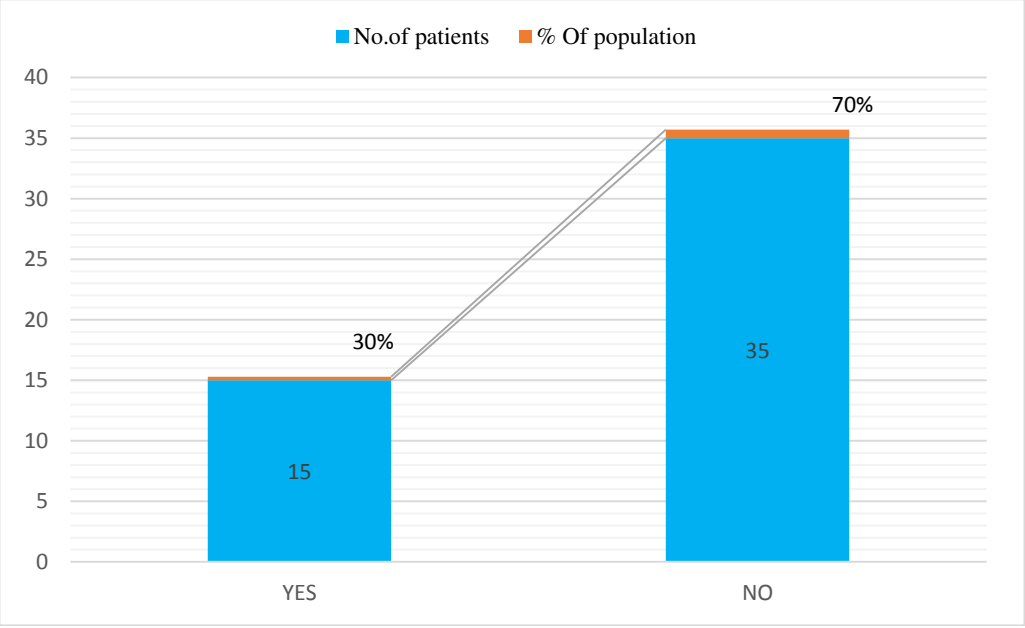
S.NO	Knowledge of first-aid	No. of patients	%0f population
1	Yes	15	30%
2	No	35	70%

Mean value = 25 SD = 14.142

P value is 0.2422 considered not significant

t value 2.500 with 1 degree of freedom

FIGURE: 13 KNOWLEDGE OF FIRST AID IN THE STUDY POPULATION



Out of 50 patient's knowledge of first aid in 15(30%) patients, NO knowledge of first aid in 35(70%) patients.

TABLE: 14 ASSESSMENT OF CLINICAL RESPONSE USING THE CLINICAL GLOPAL IMPRESSION SCALE (CGI SCALE)

Drug therapy	Global Improvement	No of Patient	Percentage
Mono therapy	Minimally Improved	5	10%
	Much Improved	23	46%
	Very Much Improved	1	2%
	No Change	5	10%
Add on therapy	Minimally Improved	1	2%
	Much Improved	9	18%
	Very Much Improved	1	2%
	No Change	5	10%

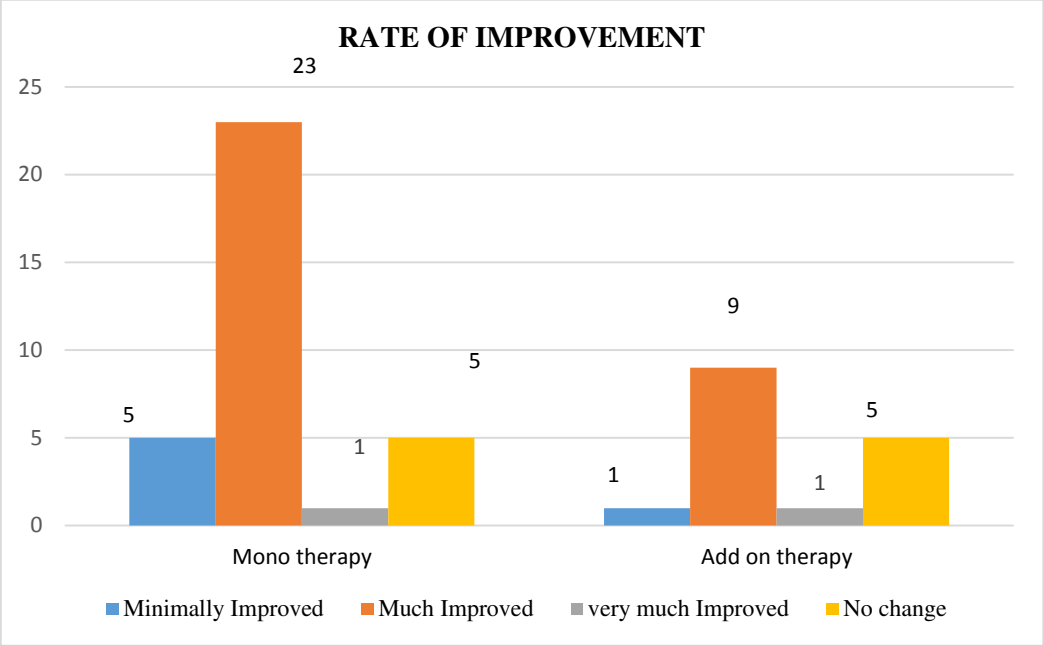
Mean value: 2.800 SD value:1.095

P value is 0.0046 considered very significant

t value is 5.715 with 4 degrees of freedom

From the above table with mono therapy 46% of patients were much improved, 10% of patients were minimally Improved. 2% of patients produce very much Improved condition with add on therapy much improved and of patients were 18% compared to other responses.

FIGURE 14 ASSESSMENT OF CLINICAL RESPONSE USING THE CLINICAL GLOPAL IMPRESSION SCALE (CGI SCALE)



CGI scale is used in epilepsy treatment. In Mono therapy treatment 34 patients are involved. 5 patients are minimally improved, 23 patients are much improved, 1 patient is very much improved, 5patients showed no change.

Add on therapy treatment in 16 patients. 1 patient in minimally improved stage, 9 patients are much improved, 1 patient in very much improved, 5 patients shows no change.

TABLE: 15 REMISSIONS OCCURRED DURING TREATMENT

S.No	Remission during therapy	No.of.Patients		% of Remission	
		+	-	+	-
1	Mono therapy	25	9	50%	18%
2	Add- on therapy	10	6	20%	12%

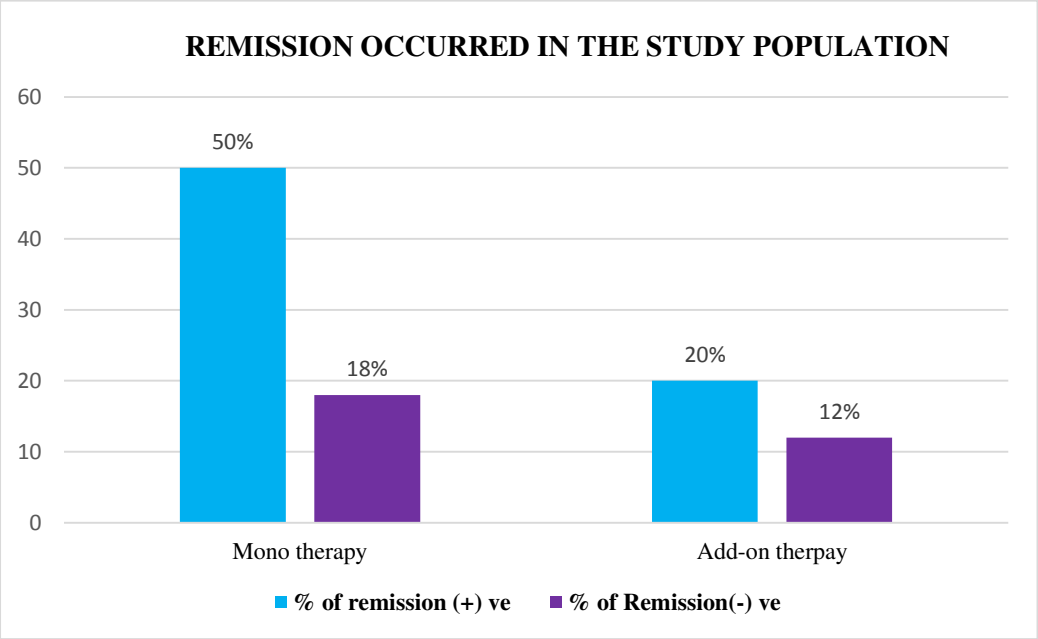
Mean value = 8.5 SD = 0.7071

P value is 0.0374 considered significant

t value 17.000 with 1 degrees of freedom

Out of 50 patients remission occurred in mono therapy 25(50%) + ve, 9(18%) –ve, patients Add on therapy 10 (20%) +ve, 6(12%) –ve patients.

FIGURE: 15 REMISSION OCCURRED DURING TREATMENT



DISCUSSION

The concept of treatment of seizures with modern therapy is relatively new in India. In developing countries the neurology treatment is become burden to the people. Due to rapid growth in population, general lack of education, health awareness and socio economic status. There is no racial geographical or social class boundaries of seizures occurs in both genders, at all ages, especially in childhood, adolescents and increasingly in ageing population, while the condition can have profound physical and psychosocial consequences, appropriate treatment can prevent long term damage. While there is no cure for the condition there are various ways-people can control or manage symptoms to improve their quality of life particularly if the condition is identified and managed early.

In this study a total of 50 patients comprising 22 (44%) males & 28 (56%) female were selected from the department of general medicine, New Life Society, Bethesda Hospital, Tuticorin. In the present study the percentage privilege of female patients is high when compared with male patients in the study population. For the treatment of epilepsy in women monotherapy is recommended during the reproductive years to reduce the risk teratogenicity seen with poly pharmacy.

On the classification of patients according to the age group the maximum number patients according to the age group the maximum number of patients were under the age group of 36-45 (30%).Other age group in 15-25 (22%), 26-35 (26%), 46-55(16%), 56-65(6%).This results indicates that most of the epilepsy patients were under the age group of 26-45.

Classification of Illness table shows, mildly ill patients are mostly in 20 (40%) moderately ill patients 10, markedly ill patients 6, Border line ill patient 14. This result showed severity of illness more in 36-45 years (32%).

The number of married patients were 39(78%) compared to unmarried patients 11(22%) .

The higher number of epilepsy patients were unemployed 12(24%) because they are not able to work. House wife 9(18%), Business man 11(22 %), Private employees 6 (12%), Student 5(10%), Agricultural 7(14%)

When comparing the etiological factors for epilepsy higher number of patients 16(32%) had a physical illness as the cause. The other causes responsible for the incidence of epilepsy were job problem 5(10%), loss of close family members 5(10%), financial problems 7(14%) family problems 6(12%) marital conflicts 7(14%), academic problem 1(2%).There is no specific reason for 3(6%)

In social habits smoker are 4(8%) of patient and smoker and alcoholic are 3(6%) and 43(86%) of patients were non smoker and non alcoholic.

12% of patients had a family history of epilepsy. 88% of patients had a no family history.

Generally most of the seizures effectively treated with Anti-epileptics and Anticonvulsants. These are prescribed according to the patient clinical response. At present according to the diagnosis following drugs were given Carbamazepine (24%), Phenytoin sodium (28%), Valproate (16%), to the patients as monotherapy treatment based upon their seizure frequency.

AED didn't show effective result then choose Add on therapy for getting effective results. In this therapy second drug is added to low doses and then gradually first AED dose was decreased and second drug is then further optimized based on seizure response. Among the different types of AED's combinations in the present study C+P (14%), P+V (10%), V+C (8%) were given to the patients as Add on therapy in the study population.

Although few studies were conducted specifically in patients with seizures who are using AED's in high doses, they found most common side effects were occurred. So most of the Anticonvulsant drugs were needed to be introduced slowly to minimize side effects such as Nausea, Vomiting etc., after first treatment of seizure the recurrence should be effectively controlled by using successful management. In this study the percentage of recurrence of seizure is gradually decreased in range of 40%, 24% and 16% for every 6 months.

In this study we found that remission (68%) had achieved most often due to mono therapy because mono therapy is the goal whenever possible. The possibility of using Add on therapy is rare in the study population because most of the patients got remission by mono therapy itself.

Out come of emotional symptoms mostly in anxiety 15 (30%) and depression in 9 (18%), mood disturbance 6(12%), migraine 10(20%), behavioral disorder 4(8%), none 6(12%).

All patients were counselled with the help of quality care check list form, during the counseling when came to know about their awareness regarding self-care and first aid. Results in 35(70%) population don't have proper knowledge of epilepsy and some have little bit of knowledge 15(30%),

CGI scale is used in epilepsy treatment. Monotherapy treatment 23(46%) patients are much improved, 5(10%) patients are minimally improved, 1(2%) patient very much improved, 5(10%) patients showed no change. Add on therapy treatment 9(18%) patients are much improved, 1(2%) patient minimally improved, 1(2%) patient very much improved, No change was observed in 5(10%)

The remission occurred during treatment are Mono therapy in number of patients

+ (25) -(9).The percentage of remission in mono therapy + (50%),-(18%).The remission occurred during treatment with Add - on therapy in number of patients +(10),-(6).The percentage of remission in Add-on therapy +(20%),-(12%).

Educating the patient about epilepsy, AED compliance, seizure first-aid is important for ensuring successful therapy. AED selection is determined by seizure type, patient medical history, and concurrent medications.

CONCLUSION

The incidence of epilepsy is 24-53% of population in developing countries. However over 30% of people with epilepsy or seizure don't have seizure control even with the best available medications.

AED's therapy is the main stay of treatment for most patients with epilepsy. The overall goal is to completely prevent seizures without causing any untoward side effects, preferably with single medication and a dosing schedule that is easy for the patient to follow. Because the response to any anti epileptic drug is unpredictable so patient should be carefully educated about approach to therapy.

Most of the generalized seizure patient take monotherapy. In this adverse effect occurrence was less compared to add on therapy. Add –on-therapy taken long term treatment with more side effect. But in monotherapy duration of treatment short with less side effect .The vast majority of patients had remission by mono therapy treatment .Co operation between the patient, physician and pharmacist results best possible outcome.

There is a long tradition of treating epilepsy patients with two or more AEDs. However, in the past decade monotherapy has emerged as the ultimate treatment strategy for both newly-diagnosed and long-term patients because of fewer side effects, better compliance, less teratogencity and lower cost.

Reducing AED polytherapy to monotherapy frequently reduces the burden of adverse effects and may also improve seizure control. AED monotherapy remains the optimal approach for managing most patients with epilepsy.

Tips regarding first aid for making the people physically and mentally ready to help the people who were getting sudden occurrence of seizures. By this way we can get tremendous change in reducing Sudden Unexpected Deaths in Epilepsy (SUDEP) and we were succeeded in achieving our main goal to maximize the quality of the life by minimizing the seizures activity.

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PATIENT PROFORMA

PATIENT DETAILS

PATIENTS HOSPITAL DETAILS:

HOSPITAL OP/IP NO:

ADDRESS:

NAME	
C/O	
DOOR NO	
STREET NAME	
AREA	
LANDMARK	
CITY/ VILLAGE	
PHONE NUMBER	
MOBILE NUMBER	

DEMOGRAPHICS:

DATE OF BIRTH: _____ AGE IN YEARS: _____

SEX : ☐ Male

☐ Female

PLACE :

OCCUPATION :

INCOME : ☐ Above 20000 per month
☐ 11000 to 20000 per month
☐ 5000 to 10000 per month
☐ Below 5000

EDUCATION : ☐ Did not Complete High School / Secondary School

☐ Completed High School / Secondary School
☐ Completed College (Bachelors)
☐ Completed Post Graduate Education (Masters/Phd.,)

MARRIAGE DETAILS : ☐ Married ☐ Unmarried ☐ Separated

SOCIAL BEHAVIOR:

Does the subject use tobacco?: ☐ Current Use ☐ Past Use ☐ Never Use

If Current Use for Long? : _____Years_____Month

Does the subject use Alcohol? ☐ Yes ☐ No

If Current Use for Long? : _____Years_____Month

Does the subject use Food? : ☐ Vegetarian ☐ Non-Vegetarian

HISTORY OF INDEX ILLNESS EPILEPTIC SEIZURES

FAMILY HISTORY

KNOWLEDGE OF FIRST AID : ☐ Yes
☐ No

ANY OF YOUR FAMILY MEMBERS HAD PREVIOUS HISTORY OF EPILEPSY? : ☐ Yes ☐ No

If, Yes Related Mention the TYPE OF EPILEPSY :

ETIOLOGICAL FACTOR : ☐ Environmental
☐ Physical Illness
☐ Drug Therapy
☐ No Specific Factor

OUT COME OF EMOTIONAL

SYMPTOMS

1. ANXIETY :
2. DEPRESSION :
3. MOOD DISTURBANCE :
4. MIGRAIN :
5. BEHAVIOUR DISORDER :
6. NONE :

MADICATION HISTORY

A. PREVIOUS TREATMENT :

DATE OF ONSET MONTH/YEAR	DURATION MONTH/YEARS

B. ONSET OF CURRENT ILLNESS…… MONTH AND YEAR

C. PRESENT TREATMENT :

MEDICATION	DOSE	START DATE	STOP DATE	RESPONSE TO TREATMENT

*Please enter one of the following.: very good, Good, Moderate, Poor, Very poor, Unknown.

VITAL SIGNS:

ORAL BODY TEMPERATURE: ☐ ^{o}C ☐ ^{O}F

WEIGHT: ☐ Kg ☐ Lbs

HEIGHT: ☐ Cm ☐ Inches

RESPIRATORY FREQUENCY:

BLOOD PRESSURE:

SITTING/ STANDING	**TIME VITAL SIGNS TAKEN (24- Hour)**	**BLOOD PRESSURE (mmHg)**	**HEART RATE(bpm)**
After 5 Minutes			
After 2 Minutes			

Are any vital signs abnormal and clinically significant? Yes….. No……

CONCOMITANT MEDICATION

Is the subject currently taking any medication ☐ **Yes** ☐ **No**

ADVERSE EFFECTS

Is here any Adverse effect is arise please enter of the following (2^{nd} visit)

Nausea ☐

Vomiting ☐

Increased Sweating ☐

Constipation ☐

Head Ache ☐

Dizziness ☐

Others ☐

RECURRENCE OF SEIZURE IN STUDY POPULATION : ☐ 0 WEEKS
☐ 24 WEEKS
☐ 48 WEEKS
☐ 72 WEEKS

PRESCRIPTION PATTERN : ☐ MONO THERAPY
☐ ADD ON THERAPY

REMISSION OCCURRED DURING TREATMENT : ☐ MONO THERAPY
☐ ADD ON THERAPY

TIME TAKEN FOR REMISSION :

;

EPILEPSY FIRST AID BOOKLET IN TAMIL

fhf;if typg;G Nehahspapd; mwpT Nfs;tpj;jhs;

1. typg;G Neha; vd;gJ?
   m) kdNeha; M) %is euk;gpay; Neha;
   ,) rhgj;jpdhy; tUtJ <) guk;giu Neha;
2. typg;G Neha; te;jhy; nra;af;$ba Kjy; cjtp?
   m) ifapy; ,Uk;G Nghd;w MAjq;fis nfhLf;f Ntz;Lk;
   M) XU Gwkhf gLf;f itj;J fhw;Nwhl;lkhf itf;f Ntz;Lk;
   ,) rj;jk; Nghl;L FYf;fp vOg;g Ntz;Lk;
   <) thapy; czT my;yJ [P]; nfhLf;f Ntz;Lk;
3. typg;G Neha; vg;gb guTfpwJ?
   m) Nehahsp ,UKk; NghJ M) Nehahspia kw;wth;fs; njhLtjpdhy;
   ,) xNu tPl;by; ,Ug;gjhy; <) vJTk; ,y;iy
4. fPo;fz;ltw;wpy; vJ rupahdJ?
   m) typg;G te;jth;fis gy te;jkhf gpbj;J fl;Lg;gLj;j Ntz;Lk;
   M) typg;G te;jtupd; ehf;if gpbj;J nfhs;s Ntz;Lk;
   ,) typg;G te;jtupd; if> fhy;fis gpbj;Jf; nfhs;s Ntz;Lk;
   <) typg;G te;jtiu Rw;wp $l;lk; Nghlhky; xU Gwk; rha;j;J gLf;f itj;J mikjpahf tplTk;.
5. fPo;fz;ltw;wpy; vJ rup? typg;G Neha; ahiu jhf;FfpwJ?
   m) Mz;fis kl;Lk; ghjpf;fpwJ
   M) gbf;fhjtu;fis kl;Lk; ghjpf;fpwJ
   ,) Viofis kl;Lk; ghjpf;fpwJ
   <) Mz;> ngz; kw;Wk; gbj;jtu; gbf;fhjtu;fs;> Vio> gzf;fhuu; vy;NyhiuAk; ghjpf;fpwJ.
6. typg;G Neha; gw;wp cq;fs; fUj;J?
   m) %isapy; kpf mjpfkhd kw;Wk; xOq;fw;w kpd;rhu rf;jp ntspg;gLtjhy; Vw;gLfpwJ.
   M) gpy;yp #dpaj;jhy; Vw;gLfpwJ
   ,) Kd;Ndhh;fs; ghtj;jpdhy; cz;lhfpwJ
   <) njupahJ

;

7. typg;G Neha; te;jth;f;F FLk;gj;jhh; nra;a Ntz;baJ?
   m) KO Mjuthf ,Uf;f Ntz;Lk;
   M) jdpahf xJf;fp tpl Ntz;Lk;
   ,) jpUkzk; nra;J itf;f $lhJ
   <) Ntiyf;F nry;;y mDkjpf;f $lhJ
8. typg;G Neha; te;jth;fs; nra;af; $baJ?
   m) thfdq;fspy; ntFJ}uk; vq;F nrd;whYk; Jizf;F xU Ms; itj;J nfhs;tJ ey;yJ
   M) ntF J}uk; thfdk; Xl;lyhk;
   ,) kUj;Jth; mwpTiug;gb kUe;J khj;jpiufis rhg;gpl Njitapy;iy.
   <) kJ mUe;jyhk;> rpfnul; Fbf;fyhk;
9. typg;G Neha; cs;sth;fis rKjhak; vg;gb elj;j Ntz;Lk;?
   m) KO MjuTld; ,Uf;f Ntz;Lk;
   M) mth;fis xJf;f $lhJ
   ,) typg;G Neuj;jpy; mth;fSf;F KjYjtp nra;a Ntz;Lk;
   <) ,it midj;Jk;
10. typg;G Nehiag; gw;wp rKjhaj;jpd; fUj;J?
   m) Fzg;gLj;jNt Kbahj Neha;
   M) KOikahf Fzg;gLj;jf;$ba Neha;
   ,) KOikahf fl;Lg;gLj;j $ba Neha;
   <) njupahJ

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Uthankudi,

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ERRATA

Page No.	Line No.	Typed as	Read as