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Research Article

Epilepsy and its Management - A Brief Review

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Abstract

Epilepsy is a neurological disorder which is characterized by sudden episodes of disturbances in sensory, loss of consciousness, that is associated with abnormal electrical impulses in the brain, which requires typically two unprovoked seizures. The incidence of a first unprovoked seizure was 61 per 100,000 compared to the incidence of epilepsy of 44 per 100,000. The International League against Epilepsy (ILAE) has proposed two major schemes for the classification of Seizures and Epilepsies: The International Classification of Epileptic Seizures and the International Classification of the Epilepsies and Epilepsy Syndromes. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. The management of Epilepsy can be done with appropriate selection of Antiepileptic Drug based on type of seizure and its frequency.

Keywords: Epilepsy; Syndromes; Antiepileptic Drugs; Cognition; Behavior

Introduction

The word "epilepsy" has its own origin in Greece which means "afflict" [1]. Epilepsy occurs by sudden asynchronization of neurons [2].

A seizure is defined as an abnormal discharging of the brain's nerve cells, resulting in a disturbance of sensory, motor, or mental function [3].

Epidemiology

Epilepsy is the common neurological condition that affects people of all different ages [4]. There are an estimation of 50 million people with epilepsy over the world [5,6].

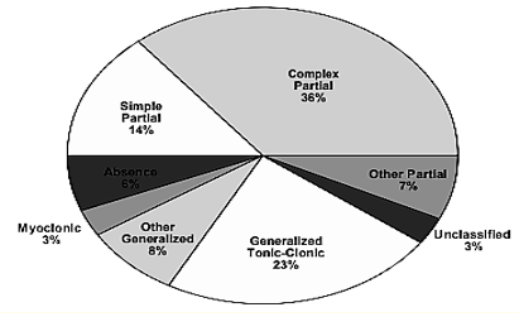


Figure 1: Epidemiology for different types of seizures [11].

Incidence

The incidence of a seizure was more compared to the incidence of epilepsy [7]. In general, the epilepsy incidence in developed countries is around 50 per 100,000 people while the incidence of epilepsy in poor under developed countries is higher in the range of 100 to 190 per 100,000/annual year [8]. Every year, 130 per 100,000 people in the United States come to medical requirement only because of a newly diagnosed seizure.

Classification

The ILAE has two different major types for the classification of Seizures and Epilepsy [9].

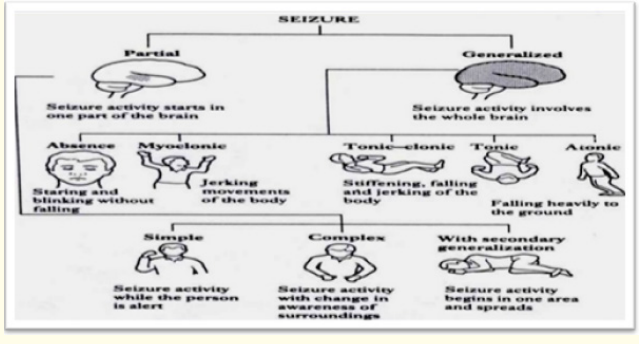
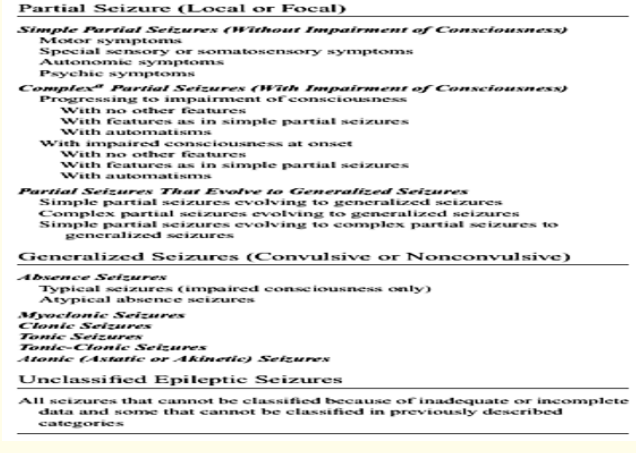


Figure 2: Classification of Epileptic seizures.

International classification of the epilepsies



Partial Seizure (Local or Focal)

Simple Partial Seizures (Without Impairment of Consciousness)
- Motor symptoms
- Special sensory or somatosensory symptoms
- Autonomic symptoms
- Psychic symptoms

Complex[a] Partial Seizures (With Impairment of Consciousness)
- Progressing to impairment of consciousness
  - With no other features
  - With features as in simple partial seizures
  - With automatisms
- With impaired consciousness at onset
  - With no other features
  - With features as in simple partial seizures
  - With automatisms

Partial Seizures That Evolve to Generalized Seizures
- Simple partial seizures evolving to generalized seizures
- Complex partial seizures evolving to generalized seizures
- Simple partial seizures evolving to complex partial seizures to generalized seizures

Generalized Seizures (Convulsive or Nonconvulsive)

Absence Seizures
- Typical seizures (impaired consciousness only)
- Atypical absence seizures

Myoclonic Seizures
Clonic Seizures
Tonic Seizures
Tonic-Clonic Seizures
Atonic (Astatic or Akinetic) Seizures

Unclassified Epileptic Seizures

All seizures that cannot be classified because of inadequate or incomplete data and some that cannot be classified in previously described categories

Figure a

Types of seizures

A patient's epilepsy is classified based on

- Seizure type (i.e., generalized and partial)
- Syndrome type
- **Partial seizures:** Partial seizures manifest as changes in motor functions. seizure starts from one hemisphere.
- **Simple Partial:** simple seizures that occurs with no loss of consciousness are classified as simple partial seizures.
- **Complex Partial:** Partial seizures with an change of consciousness are known as complex partial.
- **Secondarily generalised:** A generalized partial seizure is known to as a secondarily generalized seizure.

Generalised seizures

- Generalised Tonic- Clonic Seizures (Grand mal)
- Generalized Absence Seizures (Petitmal)
- Myoclonic Seizures
- Atonic Seizures (Drop Seizures)
- Clonic seizures
- Tonic seizures
- Status Epilepticus.

Epileptic syndromes

Accurate diagnosis of epilepsy syndromes may better guide clinicians regarding the need for drug therapy, the choice of appropriate medication, and the likelihood of successful treatment [10].

Type of Epilepsy	Etiology	Epilepsy/Epileptic Syndrome
Location-related (focal, localized, partial)	Idiopathic (characteristic age of onset)	Benign epilepsy of childhood with centrotemporal spikes; epilepsy of childhood with occipital paroxysms
	Cryptogenic or symptomatic	Variable expression depending on cause and location (e. g., temporal, frontal, parietal, or occipital lobe epilepsy)
Generalized	Idiopathic (characteristic age of onset)	Absence epilepsy of childhood (pyknolepsy); juvenile absence epilepsy; juvenile myoclonic epilepsy (impulsive petit mal); awakening grand mal epilepsy (GTCS); epilepsy with specific triggers (reflex epilepsy)
	Cryptogenic or symptomatic	West syndrome (infantile spasms, salaam seizures); Lennox–Gastaut syndrome; myoclonic-astatic epilepsy; epilepsy with myoclonic absence
	Symptomatic	Early myoclonic encephalopathy (unspecific etiology); seizures secondary to various diseases
Unsure whether focal or generalized	Idiopathic or symptomatic	Neonatal convulsions; acquired epileptic aphasia (Landau–Kleffner syndrome)
Variably focal and generalized	Symptomatic (situation-related seizure)	Febrile convulsions; isolated seizure or isolated status epilepticus; acute metabolic or toxic triggers

Figure b: Seizures and Epilepsy Syndrome.

Etiology

In any individual, the occurrence of seizures is often the result of both genetic and acquired influences and provoking factors [11]. These categories are:

- Structural
- Genetic
- Infectious
- Metabolic
- Immune and
- Unknown

Pyridoxine dependent epilepsy

Pathophysiology

A seizure occurs when there is a disturbance between the excitatory neurons and inhibitory neurons [12]. This is characterized on EEG as a sharp spike [13]. Sodium channels remain open causes hyperexcitation as a result glutamate which is an excitatory neurotransmitter releases a large amount form the neurons which binds with glutamatergic neurons triggering calcium (Ca^{2}+) release in the postsynaptic cells [14].

Clinical presentation

Seizures are divided into two main pathophysiologic groups - Partial seizures and Generalized seizures - by EEG recordings and clinical symptomatology [15].

Feature	Absence Seizure	Myoclonic Seizure	Atonic (Astatic) Seizure	Tonic-clonic Seizure
Consciousness	Impaired	Unaffected	Impaired	Impaired
Duration	A few (≤ 30) seconds	1–5 seconds	A few seconds	1–3 minutes
Symptoms and signs	Brief absence, vacant gaze and blinking followed by immediate return of mental clarity; automatisms (lip smacking, chewing, fiddling, fumbling) may occur	Sudden, bilaterally synchronous jerks in arms and legs; often occur in series	Sudden loss of muscle tone causing severe falls	Initial cry (occasionally); falls (loss of muscle tone); respiratory arrest; cyanosis; tonic, then clonic seizures; muscle relaxation followed by deep sleep. Tongue biting, urinary and fecal incontinence
Age group	Children and adolescents	Children and adolescents	Infants and children	Any age
Ictal EEG	Bilateral regular 3 (2–4) Hz spike waves	Polyspike waves, spike waves, or sharp and slow waves	Polyspike waves, flattening or low-voltage fast activity	Often obscured by muscle artifacts

Figure c: Clinical features of Generalised Seizures.

Partial seizures

Feature	Simple Partial Seizures	Complex Partial Seizures
Consciousness	Unaffected	Impaired
Duration	Seconds to minutes	Minutes
Symptoms and signs	Depend on site of origin; no postictal confusion	Depend on site of origin; postictal confusion
Age group	Any age	Any age
Ictal EEG	Contralateral epileptiform discharges; in many cases, no interictal abnormalities are detected	Unilateral or bilateral epileptiform discharges, diffuse or focal

Figure d: Clinical features of simple Partial and complex Seizures.

Diagnosis

Examination: They include Ictal Examination and Interictal Examination.

- Ictal Examination
- Interictal Examination
- Serum Prolactin levels
- Neuropsychological tests.

Other diagnostic tests: Some of the other diagnostic tests include Electroencephalogram

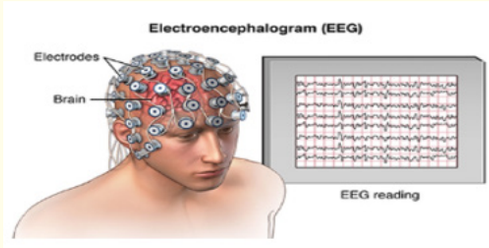


Figure 3: Elecroencephalogram.

Computerized axial tomography

Figure 4: Computerized Axial Tomography.

Positron emission tomography

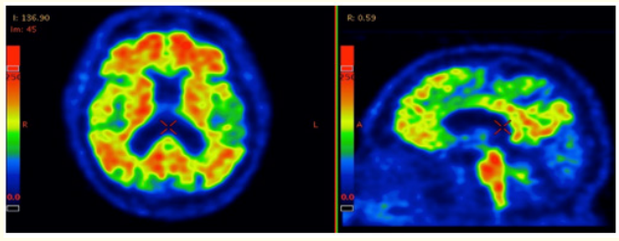


Figure 5: Positron Emission Tomography.

- Single photon emission computed tomography (spect)
- Functional magnetic resonance imaging
- Magnetic resonance imaging
- Magnetic resonance spectroscopic imaging

Management

Pharmacological therapy

The ultimate goal of treatment for epilepsy is to free from seizures with no side effects with an improved quality of life [16].

The selection of appropriate antiepileptic drug for epilepsy

The ideal AED should decrese seizures without causing any adverse effects [17].

Successful therapy is more in patients with newly diagnosed epilepsy.

First-line drugs for primary generalized tonic–clonic seizures

Valproic acid

- **Mechanism of Action:** Initially the Valproic acid increases GABA levels [18].
- **Dose:** The initial dose is 10-15 mg/kg The dose can be increased by 5-10 mg/kg
- **Adverse Effects:** The most frequently reported side effects are gastrointestinal problems including nausea, anorexia, vomiting, and weight gain. Pancreatitis is very rare. Other frequently reported side effects (e.g., drowsiness, ataxia, and postural tremor) may respond to a modification of dose.

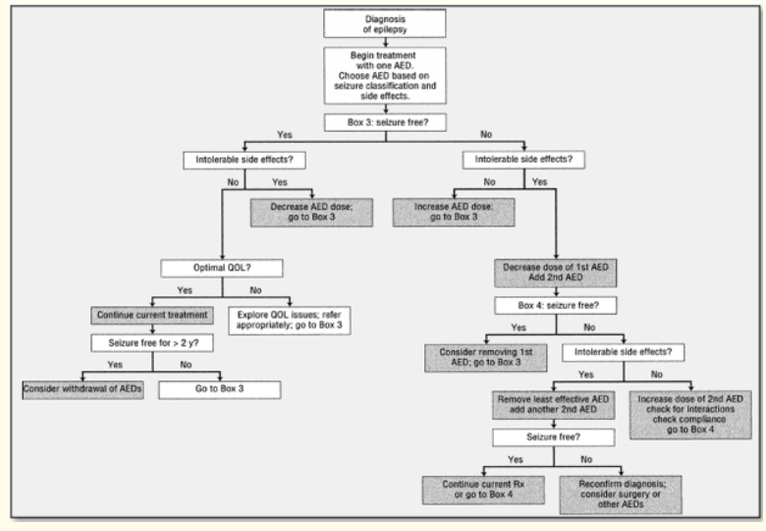


Figure 6: Algorithm for treatment of epilepsy. (Antiepileptic drug, quality of life).

Primary Generalized Tonic–Clonic Seizures	Partial Seizures*	Absence Seizures	Atypical Absence Myoclonic, and Atonic Seizures
First-line agents			
Valproic acid Lamotrigine Topiramate	Carbamazepine Phenytoin Oxcarbazepine Valproic Acid	Valproic acid Ethosuximide	Valproic acid Lamotrigine Topiramate
Alternative agents			
Zonisamide† Phenytoin Carbamazepine Oxcarbazepine Phenobarbital Primidone Felbamate	Levetiracetam† Topiramate Tiagabine† Zonisamide† Gabapentin Phenobarbital Primidone Felbamate Eslicarbazepine Vigabatrin Lacosamide Pregabalin Rufinamide	Lamotrigine Clonazepam	Clonazepam Felbamate

* Includes simple partial, complex partial, and secondarily generalized seizures.
† As adjunctive therapy.

Figure e: Selection of Antiepileptic drugs for different types of Seizures.

Lamotrigine

- **Mechanism of action:** Lamotrigine acts on inactivating voltage- sensitive sodium channels [19].
- **Dose:** 225-375mg/kg
- **Adverse Effects**: Drowsiness, ataxia, Diplopia, and headache [20].

Topiramate

- **Mechanism of Action:** Topiramate is a sulfamate-substituted monosaccharide that has involving GABA receptors, voltage-dependent sodium channels, and opposite of α-amino-3-hydroxy-5-methyl-4-isoxazole-4- propionic acid [21].
- **Dose:** 12.5 to 50 mg/day.
- **Adverse Effects:** The main adverse events of Topiramate are ataxia, impaired concentration, memory difficulties, attentional deficits, confusion, dizziness, fatigue, paraesthesia's, somnolence, and thinking abnormally, which rarely has included psychosis.

First-line drugs for partial seizure type

Carbamazepine

- **Mechanism of Action:** Carbamazepine inhibits voltage gated Sodium channels.
- **Dose:** For adults 200 mg twice daily. For children the dosage should not exceed 1,000 mg/day
- **Adverse Effects:** Side effects like blurred vision, ataxia, unsteadiness, nystagmus, diplopia, dizziness, and headache.

Phenytoin

- **Mechanism of Action:** Phenytoin mechanisms include alteration of ion fluxes associated with depolarization, repolarization, and membrane stability; alteration of calcium uptake in presynaptic terminals; influence on calcium-dependent synaptic protein phosphorylation and transmitter release; alteration of the sodium potassium ATP-dependent ionic membrane pump.
- **Dose:** Oral dosing of phenytoin should start at about 5 mg/kg per day for adults. If using oral loading doses, 20 mg/kg is typical, and the total dose should be divided by four and given at 6-hour intervals.
- **Adverse Effects:** When phenytoin is initiated, the CNS depressant effects may result in lethargy, fatigue, incoordination, blurred vision, higher cortical dysfunction, and drowsiness. These effects usually are transient and may be minimized by slow dosage titration. Nystagmus, ataxia, and altered mental status are associated with higher concentrations. One of the more common chronic side effects is gingival hyperplasia. Other chronic effects include hirsutism, acne, folic acid deficiency, carbohydrate intolerance, immunologic disturbances, hypothyroidism, and peripheral neuropathy.

Oxcarbazepine

- **Mechanism of Action:** Oxcarbazepine, which is structurally related to carbamazepine Oxcarbazepine block voltage-sensitive sodium channels, modulate the voltage-activated calcium currents, and increase potassium conductance.

- **Dose:** In adults, 300 mg once or twice a day. The dose is titrated upward at a rate of 600 mg/day per week to a maximum dose of 2400 mg/day.
- **Adverse Effects:** headache, nausea, diarrhoea, vomiting, dizziness, upper respiratory tract infections, ataxia, constipation, dyspepsia.

Ethosuximide

- **Mechanism of Action:** Ethosuximide inhibits NADPH-linked aldehyde reductase, inhibition of the sodium-potassium ATPase system, a decrease in non-inactivating Na+ currents, blocking of Ca^2+-dependent K+ channels, and inhibition of T-type Ca^2+ channel currents.
- **Dose:** A loading dose of Ethosuximide is not required.
- **Adverse Effects:** Other common side effects include drowsiness, fatigue, lethargy, dizziness, hiccups, and headaches.

Alternative Agents

Zonisamide

Mechanism of Action: Zonisamide, exert its antiepileptic effect by reducing repetitive neuronal firing via blockade of voltage-sensitive sodium channels, by reducing voltage-dependent T-type Ca^2+ channels, by facilitating dopaminergic and serotonergic neurotransmission, by weakly inhibiting carbonic anhydrase, and by blocking K+ evoked glutamate release.

Dose: In adults, 100 mg/day.

Adverse Effects: The most common adverse effects of Zonisamide include anorexia, headache, somnolence, dizziness, nausea, and irritability.

PHENOBARBITAL

Mechanism of Action: Phenobarbital decreases postsynaptic excitation, by stimulating postsynaptic GAB Anergic inhibitor response.

Dose: The concentration of phenobarbital in plasma is 10 to 25 mcg/mL. For adults, as a daytime sedative, 30 to 120 mg is given in divided doses [22].

Adverse Effects: sedation, fatigue, drowsiness, and depression, hyperactivity, porphyria, rash, such as Stevens-Johnson [23].

Levetiracetam

- **Mechanism of Action:** Levetiracetam, an S-enantiomer pyrolidone derivative, is chemically unrelated to other available AEDs. This agent may have a unique mechanism of action, including reduction in high voltage activated Ca^2+ currents and delayed-rectifier K+ currents, as well as a unique action on GABA currents. Levetiracetam also appears to bind to a specific presynaptic binding site that may modulate neurotransmitter release [24].
- **Dose:** 500-1000mg/day.
- **Adverse Effects:** Adverse effects appear to be modest, with sedation, fatigue, and coordination difficulties being the most common CNS effects. Behavioural disturbances, such as agitation, irritability, and occasionally depression, have been reported. The mechanism underlying these effects is unknown.

Gabapentin

- **Mechanism of Action:** Gabapentin is a GABA agonist alter GABA uptake by interfering with GABA transaminase. Gabapentin also may modulate specific voltage-sensitive Ca^2+ channels.
- **Dose:** 300 mg increasing to 900 mg/day
- **Adverse Effects:** dizziness, Fatigue, somnolence, and ataxia Rash is uncommon.

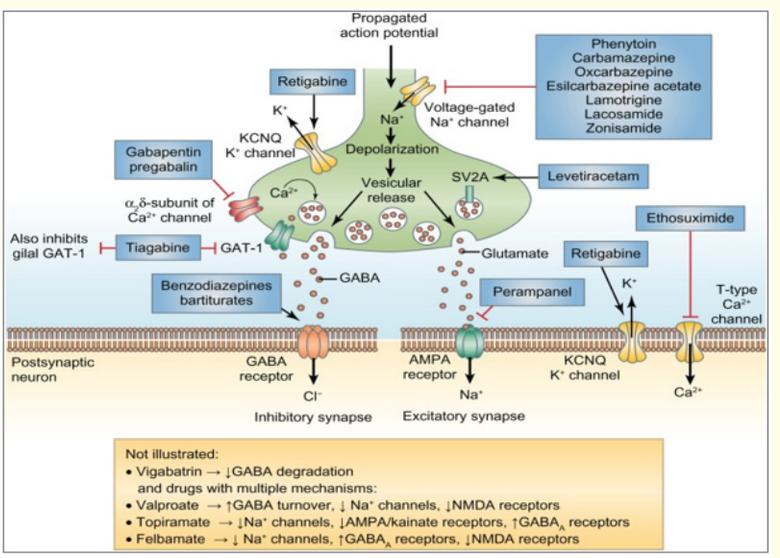


Figure 7: Mechanism of antiepileptic drugs [25].

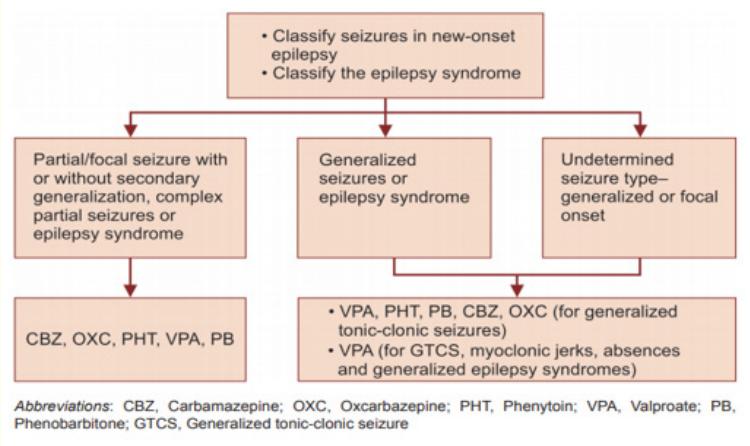


Figure 8: Choice of Antiepileptic Drug (AED) [27].

Antiepileptic drugs (AEDs)	Starting dose in average adults	Maintenance dose in average adults (mg/day)	Important side effects
Carbamazepine (CBZ)	100 mg BID	400–1000	Sedation, dizziness, ataxia, skin rash (occasionally Stevens-Johnson syndrome), hyponatremia, weight gain, seizure worsening in some epilepsy syndromes
Clobazam (CLB)	10 mg OD (HS)	10–30	Sedation, ataxia, somnolence, irritability, depression, weight gain, tolerance (reduced antiepileptic effect)
Lamotrigine (LTG)	25 mg OD (HS); lower dose VPA	100–300	Sedation, ataxia, dizziness, skin rash (occasionally Stevens-Johnson syndrome)
Levetiracetam (LEV)	250 mg BID	1,000–3000	Somnolence, dizziness, cognitive slowing, psychosis
Oxcarbazepine (OXC)	150 mg BID	600–1800	Sedation, dizziness, ataxia, headache, hyponatremia, skin rash
Phenobarbitone (PB)	60–90 mg OD (HS)	60–180	Sedation, ataxia, depression, memory problems, skin rash, hyperactivity in children
Phenytoin (PHT)	200–300 mg OD (HS)	200–400	Ataxia, sedation, gum hyperplasia, coarsening of facial features, hirsutism, memory problems, osteomalacia and bone loss, skin rash
Topiramate (TPM)	25 mg OD	100–400	Sedation, somnolence, cognitive problems, weight loss, word-finding difficulty, renal stones, seizure worsening
Valproate (VPA)	200 mg BID	500–2000	Anorexia, weight gain, nausea, vomiting, tremors, hair loss, polycystic ovarian syndrome, thrombocytopenia
Zonisamide (ZNS)	50 mg OD (HS)	200–500	Sedation, anorexia, renal stones, forgetfulness, skin rash, weight loss, distal paresthesia

Figure f: Initial dose and maintenance daily doses and some important side effects of commonly used antiepileptic drugs (AEDs) [26].

Management of status epilepticus

Status Epilepticus may present as convulsive or non-convulsive seizures. Parenteral thiamine and pyridoxine are used in the managing status epilepticus [28].

The usual dose is 10-20mg.

Surgical management

- **Focal Resection:** Removal of area of the brain which is causing seizures is called a focal resection.
- **Temporal Lobe Resection:** Removal of a portion of the temporal lobe of brain.
- **Frontal Lobe Resection:** Removal of a portion of the frontal lobe of brain.
- **Lesionectomy:** Removal of a lesion causing focal seizures is known as Lesionectomy.
- **Hemispherotomy:** A hole or several holes in the hemisphere is made instead of removing certain sections of the brain.
- **Corpus Callosotomy:** Done for people with severe generalized epilepsy with drop attacks (atonic seizures).

Neurostimulation: These are responsive neuro stimulation (RNS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS).

- Vagus nerve stimulation
- Responsive Neurostimulation
- Deep brain stimulation

Non pharmacological therapy

The ketogenic diet: There are 3 types of ketogenic diets used for epilepsy treatment the modified Atkins diet, classical ketogenic diet, and ketogenic diet with medium triglycerides [29].

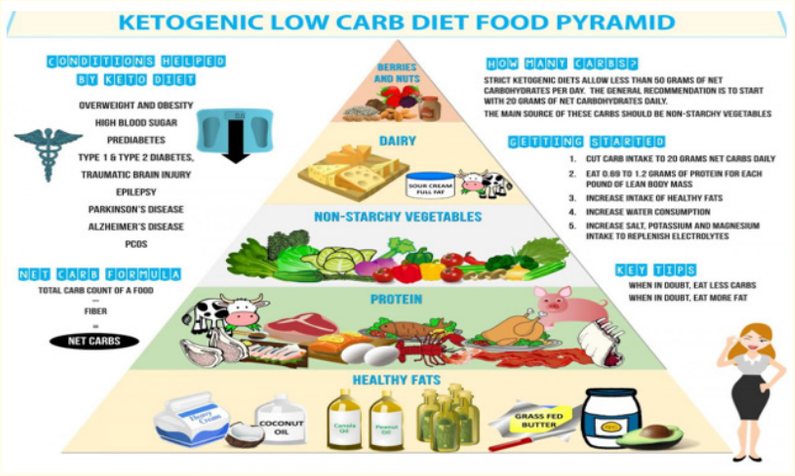


Figure 9: Diet Pyramid.

Behavioural therapy

Antistress, cognitive behavioural therapy, and relaxation programmes were applied for preventing seizures precipitated by higher mental activities [30].

Cognitive behavioural therapy

Cognitive behaviourism maintains that thoughts influence behaviour and physiology. Cognitive behavioural therapy is given in epileptic patients to improve both cognition and behavioural changes that are seen in epilepsy diseased condition and in patients using anti- epileptic medication [31]. Mini Mental Scale Examination (MMSE) [32] and Diagnostic statistical manual of mental disorders (DSM 5 scale) [33] scales are used to assess both cognitive and behavioural changes respectively in patients with epilepsy.

First aid for seizures

Figure 10: First Aid for Seizures.

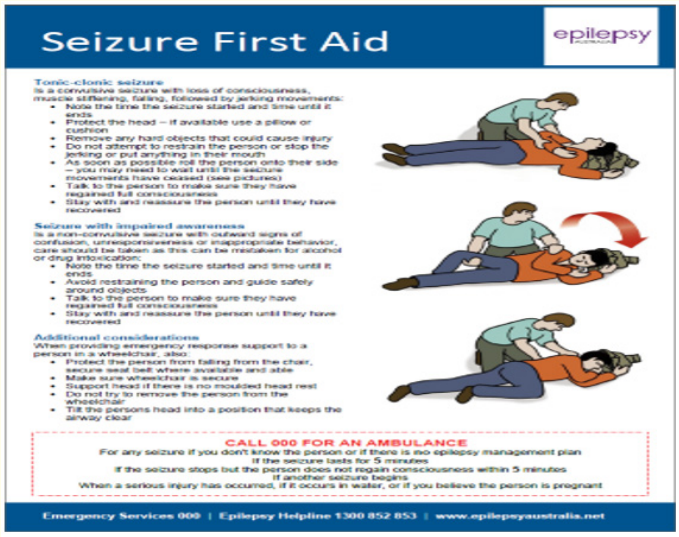


Figure 11: First aid Considerations for all types of seizures.

Cognition and behavioural changes in epilepsy

The epileptic seizures may be associated with changes in cognitive and behavioural factors in infants as well as adults [34]. It is also important to recognize that patients with epilepsy may have other neuropsychiatric comorbidities such as depression, anxiety, and sleep disturbances.

- Well-defined psychological and pathological patterns can be found in specific epilepsy syndromes [35]. Many studies report that cognitive functions get impaired in people with seizure patients [36].
- Learning disabilities, anxiety, memory impairment, Mental retardation, autism, and conduct disorders are observed in epilepsy patients [37]. Among the other co-morbidities that associates with epilepsy, the cognitive and behavioural changes are the most common [38].

Factors linked with cognitive and behavioural changes in epilepsy

- Structural brain abnormalities
- Progressive Cognitive Impairment
- Epilepsy itself is a factor

How can we overcome neuropsychological adverse effects of antiepileptic drugs....??

Behavioural and Psychiatric side effects (PBSEs) are more prevalent in patients on antiepileptic drugs (AEDs) [39].

The risk of adverse neuropsychological side effects can be minimised by [40]

- By slow titration rates (when feasible),
- By choosing lower but still efficacious target doses,
- By considering pharmacokinetics (e.g. selecting controlled-release AEDs to prevent high serum peak levels),
- By restricting polytherapy to few compatible AEDs with consideration of pharmacodynamic interactions
- By selecting and combining AEDs according to their cognitive and behavioural profile.

Mini mental state examination (MMSE)

The Mini-Mental State Examination (MMSE) or Folstein test is a 30-point questionnaire used in clinical and research to measure cognitive impairment.

Test takes 5-10 minutes and examines functions includes:

- Registration
- Orientation
- Recall
- Attention and calculation
- Language
- Copying

Instructions for taking test and scoring of the MMSE:

- Orientation (10 points):
- Registration (3 points):
- Attention and Calculation (5 points):
- Recall (3 points):
- Language and Praxis (9 points): Include Naming, Repetition, 3-Stage Command.

Method	Score	Interpretation
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Table 1: Interpretation of the MMSE: [41].

DSM-5 cross-cutting symptom measures

Dsm-5 cross-cutting assessment: This assessment is of two types.

They are:

- Level 1 cross-cutting symptom measure.
- Level 2 cross-cutting symptom measure.

DSM-5 self-rated level 1 cross-cutting symptom measure—adult:

Symptom Measure

Domain	Domain Name
I.	Depression
II.	Anger
III.	Mania
IV.	Anxiety
V.	Somatic Symptoms
VI.	Suicidal Ideation
VII.	Psychosis
VIII.	Sleep Problems
IX.	Memory
X.	Repetitive Thoughts and Behaviours
XI.	Dissociation
XII.	Personality Functioning
XIII.	Substance Us

Table 2: Interpretation of the Adult DSM-5 Self-Rated Level 1 Cross-Cutting.

Level 2 cross-cutting symptom measure [42].

The DSM-5 Level 2 Measures used to provide information on the symptoms with some of the Level 1 domains.

Conclusion

A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. The management of Epilepsy can be done with appropriate selection of Antiepileptic Drug based on type of seizure and its frequency.

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