

# Advanced Study on Anticonvulsant Drugs & It's Screening Models

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**Abstract-** The word "Fit" is sometimes used to mean convulsion or epileptic seizures. A sudden violent, irregular movement of the body caused by involuntary contraction of muscles of associated especially with brain disorder such as epilepsy, the presence of certain toxins or other agents in the blood or fever in childrens. Anticonvulsants are diverse group of pharmacological agents used in the treatment of epileptic seizure also used in the treatment of bipolar disorder and borderline personality disorder. Epilepsy has been considered as a public health problem by WHO and ILAE. The American Academy of Neurology (AAN), representing over 20,000 Neurologist and Neuroscience professionals, has taken an active interest in clinical, ethical and policy considerations. The AAN opposes generic substitution of Anticonvulsant drug for the treatment of epilepsy without attending physicians approval. The action of clinically used Anticonvulsant drugs on sustained high frequency repetitive firing of action potentials and on responses to GABA have been determined using mouse neurons in cell culture and classification Anticonvulsant drugs action have been developed in three categories based on these cellular mechanism of action: 1. Phenytoin, Carbamazepine and Valproic acid. 2. Phenobarbital, Benzodiazepines, Clonazepam, Diazepam, Nitrazepam. 3. Ethosuximide. In Novel Anticonvulsant Drug different aspects of new anticonvulsant drug (2nd generation) from preclinical and clinical testing, pharmacokinetics and mono or combination therapy in children and adult are summarized. Important data concerning the effect and tolerability of Anticonvulsant drug, can be obtained from controlled studies. Thus article will also provide review of selected anticonvulsant, focusing on drugs most likely to control seizure in small animals. The influence of aging on the activity of 5 Anticonvulsant

agent was studied in rat and mice. The mechanism, these drug classified according to their action on sustained high frequency repetitive firing (SRF) of action potentials and GABA responses and in diagnosis some test are discuss, treatment against the convulsion includes the anti seizure medications, surgery and other therapies. In this article, the Anticonvulsant as a drug class and there use in condition other than epilepsy. Such as a pain and psychiatric disorders.

**Index terms-** Anticonvulsant drug, Classification, Mechanism, Treatment and diagnosis.

## INTRODUCTION

Epilepsy is a common condition that causes repeated seizures. The seizures are caused by bursts of electrical activity in the brain that are not normal. Seizures may cause problems with muscle control, movement, speech, vision, or awareness. They usually don't last very long, but they can be scary. The good news is that treatment usually works to control and reduce seizures.

## CAUSES OF EPILEPSY

Often doctors do not know what causes epilepsy. Less than half of people with epilepsy know why they have it.

Sometimes another problem, such as a head injury, brain tumor, brain infection, or stroke, causes epilepsy.

## SYMPTOMS EPILEPSY

The main symptom of epilepsy is repeated seizures that happen without warning. Without treatment, seizures may continue and become worse and more frequent over time.

There are different kinds of seizures. You may have only one type of seizure. Some people have more than one type. Depending on what kind of seizure you have:

- Your senses may not work right. For example, you may notice strange smells or sounds.
- You may lose control of your muscles.
- You may fall down, and your body may twitch or jerk.
- You may stare off into space.
- You may faint (lose consciousness).

#### DIAGNOSIS OF EPILEPSY

Diagnosing epilepsy can be hard. If you think that you or your child has had a seizure, your doctor will first try to figure out if it was a seizure or something else with similar symptoms. For example, a muscle tic or a migraine headache may look or feel like a kind of seizure.

Your doctor will ask lots of questions to find out what happened to you just before, during, and right after a seizure. Your doctor will also examine you and do some tests, such as an EEG. This information can help your doctor decide what kind of seizures you have and if you have epilepsy.

#### EPILEPSY CAN AFFECT YOUR LIFE:

Epilepsy affects each person differently. Some people have only a few seizures. Other people get them more often. Usually seizures are harmless. But depending on where you are and what you are doing when you have a seizure, you could get hurt. Talk to your doctor about whether it is safe for you to drive or swim.

If you know what triggers a seizure, you may be able to avoid having one. Getting regular sleep and avoiding stress may help. If treatment controls your seizures, you have a good chance of living and working like everyone else.

#### EPILEPSY - HEALTH TOOLS

Health Tools help you make wise health decisions or take action to improve your health.

#### EPILEPSY – CAUSE

Epilepsy may develop even though you do not have any risk factors (things that increase your risk). A cause cannot always be identified. This is especially true in many forms of childhood epilepsy. For some people, epilepsy can result from a tumor, infection, or damage to the brain.

Children and older adults are most likely to develop epilepsy, but it can start at any age. It is possible that epilepsy may run in families. But you do not have to have a family history to develop epilepsy.

Epileptic seizures occur when abnormal bursts of electricity in the brain briefly upset normal brain function. It's not always clear what triggers the bursts of abnormal electrical activity.

Conditions that can cause seizures include:

- Head injury.
- Stroke or conditions that affect the blood vessels (vascular system) in the brain.
- Hardening of the arteries (atherosclerosis) in the brain.
- Brain tumor.
- Brain infection, such as meningitis or encephalitis.
- Alzheimer's disease.
- Alcohol or drug abuse or withdrawal.

Tumors, scar tissue from injury or disease, or abnormal brain development may damage a specific area of the brain and cause partial seizures. But you may not have any of these conditions and still develop epilepsy.

#### EPILEPSY – SYMPTOMS

Seizures are the only visible symptom of epilepsy. There are different kinds of seizures, and symptoms of each type can affect people differently. Seizures typically last from a few seconds to a few minutes. You may be alert during the seizure or lose consciousness. You may not remember what happened during the seizure or may not even realize you had a seizure.

Epileptic seizures often happen without warning, although some people may have an aura at the start of a seizure. A seizure ends when the abnormal electrical activity in the brain stops and brain activity begins to return to normal. Seizures may be either partial or generalized.

**Partial seizures** Partial seizures begin in a specific area or location of the brain. The most common types of partial seizures are:

- Simple partial seizures
- Complex partial seizures
- Partial seizures with secondary generalization.

**Generalized seizures** Seizures that begin over the entire surface of the brain are called generalized seizures. The main types of generalized seizures are:

- Generalized tonic-clonic seizures
- Myoclonic seizures
- Atonic seizures
- Tonic seizures

**TYPES OF EPILEPSY**

There are many types of epilepsy. All types cause seizures. It can be hard to determine what type of epilepsy you have because of the numerous possible causes, because different types of seizures can occur in the same person, and because the types may affect each person differently. Some specific types of epilepsy are:

1. Benign focal childhood epilepsy
2. Childhood and juvenile absence epilepsy,
3. Infantile spasms (West syndrome),
4. Juvenile myoclonic epilepsy,
5. Lennox-Gastaut syndrome.
6. Temporal lobe epilepsy

**Types and Symptoms**

Based on the type of behavior and brain activity, seizures are divided into two broad categories: generalized and partial (also called local or focal). Classifying the type of seizure helps doctors diagnose whether or not a patient has epilepsy.

Generalized seizures are produced by electrical impulses from throughout the entire brain, whereas partial seizures are produced (at least initially) by electrical impulses in a relatively small part of the

brain. The part of the brain generating the seizures is sometimes called the focus. The most common types of seizures are listed below:

Generalized Seizures (Produced by the entire brain)	Symptoms
1. "Grand Mal" or Generalized tonic-clonic	Unconsciousness, convulsions, muscle rigidity
2. Absence	Brief loss of consciousness
3. Myoclonic	Sporadic (isolated), jerking movements
4. Clonic	Repetitive, jerking movements
5. Tonic	Muscle stiffness, rigidity
6. Atonic	Loss of muscle tone

**Generalized Seizures**

There are six types of generalized seizures. The most common and dramatic, and therefore the most well known, is the generalized convulsion, also called the grand-mal seizure. In this type of seizure, the patient loses consciousness and usually collapses. The loss of consciousness is followed by generalized body stiffening (called the "tonic" phase of the seizure) for 30 to 60 seconds, then by violent jerking (the "clonic" phase) for 30 to 60 seconds, after which the patient goes into a deep sleep (the "postictal" or after-seizure phase). During grand-mal seizures, injuries and accidents may occur, such as tongue biting and urinary incontinence.

Absence seizures cause a short loss of consciousness (just a few seconds) with few or no symptoms. The patient, most often a child, typically interrupts an activity and stares blankly. These seizures begin and end abruptly and may occur several times a day. Patients are usually not aware that they are having a seizure, except that they may be aware of "losing time."

Myoclonic seizures consist of sporadic jerks, usually on both sides of the body. Patients sometimes describe the jerks as brief electrical shocks. When violent, these seizures may result in dropping or involuntarily throwing objects.

Clonic seizures are repetitive, rhythmic jerks that involve both sides of the body at the same time.

Tonic seizures are characterized by stiffening of the muscles.

Atonic seizures consist of a sudden and general loss of muscle tone, particularly in the arms and legs, which often results in a fall.

Partial Seizures(Produced by a small area of the brain)	Symptoms
1.Simple (awareness is retained) a.SimpleMotor b.SimpleSensory c.Simple Psychological	a. Jerking, muscle rigidity, spasms, head-turning b. Unusual sensations affecting either the vision, hearing, smell taste, or touch c. Memory or emotional disturbances
2.Complex (Impairment of awareness)	Automatisms such as lip smacking, chewing, fidgeting, walking and other repetitive, involuntary but coordinated movements
3. Partial seizure with secondary generalization	Symptoms that are initially associated with a preservation of consciousness that then evolves into a loss of consciousness and convulsions.

Partial Seizures

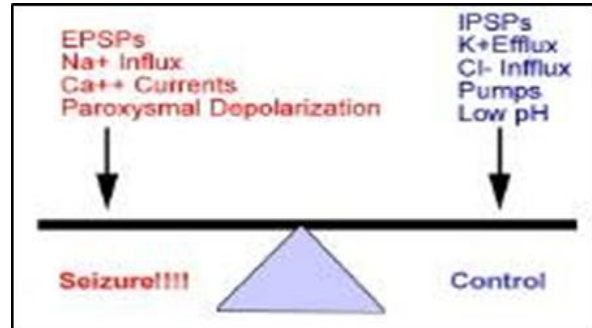
### MECHANISM OF ACTION

Modern treatment of seizures started in 1850 with the introduction of bromides, which was based on the theory that epilepsy was caused by an excessive sex drive. In 1910, phenobarbital (PHB), which then was used to induce sleep, was found to have antiseizure activity and became the drug of choice for many years. A number of medications similar to PHB were developed, including primidone.

In 1938, Houston Merrit and Tracy Putnam described animal models for screening multiple compounds for antiepileptic activity in the Journal of the American Medical Association. In 1940, phenytoin (PHT) was found to be an effective drug for the treatment of epilepsy, and since then it has become a major first-line antiepileptic drug (AED) in the treatment of partial and secondarily generalized seizures.

In 1968, carbamazepine (CBZ) was approved, initially for the treatment of trigeminal neuralgia; later, in 1974, it was approved for partial seizures. Ethosuximide has been used since 1958 as a first-choice drug for the treatment of absence seizures without generalized tonic-clonic seizures. Valproate (VPA) was licensed in Europe in 1960 and in the United States in 1978, and now is widely available throughout the world. It became the drug of choice in

primary generalized epilepsies and in the mid 1990s was approved for treatment of partial seizures.



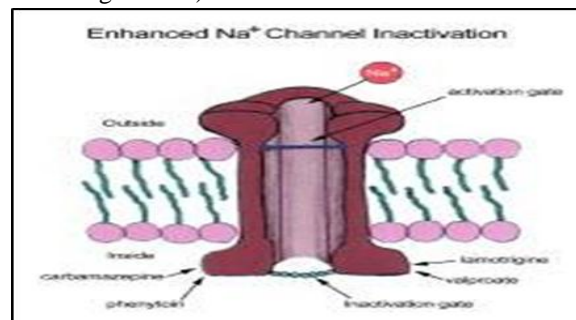
Dynamic target of seizure control in management of epilepsy is achieving balance between factors that influence excitatory postsynaptic potential (EPSP) and those that influence inhibitory postsynaptic potential (IPSP).

Antiepileptic drugs can be grouped according to their major mechanism of action. Some antiepileptic drugs work by acting on combination of channels or through some unknown mechanism of action.

#### Sodium channel blockers

The firing of an action potential by an axon is accomplished through sodium channels. Each sodium channel dynamically exists in the following 3 states:

- A resting state, during which the channel allows passage of sodium into the cell
- An active state, in which the channel allows increased influx of sodium into the cell
- An inactive state, in which the channel AEDs that target the sodium channels prevent the return of these channels to the active state by stabilizing them in the inactive state. In doing so, they prevent repetitive firing of the axons (see the image below).

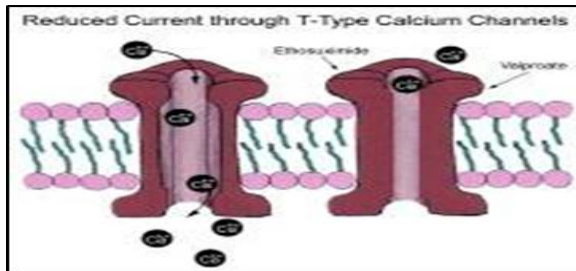


Some antiepileptic drugs stabilize inactive configuration of sodium (Na+) channel, preventing high-frequency neuronal firing.

#### Calcium channel blockers

Calcium channels exist in 3 known forms in the human brain: L, N, and T. These channels are small and are inactivated quickly. The influx of calcium currents in the resting state produces a partial depolarization of the membrane, facilitating the development of an action potential after rapid depolarization of the cell.

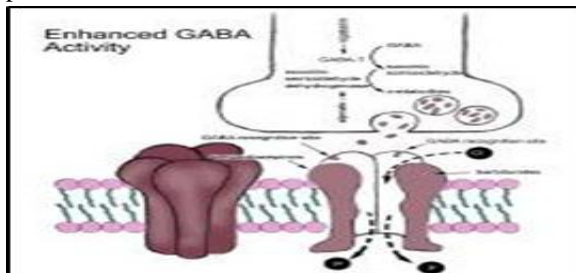
Calcium channels function as the "pacemakers" of normal rhythmic brain activity. This is particularly true of the thalamus. T-calcium channels have been known to play a role in the 3 per second spike-and-wave discharges of absence seizures. AEDs that inhibit these T-calcium channels are particularly useful for controlling absence seizures (see the image below).



Low-voltage calcium (Ca<sup>2+</sup>) currents (T-type) are responsible for rhythmic thalamocortical spike and wave patterns of generalized absence seizures. Some antiepileptic drugs lock these channels, inhibiting underlying slow depolarizations necessary to generate spike-wave bursts.

**GABA enhancers**

Gamma-aminobutyric acid (GABA) has 2 types of receptors, A and B. When GABA binds to a GABA-A receptor, the passage of chloride, a negatively charged ion, into the cell is facilitated via chloride channels (see the image below). This influx of chloride increases the negativity of the cell (ie, a more negative resting membrane potential). This causes the cell to have greater difficulty reaching the action potential. The GABA-B receptor is linked to a potassium channel.



Gamma-aminobutyric acid (GABA)-A receptor mediates chloride (Cl<sup>-</sup>) influx, leading to hyperpolarization of cell and inhibition. Antiepileptic drugs may act to enhance Cl<sup>-</sup> influx or decrease GABA metabolism.

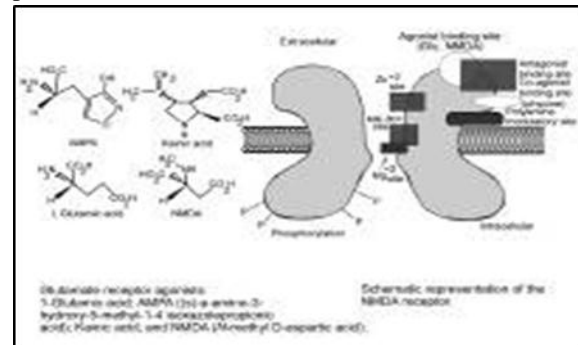
**Glutamate blockers**

Glutamate receptors bind glutamate, an excitatory amino acid neurotransmitter. Upon binding glutamate, the receptors facilitate the flow of both sodium and calcium ions into the cell, while potassium ions flow out of the cell, resulting in excitation.

The glutamate receptor has 5 potential binding sites, as follows:

- The alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) site
- The kainate site
- The N-methyl-D-aspartate (NMDA) site
- The glycine site
- The metabotropic site, which has 7 subunits (GluR 1-7)

In activation and inactivation time courses, desensitization kinetics, conductance, and ion permeability. Three main glutamate receptor subtypes are N-methyl-D-aspartate (NMDA), metabotropic, and non-NMDA (alpha-amino-3-hydroxy-5-methylisoxazole-propionic acid [AMPA] and kainate receptors). Antiepileptic drugs known to possess this



Schematic representation of N-methyl-D-aspartate (NMDA) receptor.

**Epilepsy - Risk**

The risk for epilepsy increases if you have:

- Family history of epilepsy.
- Head injury (for example, a penetrating wound or skull fracture) with amnesia or loss of

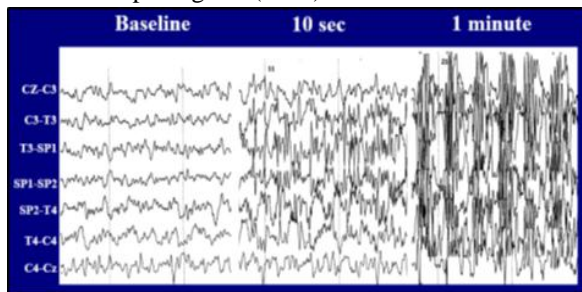
consciousness for more than 24 hours. The more severe the injury, the higher the risk.

- Stroke or conditions that affect the blood vessels (vascular system) in the brain.
- Brain tumor.
- Brain infection, such as encephalitis or meningitis.
- Lead poisoning.
- Problems with brain development that occurred before birth.
- Substance abuse.
- Fever seizures that last a long time (also known as febrile convulsions).
- Alzheimer's disease.

Epilepsy may develop even though you do not have any risk factors. This is especially true of many forms of childhood epilepsy.

#### Epilepsy - Exams and Tests

##### Electroencephalogram (EEG)



#### Imaging tests (MRI and CT)

Magnetic resonance imaging (MRI) and computed tomography (CT) are imaging tests that allow a doctor to view the brain and evaluate the cause and location of a possible source of epilepsy within the brain. The scans can reveal scar tissue, tumors, or structural problems in the brain that may be the cause of seizures or epilepsy. MRI is the more helpful test in most cases. Imaging tests may not be done after a first seizure, but they are recommended in many situations (such as after a first seizure in adults or after a head injury).

#### Epilepsy - Prevention

Since the cause of epilepsy is often not clear, it generally is not possible to prevent it.

Head injury, a common cause of epilepsy, may be preventable. Always wear your seat belt in the car

and a helmet when riding a bike or motorcycle, skiing, skating, or horseback riding.

#### Epilepsy - Home Treatment

Controlling seizures caused by epilepsy requires a daily commitment to following your treatment plan. If you are using antiepileptic medicine, you must take your medicine exactly as prescribed. Not following the treatment plan is one of the main reasons why medicines fail to control seizures.

As you follow your treatment plan, also try to identify and avoid things that may make you more likely to have a seizure, such as:

- Not getting enough sleep.
- Using drugs or alcohol.
- Being emotionally stressed.
- Skipping meals.

If your child or someone else in your family has epilepsy, learn what to do when someone has a seizure.

If you have epilepsy (or your child has epilepsy):

- Be sure that any doctor treating you for any condition knows that you have epilepsy and knows what medicines you are taking, if any.
- Wear a medical identification bracelet.

#### Epilepsy - Medications

Medicines to prevent epileptic seizures are called antiepileptics. The goal is to find an effective antiepileptic medicine that causes the fewest side effects.

Taking only one antiepileptic medicine prevents seizures in up to 7 out of 10 people who have partial seizures. About 8 out of 10 people have complete seizure control when they take more than one antiepileptic medicine.<sup>2</sup> Although many people experience side effects, medicine is still the best way to prevent epileptic seizures. The benefits of treatment with medicine usually outweigh the drawbacks.

#### Epilepsy - Surgery

Even though medicine is the most common approach to treating epilepsy, it does not always work. In almost one-third of people with epilepsy, medicine cannot control their seizures adequately (or at all, in some cases). This number is even higher in people

with focal epilepsy. Surgery can greatly improve the lives of some people who have epilepsy.

You may be a good candidate for surgery if your seizures:

- Occur often enough to severely disrupt your life.
- Tend to result in injury or harm (for instance, if seizures cause frequent falls).
- Change or alter your consciousness.
- Are not controlled well with medicine, or you cannot tolerate the side effects of the medicines.

#### Epilepsy - Other Places To Get Help

##### Organizations

National Institute of Neurological Disorders and Stroke

NIH Neurological Institute

P.O. Box 5801

Bethesda, MD 20824

Phone: 1-800-352-9424

Phone: (301) 496-5751

TDD: (301) 468-5981

Web Address: [www.ninds.nih.gov](http://www.ninds.nih.gov)

The National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health, is the leading U.S. federal government agency supporting research on brain and nervous system disorders. It provides the public with educational materials and information about these disorders.

American Academy of Neurology

1080 Montreal Avenue

Saint Paul, MN 55116

Phone: 1-800-879-1960

Phone: (651) 695-2717

Fax: 651-695-2791

Web Address: [www.thebrainmatters.org](http://www.thebrainmatters.org)

Epilepsy Therapy Project

P.O. Box 742

Middleburg, VA 20118

Phone: (540) 687-8077

Fax: (540) 687-8066

Email: [info@epilepsytherapyproject.org](mailto:info@epilepsytherapyproject.org)

Web Address: [www.epilepsy.com](http://www.epilepsy.com)

Epilepsy Foundation

8301 Professional Place

Landover, MD 20785

Phone: 1-800-332-1000

Email: [info@efa.org](mailto:info@efa.org)

Web Address: [www.epilepsyfoundation.org](http://www.epilepsyfoundation.org)

KidsHealth for Parents, Children, and Teens

10140 Centurion Parkway North

Jacksonville, FL 32256

Phone: (904) 697-4100

Fax: (904) 697-4220

Web Address: [www.kidshealth.org](http://www.kidshealth.org)

MedicAlert Foundation International

2323 Colorado Avenue

Turlock, CA 95382

Phone: 1-888-633-4298

Web Address: [www.medicalert.org](http://www.medicalert.org)

#### Epilepsy - Other Treatment

For many years, antiepileptic medicine was the only treatment for people with epilepsy. This is still true for many people, although surgery is now an option for some. Seizures that cannot be controlled with medicine or treated by surgery may sometimes respond to other treatments.

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