



A brief overview on current and future antiepileptic drugs

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Abstract

The search for antiepileptic agents with more selectivity and lower toxicity continues to be an area of investigation in medicinal chemistry. The mechanisms of action of the antiepileptic drugs (AEDs) consist in the blockade of voltage-dependent Na⁺ channels or T-type Ca²⁺ channels, inhibition of glutamatergic transmission and facilitation of γ -aminobutyric acid (GABA) inhibitory neurotransmission.

Keywords: Antiepileptic drugs, medicinal chemistry, new investigation

Introduction

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is one of the most common neurological conditions, occurring in about 1% of the global population. It is second most common disorder after stroke. Several new drugs have been licensed and many others are in various stages of development, e.g. remacemide, lamotrigine, flunarizine, lorclezole and levetiracetam. Despite optimal use of the 16 antiepileptic drugs marketed in the United States, many patients with epilepsy fail to express seizure control and others do so only at the expense of significant toxic side effects. Phenytoin, Carbamazepine and Sulfamate topiramate (TPM) are antiepileptic drugs that have been clinically effective against different types of seizures [1]. Estimates suggest that available medication controls the seizures in only 50% of patients or decreases the incidence in only 75% of patients.

Causes

All forms of epilepsy have their origin in the brain. The different types of epilepsies are not based on a single underlying mechanism, but are multifactorial in origin. Epilepsy results when many neurons in union, under a high excited stage, deliver massive discharges abolishing a finely organized pattern of the integrative activity of the brain. John Jackson proposed that these seizures are caused by occasional, sudden, excessive, rapid and local discharges of grey matter and once initiate by the abnormal focus, the seizures attack the neighboring normal brain resulting into generalized convulsions. This abnormal focus may originate as a result of local biochemical changes, ischemia or the loss of vulnerable cell inhibitory systems. However, certain physiological changes may trigger the focus and thus facilitate the spread of abnormal electrical activity to normal tissue. Such factors include

- a. Changes in blood glucose concentration
- b. Plasma pH

- c. Total osmotic pressure and electrolytes composition of extra cellular fluids
- d. Fatigue
- e. Emotional stress
- f. Nutritional deficiency
- g. Trauma, infection meningitis, brain tumors, cerebrovascular disease or metabolic abnormalities.

Epileptic seizures of unidentified cause are known as primary or idiopathic epilepsy while epileptic attacks of known causes are called as secondary or symptomatic epilepsy

Classification

a. Generalized epilepsy: Once initiated, it spreads quickly into the entire or at least the greater part of the brain. It can be further classified into

1. **Tonic clonic seizures** (grandmal type): It has a close resemblance with electrically induced convulsions where the mass stimulation of cortical neurons occurs. As the name indicates, initially there is a generalized tonic activity followed by clonic phase.
2. **Absence or minor seizures** (petitmal): It is reported to occur mainly in young children between the ages of 6 to 14 years. Seizures generally disappear spontaneously after adolescence.
3. **Myoclonic seizures:** The attack characterized by the jerky muscular movements of head, limbs or body as a whole. The etiology of attack is not known and is supposed to be due to brain damage.
4. **Infantile spasms:** The attack sometimes begins with a cry and is often associated with memory unconsciousness.

b. Partial or focal epilepsy: In this type the initial neuronal discharge originates from a specific limited cortical area. It can further be classified as

- 1. Complex partial seizures** (psychomotor or lobe seizures); It usually originates in the anterior temporal lobe and is characterized by hallucinations, fear, hate or other emotional and behavioral abnormalities.
- 2. Motor epilepsy:** Only one, entire side is affected, consciousness is not lost. Motor epilepsy is mainly witnessed in child hood and is due to more limited cortical abnormalities.
- 3. Sensory epilepsy:** Similar to motor epilepsy except the fact that it arises in the sensory cortex area.
- 4. Akinetic seizures:** Superficially no convulsions are seen. Patient may suddenly fall down on the ground without loss of consciousness.

c. Status epilepticus (acute repetitive seizures): It is the condition in which one attack follows another without patient regaining consciousness. If it remains untreated it may be fatal.

Mechanisms

a. Neuronal Sites of Action of antiepileptics² –Antiepileptic drugs acting upon neuronal site have been shown by Fig.1.

b. Sites of Action of antiepileptics in GABAergic Synapse²–Antiepileptic drugs acting through GABAergic Synapse have been shown by Fig.2.

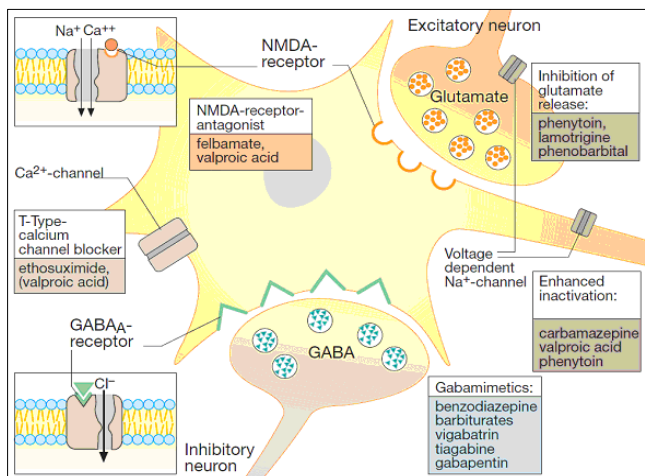


Fig 1: Neuronal sites of action of AEDs

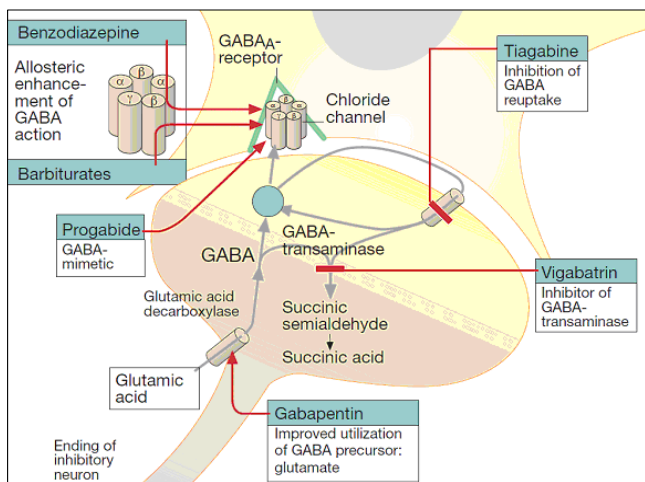


Fig 2: Site of action of AEDs in GABAergic synapse

Targets and treatment approaches for anti-epileptic drugs

There are few targets for the Anti-Epileptic drugs

- Inhibition of excitatory neurotransmitter, Glutamate
- Enhancement of inhibitory neurotransmitter, GABA
- Blockage of voltage-gated positive current, Na⁺ and Ca²⁺
- Increase outward positive current, K⁺

Treatment Approaches

The only effective means of treating epilepsy currently available are medication and, in a small proportion of patients in whom medication is not effective, surgery on the brain. Treating epilepsy by "natural" means alone (e.g. with herbal remedies) is ineffective and may be dangerous.

a. Treatment by Medication/Drugs

1. Drugs acting through increasing inhibition

Gabapentin and Progabide were the first drugs of this type to be developed. They are active against a wide spectrum of seizures. Vigabatrin appears to be a very useful medication in treating various forms of epilepsy that have not responded to other drugs. Early reports of degenerative changes in neurons of animals treated with Vigabatrin led to the most stringent appraisal of its safety in humans, but no similar effect has so far been reported in man.

2. Drugs Which Reduce Excitation of Neurons

Lamotrigine partly blocks the release of the excitatory neurotransmitter glutamate from nerve endings, and reduces the influx of sodium in the recipient neuron (this influx of sodium is vital to nervous transmission). It too appears to have a wide range of anti-epileptic activity. Allergic reactions, especially skin rashes, are relatively common. It is used as an additional treatment in patients with partial seizures with or without secondary generalization, where seizures have not been controlled by other anticonvulsant drugs. Topiramate has been shown to significantly reduce the frequency of epileptic seizures, including refractory partial seizures. It appears to help balance electrical activity in the brain while blocking other substances that increase activity.

3. Drugs that affect the availability of gamma aminobutyric acid (GABA)

Gabitril (tiagabine hydrochloride) is one of a new class of compounds that affects the availability in the brain of gamma aminobutyric acid (GABA), a naturally occurring chemical that is thought to suppress the abnormal, repetitive pattern of central nervous system activity that can lead to seizures. Gabitril appears to work by inhibiting neuronal reuptake of GABA, thereby prolonging the amount of time it is available at receptor sites.

b. Surgery for Epilepsy

The idea of treating epilepsy by surgery is not new; the first operation for epilepsy was carried out in 1886. Interest in surgery has been revived in recent years, for it is now realized that it does have an important part to play in a small minority of patients, namely those who have a single solitary epilepsy-producing abnormality of the brain, situated in an area where removal does not leave any significant defect in the brain's function. Even in these patients, operation is contemplated only when satisfactory control cannot be achieved with medication. To determine that a

patient does indeed have only one area of the brain giving rise to epilepsy, new nuclear medical techniques (SPECT and PET scanning) are used to supplement information from special EEG techniques including EEG telemetry, sleep studies, and recording from pharyngeal or sphenoidal electrodes as appropriate.

The currently used therapy of epilepsy includes various drugs that act through different mechanisms. There are several classes of antiepileptic drugs (AEDs) that have been divided on the basis of their chemical structure. Different established AEDs and newer antiepileptic drugs along with the drugs in pipeline are summarized in Table 1 and 2.

Antiepileptic Drugs

Table 1: General Description of Established Antiepileptic Drugs

Drug	Clinical Uses	Mechanism
Phenytoin (Dilantin)	Partial and tonic-clonic	Prolongs closing of inactivating gate of sodium channels of excitatory NT receptors in the CNS
Carbamazepine (Tegretol)	Partial and tonic-clonic	Prolongs closing of inactivating gate of sodium channels of excitatory NT receptors in the CNS
Phenobarbital (Luminal®)	Partial and tonic-clonic	Facilitates the inhibitory action of GABA, increases the duration of chloride channel opening at GABA-A receptors
Ethosuximide (Zarontin®)	Absence seizures	Inhibits low-threshold T-type calcium currents in thalamic neurons
Valproic acid (Depakene®) Divalproex Na (Depakote®)	Partial and tonic-clonic and absence seizures	Prolongs inactivation of sodium channels of excitatory NT receptors in CNS Inhibits low-threshold T-type calcium currents in thalamic neurons. Increases the amount of GABA in CNS. Increases GAD activity. Decreases GABA-T and succinic semialdehyde dehydrogenase activity
Clonazepam (Klonopin®)		Facilitates the inhibitory actions of GABA
Diazepam (Valium®)		Increases the frequency of opening of chloride channel of GABA-A receptor
Lorazepam (Ativan®)		Increases the frequency of opening of chloride channel of GABA-A receptor
Chlorazepate (Tranxene®)		Increases the frequency of opening of chloride channel of GABA-A receptor
Trimethadione Bromide		Inhibits low-threshold T-type calcium currents in thalamic neurons Not known

Structure of AEDs

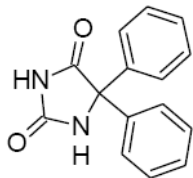
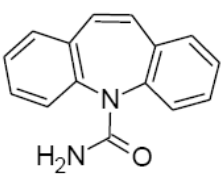
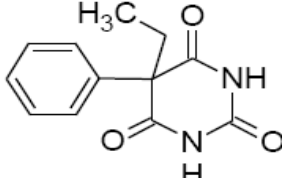
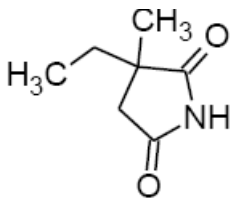
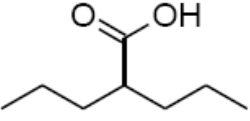
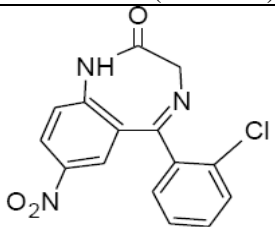
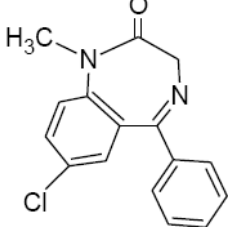
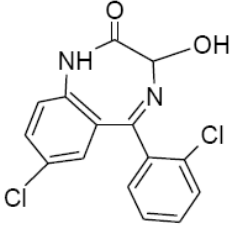
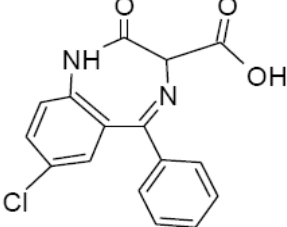
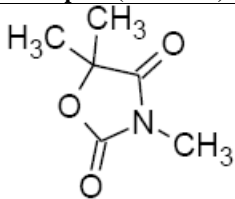
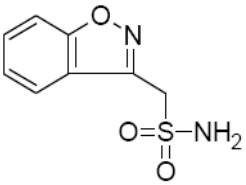
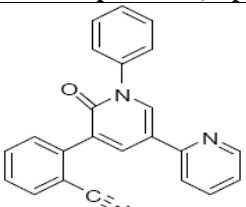
		
Phenytoin (Dilantin)	Carbamazepine (Tegretol)	Phenobarbital (Luminal®)
		
Ethosuximide (Zarontin®)	Valproic acid (Depakene®) Divalproex Na (Depakote®)	Clonazepam (Klonopin®)
		
Diazepam (Valium®)	Lorazepam (Ativan®)	Chlorazepate (Tranxene®)
		
Trimethadione		

Table 2: General Description of Newer Marketed AEDs

Drug	Mechanism	Clinical Uses	Side Effects
Eslicarbazepi (Zebinix; Exalief)	Novel voltage gated Na ⁺ -channel blocker	As adjunct in Partial onset seizures; also, in bipolar disorder and trigeminal neuralgia	
Felbamate (Felbatrol)	Possible blockade of NMDA receptor	Partial seizures. Lennox-Gastaut syndrome	Severe hepatitis Aplastic anemia
Flunarizine (Sibelium)	Ca ²⁺ -channel blocker with Calmodulin binding property and Histamine blocking activity		
Gabapentin (Neurontin)	Increases the release of GABA	Adjunct drug for partial and generalized tonic-clonic seizures	Somnolence Dizziness Ataxia Headache
Lacosamide (Vimpat)	Enhances slow activation of voltage gated Na ⁺ -channel		
Lamotrigine (Lamictal)	Prolongs closing of inactivating gate of Na ⁺ channel	Partial seizures	Dizziness Headache Diplopia Somnolence Skin Rash
Levetiracetan (Keppra)	Binds to synaptic vesicle protein SV2A thereby impeding nerve conduction across synapse	Adjunct for partial seizures with or without secondary generalization	Minimal, drowsiness Anxiety, Amnesia
Oxcarbazepine (Trileptal)	Blockade of voltage sensitive sodium channels	Partial seizures with or without generalization	CNS side effects, hematological abnormalities and effects on drug metabolizing enzymes are less than carbamazepine
Pregabalin (Lyrica)	Not known	For neuropathic pain and adjunct therapy for partial seizure	
Tiagabine (Gabatril)	Inhibition of GABA uptake	Adjunct for partial seizures	Nervousness Dizziness Tremor Depression
Topiramate (Topamax)	Prolongs closing of inactivating gate of Na ⁺ channel, potentiates the GABA effect and blocks AMPA receptors	Partial and generalized tonic-clonic seizures	Somnolence Fatigue Dizziness Paresthesia Confusion
Vigabatrin (Sabril)	Irreversible inhibitor of GABA aminotransferase (GABA-T)	Partial seizures	Drowsiness Dizziness Weight gain Psychosis
Zonisamide (Zonegran)	Inactivation of Na ⁺ and Ca ⁺⁺ channels	Partial and generalized tonic-clonic seizures	Drowsiness Cognitive impairment
Perampanel (E2007)	Selective antagonist for the AMPA subtype of ionotropic glutamate receptors	Drug suggests efficacy and safety in refractory epilepsy	Dizziness drowsiness irritability headache falls ataxia

Structure of new AEDs

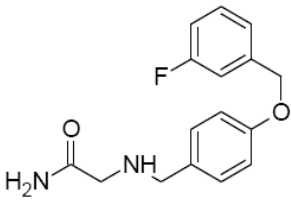
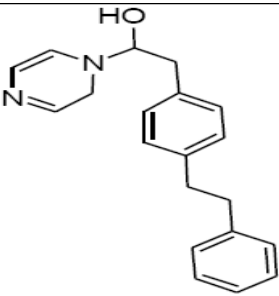
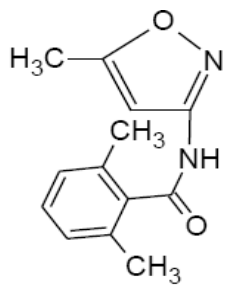
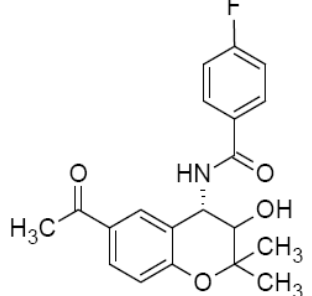
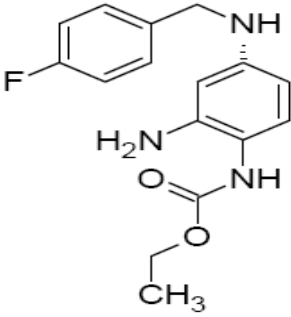
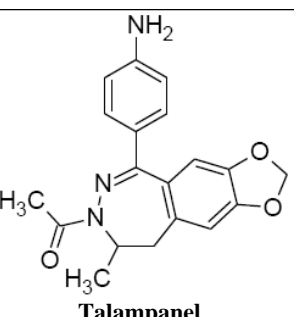
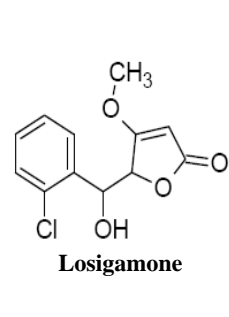
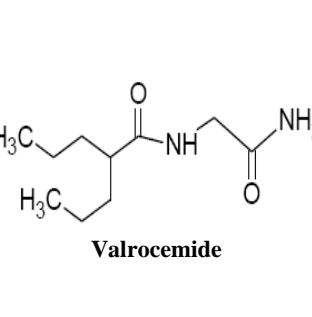
 Eslicarbazepine (Zebinix; Exalief)	 Felbamate (Felbatrol)	 Flunarizine (Sibelium)	 Gabapentin (Neurontin)
 Lamotrigine (Lamictal)	 Levetiracetan (Keppra)	 Lacosamide (Vimpat)	 Oxcarbazepine (Trileptal)
 Pregabalin (Lyrica)	 Tiagabine (Gabatril)	 Zonisamide (Zonegran)	 Vigabatrin (Sabril)

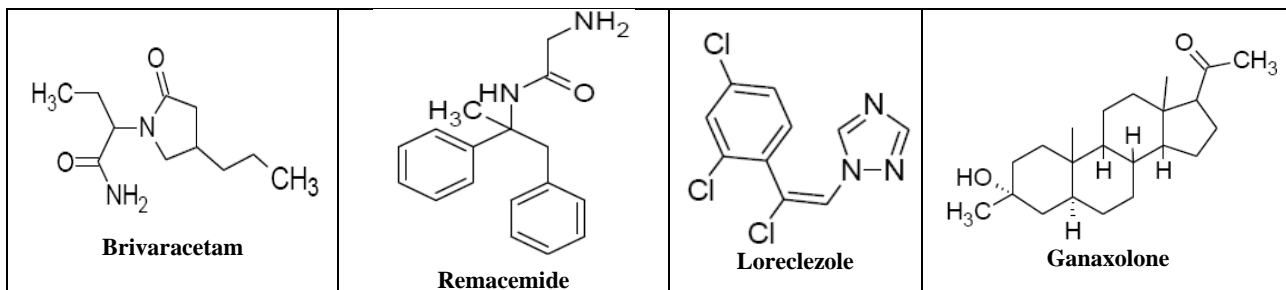
Pregabalin (Lyrica)	Topiramate (Topamax)	Tiagabine (Gabatril)	
 <p>Zonisamide (Zonegran)</p>	 <p>Perampanel (E2007)</p>		

B) Newer developed AEDs

Drug	Description
Safinamide	<ul style="list-style-type: none"> ▪ Monoamine oxidase B inhibitor ▪ Glutamate release inhibitor ▪ Inhibit Dopamine reuptake
Denzimol	<ul style="list-style-type: none"> ▪ Imidazole derivative
Soretolide	<ul style="list-style-type: none"> ▪ Does not interact with Glutamate or GABA receptors nor affects Na⁺ or Ca⁺⁺ channel ▪ Effective in MES test in rodents
Carabersat	<ul style="list-style-type: none"> ▪ Does not bind to ion channels, purinergic, aminergic, opioid and other peptidergic receptors ▪ No effect on sodium channel, GABAergic or Glutamate pathway ▪ Active against MES induced seizures and sc PTZ induced clonic seizures in rodents
Retigabine	<ul style="list-style-type: none"> ▪ Activates M-type potassium current and reduces excitability of neurons ▪ Effective against MES induced seizures and sc PTZ induced clonic seizures in mice and rats
Talampanel	<ul style="list-style-type: none"> ▪ Blocks AMPA receptors in a stereo-selective and non-competitive fashion via an allosteric site
Valroceamide	<ul style="list-style-type: none"> ▪ N- valproyl derivative of GABA and Glycine ▪ Effective against MES induced seizures and sc PTZ-induced seizures ▪ Also used in corneal and hippocampal kindling model
Brivaracetam	<ul style="list-style-type: none"> ▪ 4- n- propyl analog of levetiracetam in a racetam derivative ▪ Binds to ubiquitous synaptic vesicle protein SV2
Ganaxolone	<ul style="list-style-type: none"> ▪ A steroid drug related to pregnanolone which has sedative, anxiolytic and anticonvulsant effects ▪ Potent and selective positive allosteric modulator of GABA receptor ▪ Well tolerated in case of partial seizures
Losigamone	<ul style="list-style-type: none"> ▪ Potential GABA dependent Chloride influx
Remacemide	<ul style="list-style-type: none"> ▪ Low affinity NMDA antagonist with Na⁺-channel blocking property
Loreclezole	<ul style="list-style-type: none"> ▪ A sedative and anticonvulsant which acts as a GABA agonist

Structure of newer AEDs

 <p>Safinamide</p>	 <p>Denzimol</p>	 <p>Soretolide</p>	 <p>Carabersat</p>
 <p>Retigabine</p>	 <p>Talampanel</p>	 <p>Losigamone</p>	 <p>Valroceamide</p>



Pharmacophore model for new anticonvulsant agents

A suggested pharmacophore model showed that four pharmacophoric elements are necessary for good anticonvulsant activity [3,4]. These are (a) hydrophobic domain, A (b) Hydrogen bonding domain, HBD (c) distal hydrophobic domain, D (d) electron donor moiety, C. The pharmacophoric elements were thought to be a lipophilic aryl ring and hydrogen bonding moiety. The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring is to increase the van-der waal's bonding at the binding site and to increase potency [5,6]. Substitutions in the aryl ring by halogens have been found to increase potency in the MES screen [5,7]. Anti-convulsant medications are the category of medications that work to relieve nerve pain. These medications alter the function of the nerve and the signals that are sent to the brain. The most commonly prescribed anticonvulsant medication for nerve pain is called Neurontin (Gabapentin). Another option that has more recently emerged, specifically for the treatment of fibromyalgia, is called Lyrica (Pregabalin) [8].

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