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MECHANISM OF ACTION OF ANTICONVULSANT DRUGS: A REVIEW

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ABSTRACT

Epilepsy is a neurological disorder characterized by excessive electrical discharge in brain, which causes seizures. The therapeutic strategy in countering epilepsy involves reducing neuronal excitability through different mechanistic pathway. Most therapeutics currently used in the treatment of epilepsy is either directed towards blocking voltage-gated sodium and calcium channels or potentiating gamma amino butyric acid (GABA)-mediated neurotransmission, with little focus on voltage gated potassium ion channels, despite these channels having a major role in the control of all aspects of neuronal excitability. It is reported that functional impairment of potential channel, either by mutation or inhibition, result in epilepsy.

INTRODUCTION: Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. About 50 million people worldwide have epilepsy at any one time [1]. Epilepsy is usually controlled, but not cured, with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are life long some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as a group of syndromes with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain [2, 3, 4].

Types of Seizure: The numerous epileptic seizure types are most commonly defined and grouped according to a scheme proposed by the International League against Epilepsy (ILAE) in 1981. Distinguishing between seizure types is important since different types of seizure may have different causes, prognosis and treatments [5].

International classification of seizure types (1981): This classification is based on observation (clinical and EEG) rather than the underlying pathophysiology or anatomy.

1. **Partial seizures (Older term: focal seizures)**

a. **Simple partial seizures**: Consciousness is not impaired-

- With motor signs
- With sensory symptoms
- With autonomic symptoms or signs
- With psychic symptoms

b. **Complex partial seizures:** Consciousness is impaired (Older terms: temporal lobe or psychomotor seizures)

- Simple partial onset, followed by impairment of consciousness
- With impairment of consciousness at onset

c. **Partial seizures** evolving to secondarily generalized seizures

- Simple partial seizures evolving to generalized seizures
- Complex partial seizures evolving to generalized seizures
- Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

2. **Generalized seizures:**

a. **Absence seizures (Older term: petit mal)**

- Typical absence seizures
- Atypical absence seizures

b. **Myoclonic seizures**

c. **Clonic seizures**

d. **Tonic seizures**

e. **Tonic-clonic seizures (Older term: grand mal)**

f. **Atonic seizures**

3. **Unclassified epileptic seizures:** In terms of their origin within the brain, seizures may be described as either *partial* (focal) or *generalized*. Partial seizures only involve a localized part of the brain, whereas generalized seizures involve the whole of both hemispheres. The term secondary generalization may be used to describe a partial seizure that later spreads to the whole of the cortex and becomes generalized. Whilst most seizures can be neatly split into partial and generalized, there exists some that don't fit. For

example: the seizure may be generalized only within one hemisphere. Alternatively there may be many focal points (*multifocal seizures*) that are distributed in a symmetrical or asymmetrical pattern.

- **Partial Seizures:** Partial seizures may be further subdivided into both simple and complex seizures. This refers to the effect of such a seizure on consciousness; simple seizures cause no interruption to consciousness (although they may cause sensory distortions or other sensations), whereas complex seizures interrupt consciousness to varying degrees. This does not necessarily mean that the person experiencing this sort of seizure will fall unconscious (like fainting).

For example, a complex partial seizure may involve the unconscious repetition of simple actions, gestures or verbal utterances, or simply a blank stare and apparent unawareness of the occurrence of the seizure, followed by no memory of the seizure. Other patients may report a feeling of tunnel vision or dissociation, which represents a diminishment of awareness without full loss of consciousness. Still other patients can perform complicated actions, such as travel or shopping, while in the midst of a complex partial seizure.

The effects of partial seizures can be quite dependent on the area of the brain in which they are active. For example, a partial seizure in areas involved in perception may cause a particular sensory experience (for example, the perception of a scent, music or flashes of light) whereas, when centered in the motor cortex, a partial seizure might cause movement in particular groups of muscles. This type of seizure may also produce particular thoughts or internal visual images or even experiences which may be distinct but not easily described. Seizures centered on the temporal lobes are known to produce mystical or ecstatic experiences in some people. These may result in a misdiagnosis of psychosis or even schizophrenia, if other symptoms of seizure are disregarded and other tests are not performed. Unfortunately for those with epilepsy, anti-psychotic medications prescribed without anticonvulsants in this case can actually lower the seizure threshold further and worsen the symptoms.

When the effects of a partial seizure appear as a 'warning sign' before a larger seizure, they are known as an aura: it is frequently the case that a partial seizure will spread to other parts of the brain and eventually become generalized, resulting in a tonic-clonic convulsion. The subjective experience of an aura, like other partial seizures, will tend to reflect the function of the affected part of the brain.

- **Generalized Seizures:**
  - Primarily generalized seizures can be sub-classified into a number of categories, depending on their behavioral effects:
  - Absence seizures involve an interruption to consciousness where the person experiencing the seizure seems to become vacant and unresponsive for a short period of time (usually up to 30 seconds). Slight muscle twitching may occur.
  - Myoclonic seizures involve an extremely brief (<0.1 second) muscle contraction and can result in jerky movements of muscles or muscle groups.
  - Clonic seizures are myoclonuses that are regularly repeated at a rate typically of 2-3 per second.

- Tonic-clonic seizures involve an initial contraction of the muscles (tonic phase) which may involve tongue biting, urinary incontinence and the absence of breathing. This is followed by rhythmic muscle contractions (clonic phase). This type of seizure is usually what is referred to when the term 'epileptic fit' is used colloquially.

- Atonic seizures involve the loss of muscle tone, causing the person to fall to the ground. These are sometimes called 'drop attacks' but should be distinguished from similar looking attacks that may occur in narcolepsy or cataplexy.

- **Continuous Seizures:** Status epilepticus refers to continuous seizure activity with no recovery between successive seizures. When the seizures are convulsive, it is a life-threatening condition and emergency medical assistance should be called immediately if this is suspected. A tonic-clonic seizure lasting longer than 5 minutes (or two minutes longer than a given person's usual seizures) is usually considered grounds for calling the emergency services.

  Epilepsia partialis continua is a rare type of focal motor seizure (hands and face) which recurs every few seconds or minutes for extended periods (days or years). It is usually due to strokes in adults and focal cortical inflammatory processes in children (Rasmussen's encephalitis), possibly caused by chronic viral infections or autoimmune processes [6, 7, 8, 9, 10].

Classification [11]:

- **According to Chemical Classification:**

i. **Barbiturate:** Phenobarbitone, Mephhobarbitone

ii. **Hydantoins:** Phenytoin, Mephenytoin, Phenyl ethyl hydantoin, Ethotoin.

iii. **Oxazolidinediones:** Trimethadone, Paramethadione.

iv. **Phenacemide:** Phenacemide, Phenyl ethyl acetyl urea.

v. **Benzodiazepines:** Nitrazepam, Clonazepam.

vi. **Iminostilbenes:** Carbamazepine.

vii. **Miscellaneous:** Ethoxazolamide, Suthiame, Sodium Valproate (Valproic acid)

According to Mode of Action:

(i) Modulation of Ion Channels: Phenytoin, Carbamazepine, Lamotrigine, Oxcarbazine, Ethosuximide, Zonasamide.

(ii) Potentiation of γ-amino Butyric Acid: Phenobarbital, Benzodiazepines, Vigabatrin, Tiagabine.

(iii) Drugs with multiple mechanism of action: Sodium Valproate, Gabapentin, Felbamate, Topiramate.

(iv) Drugs with unknown mechanism of action: Levetiracetam.

Mechanism of Action: The Mechanism of Action of the Anti-epileptic drugs (AEDs) are not yet completely understood but these will help in the control of the symptoms i.e. suppression of the seizures. It is believed that AEDs act on diverse molecular targets to selectively modify the excitability of neurons so that seizures related firing can be blocked without disturbing non-epileptic activity which sub serves normal signal between neurons. At the cellular levels, three basic mechanisms are recognized, modulation of voltage-dependent ion channels (Na^+, Ca^{2+}, K^+), enhancement of GABA mediated inhibitory

neurotransmission and attenuation of excitatory transmission. Ion channels activity is important for signaling. The inflow and out flow of ions is controlled by the differential permeability and gating of the ion channels. Na^+ and Ca^{2+}channels are important for mediating excitation whereas the opening of K^+ and Cl^- channel may promote inhibition [12, 13, 14, 15].

Targets for the action of Antiepileptic drugs: Voltage dependent ion channels are the molecular targets of a number of chemically different anticonvulsant drugs. These ion channels include Sodium, Calcium and Potassium channels.

- **Ion Channels:**

- **Na^+ channels:** The flow of cations across surface and internal cell membranes is controlled through voltage-gated ion channels. The neuronal Na^+ channel has a multi-subunit structure that forms a Na^+ selective, voltage-gated pore through the plasma membrane. The protein structure undergoes conformational alterations in response to changes in membrane potential, regulating conductance through the intrinsic pore. A-subunit is the main structural component of the neuronal Na^+ channel. In the mammalian brain, the α-subunit associates with two auxiliary subunits β_1 and β_2. The β-subunits are not required for basic Na^+ channel activity. At normal membrane potentials, most Na^+ channels exist in a closed, resting state. Upon depolarization, the channel activates, facilitating ion flux. Thereafter, the Na^+ channel enters an inactivated state, from which it is not readily re-activated. Repolarization of the neuronal membrane rapidly converts the channel back to a lasting state, from which it can respond to subsequent depolarizations [16, 17].

- **Ca^{2+} channels:** Voltage dependent ion channels are the analogue of Na^+ channels. The α-subunit of the Ca^{2+}channel is the homologue of the α_1-subunit of the Na^+ channel. It forms the Ca^{2+}sensitive channel pore and confers voltage dependency. According to membrane potential Ca^{2+} channels are categorized into low or high threshold. The low-threshold T-type Ca^{2+} channel is expressed predominantly in thalamocortical relay neurons, and believed in the generation of the rhythmic 3-Hz spike-and-wave discharge which is characteristic of generalized absence seizures. High-threshold Ca^{2+} channels are sub classified by their pharmacological properties into L-, N-, P-, Q-, and R-types these channels are distributed throughout the nervous system on dendrites, cell bodies, and nerve terminals. The N-, P-, and Q-type channels, in particular, have been implicated in the control of neurotransmitter release at the synapse. Many AEDs are acted by blocking voltage sensitive Ca^{2+} channel to contribute Anti-epileptic drugs [18].

- **K^+ channels:** K^+ channels are tetrameric in nature of large protein complexes and their monomers are structurally and genetically related to the Na^+ and Ca^+ channel through α and α_1 subunits respectively. K^+ channels involved in the excitation. They are responsible for the repolarization of plasma membrane of Na^+ channel. Direct activation of voltage-dependent K^+ channels hyperpolarizes the neuronal membrane and limits action potential firing. Accordingly, K^+ channel activators have anticonvulsant effects in some experimental seizure models whereas K^+ channel blockers precipitate seizures. Potentiation of voltage-sensitive K^+ channel currents may prove to be an important target for future AED development [19].

- **γ- Aminobutyric acid-mediated inhibition*:*** GABA is the major inhibitory neurotransmitter in the mammalian CNS. Impairment of GABA function is widely recognized to provoke seizures, whereas facilitation has an anticonvulsant effect. GABA is synthesized in GABAergic neurons, by the action of the enzyme glutamic acid decarboxylase. GABA plays an important part in controlling glutamate-mediated excitatory activity within the cortex, as well as excitatory output from cortex. There are two subtypes of GABA receptors, designated $GABA_A$ and $GABA_B$ and the newly characterized $GABA_C$. $GABA_A$ receptors are located predominantly on postsynaptic membranes and are involved in fast neurotrans-mission. It belongs to the ligand-gated ion channel superfamily and responds to GABA binding by increasing Cl^- conductance, resulting in neuronal hyperpolarization. $GABA_B$ receptors are G-protein-linked, activation of which leads to an increase in K^+ conductance.

The $GABA_A$ receptor is part of the trans-mitter-gated channel which consists of five membrane-spanning subunits that form the pore through which chloride ions enter the postsynaptic neuron following $GABA_A$ receptor occupation. Each of the five subunits in turn consists of four distinct transmembrane spanning domains. Thesis subunits, which form the ionophore, have been designated α, β, -γ, δ and ρ, and each; with the exception of δ, have multiple isoforms, there are six a subunits (α_l- α_6), four β subunits ((β_1~β_4), three *y* subunits (γ_1-γ_3), a single δ subunit, as well as two ρ sub-units (ρ_l-ρ_2), with the latter appearing to be localized in the retina.

GABA transports located on presynaptic nerve endings and glial cells terminate the synaptic action of GABA. Four GABA transporter proteins (GAT-1, GAT-2, GAT-3, BGT-1) have been identified. GABA transporter activity requires transmembrane Na^+ and Cl^- gradients for the GABA transport [20, 21].

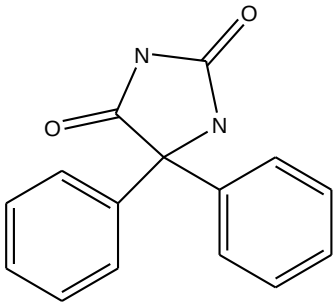
- **Glutamate Mediated Receptor:** Glutamate is the principal excitatory neurotransmitter in the mammalian brain. Focal injection of glutamate induces seizures in animals and over-activation of glutamatergic transmission or abnormal glutamate receptor properties are observed in certain experimental seizure models and human epilepsy syndromes. Glutamate exerts its pharmacological effects on several receptors. Glial glutamate uptake is of principal importance, Glial cells convert glutamate into glutamine by the "action of the enzyme glutamine synthetase. Glutamine is subsequently transferred to glutamatergic neurons, completing the cycle.

Like GABA receptors, ionotropic glutamate receptors are comprised of various combinations of subunits forming tetrameric and pentameric arrays. They are classified into three specific subtypes, α-amino-3-hydroxy-5-methyl-iso-xazole-4-propionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA), which forms ligand-gated ion channels, permeable to Na^+ and depending on subtype and subunit composition, Ca^{2+} ions. The NMDA receptor is further distinguished by having glycine as a co-agonist. The AMPA and kainate subtypes of the glutamate receptor are implicated in fast excitatory neurotransmission, whereas the NMDA receptor, quiescent at resting membrane potential, is recruited during periods of prolonged depolarization [22, 23].

Modulation of ion channels by Antiepileptic drugs [24, 25]:

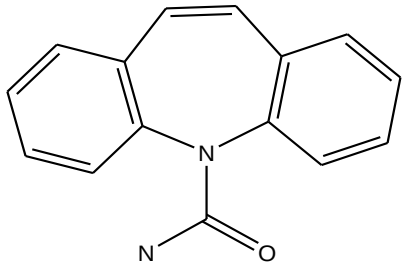
- **Phenytoin:** Phenytoin (PHT) was synthesized as a barbiturate analogue, but shelved due to poor sedative property. It has become first line treatment for partial and generalized tonic-clonic

seizures. PHT exert its anticonvulsant effect primarily by an action on voltage-dependent Na^+ channels. PHT inhibits high-frequency repetitive firing in a voltage-dependent manner, with limitation of firing increased after depolarization and removed by hyperpolarization. This is achieved prolonging the inactivated state of voltage sensitive neuronal Na^+ channel that governs the refractory period of the neurone. As a result high frequency discharges are inhibited with little effect on normal low frequency discharges which allow Na^+ channels to recover even when inactivation is prolonged. PHT has also been reported to block high voltage-activated Ca^{2+} channels to attenuate glutamate release and, paradoxically, to reduce K^+ current.



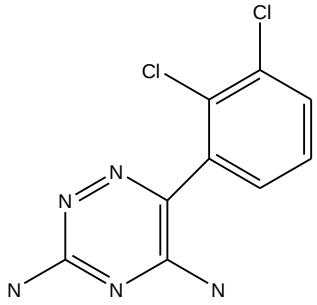
Phenytoin

- **Carbamazepine:** Carbamazepine (CBZ) is widely used in the treatment of partial and generalized tonic-clonic seizures and chemically related to the tricyclic antidepressants. CBZ modifies maximal electroshock seizures as well as raises threshold to PTZ and electro shock convulsion. Though its action on Na^+ channels (prolongation of inactivated state) it has greater binding rate constant. Inhibition of glutamatergic neurotransmission has also been implicated in the mechanism of CBZ action. It inhibits the rise in intracellular free Ca^{2+} induced by NMDA and glycine in rat cerebral granule cells and blocks veratrine-induced release of endogenous glutamate.



Carbamazepine

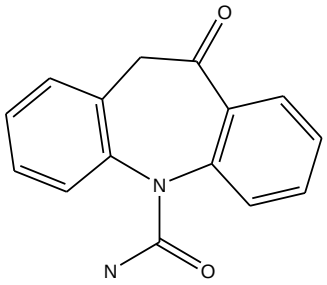
- **Lamotrigine:** Lamotrigine (LTG) is a new AEDs, it is a derivative of LTG is derivative of phenyltriazine from the group of folic acid antagonists. The main action of LTG is blockade of sodium channels. LTG acts pre- and-postsynaptically. Presynaptically, it inhibits the release of neurotransmitters, among them the excitatory amino acids Glu and Aspartate. Postsynaptically, it diminishes the excitability of neurons like other anticonvulsive sodium channel blockers. Apart from inhibiting the sodium conductance LTG may reduce high-voltage activated calcium currents. LTG is a broad spectrum Antiepileptic agent. Initially found useful as add on therapy in refractory cases of partial seizures and GTCS, it has now been shown effective monotherapy as well.



Lamotrigine

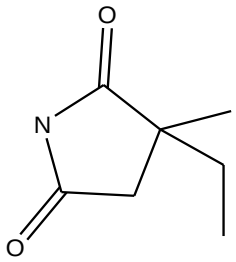
- **Oxcarbazine:** Oxcarbazepine (OXC) is a relatively novel AED, in structure It is closely related to CBZ The keto substitutions at the 10 and 11 positions of the dibenzazepine nucleus do not affect the therapeutic profile of the drug when compared with CBZ, but result in altered biotransformation

and better tolerability. Like CBZ and PHT, OXC inhibits voltage-dependent fast sodium channels. In particular its frequency-dependent effect gives the substance special significance in seizures. Moreover, in contrast to CBZ; OXC also has favorable influences on potassium channels, calcium channels.



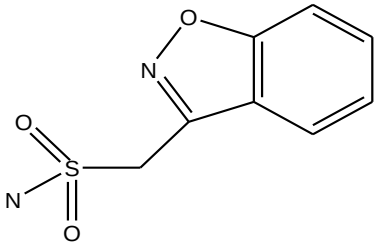
Oxcarbazepine

- **Ethosuximide:** Ethosuximide (ESM) has been used in the treatment of generalised absence seizures. The most prominent action of ESM is antagonism of PTZ induced clonic seizures at doses which produce no other discrenable action. The primary action appears to be exerted on thalamocortical system which is involved in the generation of absence seizures. The ECG in absence seizures shows characteristics bilaterally synchrhonous 3Hz spike and wave rhythm generated by oscillation of impulses between thalamus and neocortex through reverberatory synaptic connections. Thalamic neurons exhibit prominent 'T' (transient) current which is low threshold Ca^{2+} current(due to inward flow of Ca^{2+} through T type Ca^{2+} channels) that acts as the pacemaker and amplifies repetitive spikes.



Ethosuximide

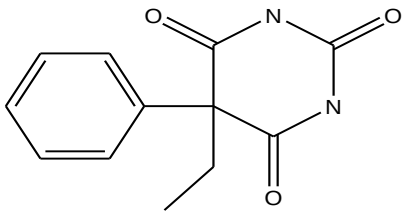
- **Zonasamide:** Zonasamide (ZNS) is a benzisoxazole with a sulfonamide side chain. The main actions of ZNS are blockade of sodium channels, reduction of voltage dependent T-type calcium currents, and Glu-induced synaptic excitation decrease. It also blocks low-threshold T-type Ca^{2+} currents, which may account for its anti-absence effects. ZNS also inhibits carbonic anhydrase, although this action is believed to be too weak to contribute to its antiepileptic effect.



Zonasamide

Potentiation of y-aminobutyric acid by antiepileptic drugs [26, 27, 28]:

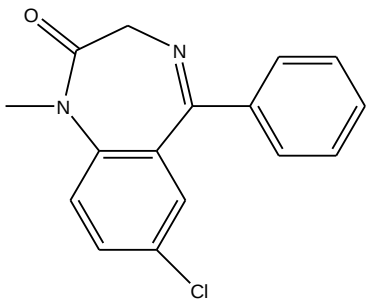
- **Phenobarbital:** Phenobarbitone (PB) was the first efficacious anti-epileptic introduced in 1912. PB is still commonly prescribed worldwide for epilepsy, although its cognitive and behavioral side effects have limited its use, particularly in the developed world. The mechanism of action of PB is due to the allosteric activation of $GABA_A$ receptor leads to increasing in the duration of Cl^- channel opening, without affecting the frequency of opening or channel conductance. Additional mechanisms of barbiturate action have been reported, including blockade of high-voltage-activated Ca^{2+} channels and an inhibitory effect on the AMPA/kainate subtype of glutamate.



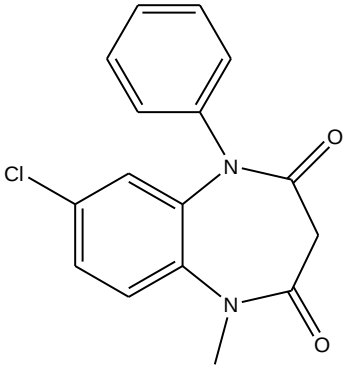
Phenobarbital

- **Benzodiazepines:** Many numbers of BZDs are presently marketed in the world. The most commonly used AEDs are Diazepam, Lorazepam, Clobazam, and Clonazepam. These Antiepileptic BZDs have the efficacy in the partial and idiopathic generalized epilepsies and for the acute epilepsies. The BZDs bind with the α-subunit of $GABA_A$ receptor, binding with these results in the activation of the receptor, which leads to the increasing in the frequency of Cl^- channel opening without affecting duration or channel conductance.

The BZDs are unable to activate the $GABA_A$ receptor directly in the absence of GABA as in the barbiturates. Augmentation of GABAergic inhibition in the thalamus can result in the de-inactivation of T-type Ca^{2+} channels, triggering a strong low-threshold burst and enhancing development of the thalamocortical rhythmicity that is characteristic of absence seizures.

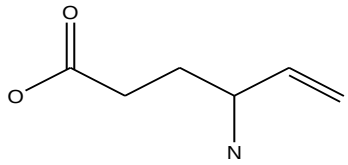


Diazepam



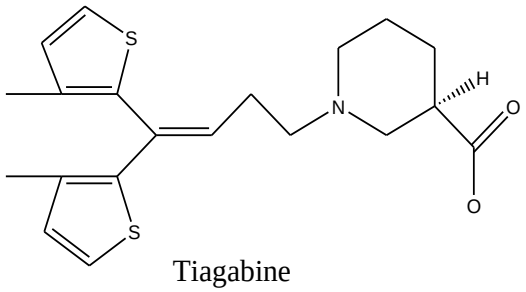
Clobazam

- **Vigabatrin:** Vigabatrin (VGB) became the first of the new generation of AEDs to be licensed in the United Kingdom. It was initially approved as adjunctive therapy for partial seizures with or without secondary generalization. It is an inhibitor of GABA-transaminase, the enzyme which degrades GABA. Anticonvulsant action may be due to increase in synaptic GABA concentration. It suppresses maximal electroshock and kindled seizures, and is effective in many patients with refractory epilepsy, especially partial seizures with or without generalization.



Vigabatrin

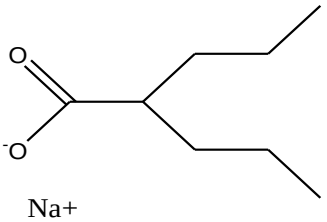
- **Tiagabine:** Tiagabine (TGB) is a novel AED, recently licensed widely for the adjunctive treatment of partial seizures with or without secondary generalization. TGB inhibits GABA uptake into synaptosomal membranes, neurones, and glial cells. It has a greater affinity (2.5-fold) for glial than for neuronal uptake. TGB has a selective action on the GAT-1 GABA transporter, with little or no activity on GAT-2, GAT-3, or BGT-1. TGB potentiates GABA mediated neuronal inhibition by depressing GABA transporter GAT 1 which removes synaptically released GABA into neurons and glial cells. Maximal electroshock and kindled seizures are suppressed.



Tiagabine

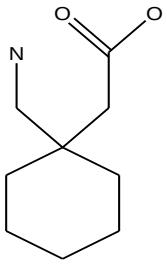
Antiepileptic Drugs with multiple mechanisms of action:

- **Sodium Valproate:** It is a branched chain aliphatic carboxylic acid with a broad spectrum Anticonvulsant action. It is more potent in blocking PTZ seizures. Valproate appears to act by multiple mechanisms: (a) Phenytoin like frequency dependent prolongation of Na^+ channel inactivation, (b) Weak attenuation of ca^{2+} mediated 'T' current, (c) Augmentation of release of inhibitors transmitter GABA by inhibiting degradation as well as probably by increasing its synthesis from glutamic acid. The precise most it exerts anti- epileptics effects remains to be conclusively determined. VPA may also block T-type Ca^{2+} channels in a manner similar lo that reported for ESM. Such an effect would explain its efficacy against generalized absence seizures. However, the reduction of T-type Ca^{2+} currents observed with VPA in rat primary afferent neurons is modest and requires relatively high drug concentrations.



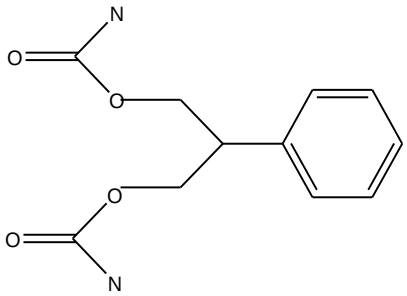
Sodium Valproate

- **Gabapentin:** Gabapentin (GBP) is a novel compound, structurally related to GABA, which is effective in the adjunctive treatment of partial seizures, with or without secondary generalization. This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_A$ receptor. Gabapentin is considered to be a first ine drug for pain due to diabetic neuropathy and post therapeutic neuralgia has some prophylactic effect in migraine also. Early efforts to identify the mechanism of action of GBP proposed an interaction with the L-amino acid transport system, resulting in alterations in the cytosolic and extracellular concentrations of several amino acids, including L-leucine, L-valine and L-phenylalanine.



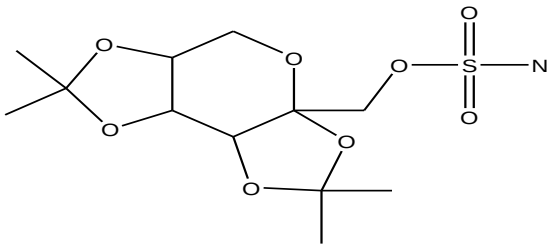
Gabapentin

- **Felbamate:** Felbamate (FBM) is a dichromate which was approved by the food and Drug Administration for partial seizures. FBM is believed to be the first effective AED with a direct action on the NMDA subtype of glutamate receptor. It inhibits NMDA/glycine-stimulated increases in intracellular Ca^{2+}, reduces inward currents evoked by NMDA application to striated neurons, and blocks NMDA receptor-mediated excitatory postsynaptic potentials. Considerable evidence suggests that FBM interacts with the strychnine-insensitive glycine recognition site on the NMDA receptor complex. FBM inhibits the binding of high-affinity glycine antagonists at this site and its anticonvulsant effects in several experimental models are blocked by glycine, and synthetic glycine site compounds.



Felbamate

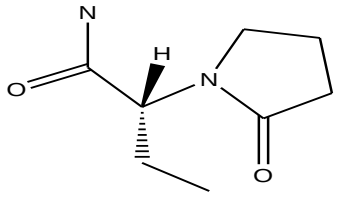
- **Topiramate:** Topiramate (TPM) the sulfamate derivative is active against partial-onset and generalized seizures in humans. TPM is a newly developed anticonvulsive substance approved for use since 1998. It is characterized by a complex mechanism of action. TPM has a broad spectrum of action it modulates voltage-activated sodium channels and cation influx through AMPA and KA receptor channels. Further mechanisms of action are potentiation of $GABA_A$ receptor-mediated currents and the inhibition of carbonic anhydrase isoenzymes. TPM also inhibits carbonic anhydrase, although, like ZNS, this effect is not believed to contribute to its antiepileptic action.



Topiramate

Antiepileptic Drugs with Unknown Mechanisms of Action [28, 29, 30]:

- **Levetiracetam:** Levetiracetam (LEV) is newly developed Anticonvulsants which has been approved for clinical uses. LEV is a pyrolidine, S-enantiomer of the ethyl analogue of piracetam, a widely used nootropic agent in the elderly. It has been reported that the synaptic vesicle protein SV2A with a mass of about 90 kDa is the specific LEV binding site. This suggest, together with the strong correlation between binding affinities of LEV and LEV derivatives and their anti-seizures potencies, that LEV acts by modulating the exocytolic function of SV2A. Thus, LEV possibly enhances the release of inhibitory neurotransmitter. LEV possesses a presynaptic mechanism of action of distinct from that of the other AED. *LEV* and LTG were able to reduce both amplitude and duration of PDSs, as well as concomitant elevation in intracellular Ca^{2+} in a concentration-dependent fashion. At high-concentrations, beyond therapeutic relevance, LEV induced a small reduction in the peak amplitude and a prolongation of the decay phase of GABA-gated currents. Other experimental work indicated that neither basic cell functions nor normal neurotransmissions are changed by this substance [31].



Levetiracetam

CONCLUSION: According to the definition, epilepsies are the group of disorders. There is an immediate need to fully understand the mechanism of action of the each AEDs individually in order to understand the path physiology of the seizures and for the better treatment of the epilepsies. From the currently available evidence based on assessed data one can conclude that GBP, LEV, LTG. OXC, PGB, TPM, TGB and ZNS were *found* to be appropriate *for* adjunctive treatment of refractory partial seizures. In adults, GBP, LEV, LTG, OXC and TPM can also be used, for the treatment of refractory partial seizures in children.

The mechanism of action of anti-convulsant drugs on post-synaptic GABA receptor are Barbiturate, Benzodiazepines, Vigabatrin, Sodium Valproate, Gabapentin, Tiagabine, or through inhibition of action on voltage sensitive ion channels are Phenytoin, Carbamazepine, Lamotrigine, Topiramate, Zonisamide, or through inhibition of 'T' type calcium current are Ethosuximide, Trimethadione and Sodium Valproate. The future of the treatment of the epilepsies is centered on the mechanism of action of the individual drugs and on the patient.

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