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REVIEW ARTICLE

RECENT DEVELOPMENT IN ANTI-EPILEPTIC DRUGS

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ABSTRACT

Epilepsy is among the most common serious neurological disorder and affects at least 50 million people worldwide. Almost 30% of epileptic patients suffer from various difficulties i.e. pharmacoresistance, which is associated with social isolation, dependent behavior, unemployment, psychological issues and reduced quality of life. Considering that the conventional first-generation antiepileptic drugs took more than 70 years to license, the past 22 years have been truly amazing and there are now more than 20 antiepileptic drugs that can be prescribed on a long-term basis for the management of epilepsy. Currently available antiepileptic drugs have a limited efficacy, limited their use and difficulties in patient management. Antiepileptic drugs can provide only symptomatic relief as these drugs suppress seizures but do not have ability to cure epileptogenesis.

The long term use of antiepileptic drugs can cause adverse effects, withdrawal symptoms, deleterious interactions with other drugs and economic burden. Furthermore, some of the available antiepileptic drugs may even potentiate certain type of seizures.. This review will highlight the recent advancement in AEDs, i.e. used in the treatment and management of epilepsy.

KEYWORDS: antiepileptic, seizure, pharmacoresistance, recent developments.

ABBREVIATIONS: AEDs- Anti-Epileptic Drugs, EEG- Electro Encephalogram, AS- Absence Seizure, MS- Myoclonic Seizure, CAE- Childhood Absence Epilepsy, JAE- Juvenile Absence Epilepsy, JME- Juvenile Myoclonic Epilepsy, MAE- Myoclonic Absence Epilepsy, IGE- Idiopathic Generalized Epilepsy, NISCARE - National Institute of Science Communication And Information Resources, NML - National Medical Library.

INTRODUCTION:

Anticonvulsants are drug which inhibit discharge and then produce hypnosis. The drugs act either by altering the permeability of all the membranes to ion or by modifying the neurotransmitters of the brain.[1] Epilepsy is perhaps one of the oldest recorded medical illnesses in history. In ancient times, epilepsy was described as a condition representing an evil state of mind or possession. People have known about epilepsy for thousands of years but have not understood it until recently. The ancient ***Babylonians & Romans*** wrote about the symptoms and causes of epilepsy 3000 years ago.[2] They thought that seizures were caused by demons attacking the person. Different spirits were thought to cause the different kinds of seizures.

In 400 BC, ***Hippocrates***, the Father of Medicine, wrote a book saying that people do not get epilepsy from the gods, because that would be thinking bad of the gods. His cure for epilepsy was medicine and diet based on his own unscientific theories of the balance between hot and cold[3-4]. ***Hippocrates*** linked the seizures to a problem in brain function more than 2,000 years ago. The first modern definition of epilepsy was given in 1875 by ***Hughling Jackson***, who recognized a seizure as being due to disordered brain electricity, which can alter consciousness, sensation, and behavior.[5] The discovery of the EEG in the 1920s helped in correlating the neuronal activities to the behavioral disorders.[6] During the last two decades, several new antiepileptic drugs and improved formulations of older drugs have been licensed for the treatment of epilepsy.[7]

According to ***Cheymol*** (1950), convulsion arises due to a sudden excessive and rapid discharge in the gray matter of the brain. Convulsion have the focal origin, the form of seizures depending on the site of focus in the brain.[8] When the cause is not identified or found it is classified as either idiopathic or cryptogenic epilepsy. Approximately 30% of epilepsy is associated with neurocysticercosis in developing countries. Poor sanitation

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and the consumption of contaminated foods, including vegetables and undercook meat, other parasites, malariasis, toxoplasmosis and toxocariasis can cause not only acute symptomatic seizure but also symptomatic epilepsy.[9] Typical absence seizure (AS) constitute about 10% of seizures in children with epilepsy. The commission on classification and terminology of the **International League Against Epilepsy** recognizes four epileptic syndrome with typical AS: Childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and myoclonic absence epilepsy (MAE). Valproate and Ethosuximide are the most commonly used drugs for AS.[10]

Valproate is considered the drug of choice in JME. Lamotrigine used to be considered a second line drug, reserved for intractable AS but its use has increased with time. It is especially valued in situation where sodium valproate leads to weight gain and also for women of childbearing age.[10] Idiopathic generalized epilepsy (IGE) are genetically determined and affect normal people of both sexes and races. They manifest with generalized tonic-clonic seizures, typical absence seizures and myoclonic jerks alone or in varying combination and severity. Monotherapy is considered to be the goal in the first line pharmacologic management of epilepsy as it is effective, well tolerated and associated with low costs, better patient, compliance and higher quality of life. Although conventional anti-epileptic drug (AED) valproate, and modern AED lamotrigine are identified as optimal first line or second line monotherapy for idiopathic generalized epilepsies, effectiveness and course of treatment vary between the patient. Valproate is a very effective AED for IGE however it carries some risk related with its side effects profile.[11] In children with intractable, surgically approachable epilepsy, the ketogenic diet is often perceived as less efficacious than surgery. For over 80 years, the ketogenic diet has been used to treat children with intractable epilepsy.[12] ***Goodyer*** used first time the term 'convulsion' in his translation. In 17th century English medicine, as for instance in *Willis's Pathologiae cerebri* (pathology of the brain and nervous stock), the word convulsion seems to have been used to embrace various non-epileptic muscle contraction, spasm and other involuntary movements rather than epileptic phenomena.[13]

EPIDEMIOLOGY OF EPILEPSY:

Around 50 million people in the world have epilepsy and approximately 5% of the general population experience at least one seizure, excluding febrile seizures. The prevalence of epilepsy is around 0.5-1%[14], and its overall annual incidence ranges from 50-70 cases per 100,000 in industrialized countries and up to 190 per 100,000 in developing countries. Mortality in epileptic patients is two- to three-times that of the general population, and **sudden unexpected death in epilepsy** (SUDEP) is the most important direct epilepsy-related cause of death. SUDEP is defined as a non-traumatic and non-drowning death in patients with epilepsy that is sudden, unexpected, witnessed or unwitnessed, and with or without evidence of a seizure [15]. Risks for SUDEP are higher if patients are male, 20-40 years of age, have generalized seizures, and are pharmacoresistant. [16] The incidence of epilepsy is higher in childhood and in the elderly than in young people.[17-18] Epilepsies in early childhood frequently are difficult to treat. This may depend on physiological immaturities in ion homeostasis and other developmental characteristics, but also on the severity of early onset epilepsy. Neonatal brain dysfunction and its behavioral expression may originate in the antepartum period.[19-20] Epileptic seizures are considered as the third most frequent neurological problem encountered in the elderly [21]. Treatment of epilepsy in the elderly is complicated since these patients are very often prescribed other long term medication for disorders other than epilepsy that may result in deleterious drug interactions [22].

ETIOLOGY OF EPILEPSY:

Epileptic seizures are result from hyperexcitable neurons caused by:

1. Increased activity of voltage-gated ion channels (e.g., Na+, K+ & Ca++ channels)

2. Decreased inhibitory (i.e., GABA) neurotransmission

3. Increased excitatory neurotransmission (i.e., glutamate receptors)

4. Alteration of extracellular ion concentration (e.g., potassium, calcium).

Table 1: CLASSIFICATION OF SEIZURE:

Seizure Type	Frequency	Loss of consciousness	Duration	Features
Partial (Focal)				
Simple partial	10%	No	20-60 Sec	Focal motor (specific muscle groups), sensory (e.g., tingling, hot or cold sensations) or speech disturbances
Complex partial	35%	Impaired	30-120 Sec	Complex symptoms; confused behavior, dreamy state, amnesia; often associated with automatisms (purposeless movements).
Partial with generalized tonic-clonic seizure	10%	Yes	60-120 Sec	Simple or complex partial seizure evolves into loss of consciousness, rigid extension of trunk and limbs (tonic), then rhythmic contraction of arms and legs (clonic).
Generalized				
Tonoc-Clonic (grand mal)	30%	Yes	1-5 min	Loss of consciousness; massive contraction of skeletal muscle; rigid extension of trunk and limbs (tonic; posture called opisthotonos), then rhythmic contraction of arms and legs (clonic).
Absence (petit mal)	10%	Impaired	< 30 sec	Abrupt brief onset of impaired consciousness, cessation of activities and staring. Characteristic 3 per second spike and wave pattern on EEG. Commonly in children (3 - 15 years old).
Myoclonic	< 3%	No	1-5 sec	Brief, shocklike contraction of muscles; may be restricted to part of extremity or may be generalized. Can occur in clusters for several min.
Atonic/Akinetic	< 2%	Yes	5 sec- min	Sudden loss of postural tone leading to sagging of the head or falling. Sudden freezing of motion (called “akinetic”)
Status Epilepticus	7%	Usually	>5 min	A state of continuous seizure (of any type) of > 5 min **or** 2 or more discrete seizures between which baseline consciousness is not regained. This is a medical emergency that can be fatal up to 35% of the time

PHARMACORESISTANT EPILEPSY:

Pharmacoresistance may be defined as poor seizure control despite accurate diagnosis and carefully monitored pharmacologic treatment. Clinically available anticonvulsant drugs fail to control seizures in around 30% of epileptic patients. About 75% of patients diagnosed with mesial temporal lobe epilepsy have pharmacoresistant seizures and more than 50% of patients with Lennox–Gastaut syndrome are classified as pharmacoresistant.[23] The condition is more complicated in certain brain abnormalities, for example, when hippocampal sclerosis is combined with focal dysplasia.[24] Despite the introduction of new drugs, the problem of pharmacoresistance has not been solved, although most of the new drugs have better safety profiles than those of older drugs. Surgical treatment of epilepsy may be an alternative, but at present, surgery is possible in only a small proportion of pharmacoresistant patients and after the surgery most of the patients are still prescribed antiepileptic drugs for full seizure control. It is not well established, why and how epilepsy becomes drug resistant in some patients while others with seemingly identical seizure types and epilepsy syndromes can achieve seizure control with medication. Thus, there is a clear need to understand the pathomechanisms involving epilepsy and new drugs with improved efficacy and safety profile for pharmacoresistant patients. Three major pathomechanisms have been proposed to explain pharmacoresistance in around 30% of patients: disease-related, drug-related mechanism and genetics mechanism.[25] However the detailed mechanisms leading to pharmacoresistance is still unknown.

HISTORY OF AEDs DEVELOPMENT:

Epileptic disorders have been treated for thousands of years with a variety of herbs.[26] **Potassium bromide** was the first single compound in 1850, which was used for the treatment of epilepsy.[27] These were used regularly for the next 50 years, despite their limited efficacy and terrible side effects. Phenobarbital was the second single compound (1912) discovered for the first clinical use in the treatment of epilepsy. Its anticonvulsant properties were accidentally discovered in 1912 by ***Alfred Hauptmann***, who originally used it as a tranquilizer for his epileptic patients and found that phenobarbital attenuated the epileptic attacks of these patients.[28] Since that time phenobarbital has been widely used as an antiepileptic drug worldwide.[29]

The use of a ketogenic diet was introduced for the treatment of epilepsy in the 1920s.[30] This special diet, which has high fat, low protein, and negligible amounts of carbohydrate content, was prepared to mimic some of the characteristics of fasting, a state known to decrease seizures in some individuals.[31] Phenytoin (one of the drugs of first choice for generalized tonic, clonic and partial seizures) was the first antiepileptic drug discovered using an animal seizure model. Phenytoin was synthesized in 1908, and was recognized as a first non sedating antiepileptic drug after the pioneering studies of ***Merritt and Putnam*** using an electroshock-induced seizure model in cats.[32] Since then electroshock-induced seizure model has been used for identifying the new compounds for the treatment of epilepsy and drugs that are effective in blocking tonic hind limb extension in animals induced by electroshock generally have been found to be effective against generalized tonic-clonic seizures in human beings.[33] Trimethadione, the first treatment specifically for absence seizures was licensed in the 1940s, following laboratory evaluation with the pentylenetetrazole animal seizure model by ***Richards and Everett*** in 1944[34] and clinical evaluation by ***Lennox*** in 1945[35].

Primidone was introduced as an antiepileptic drug in the 1950s. Ethosuximide was introduced into clinical practice in 1960 and has been the drug of choice for children with absence seizures.[36] Diazepam, widely used for the treatment of status epilepticus, was introduced in the late 1960s.[37] Carbamazepine was synthesized by ***Schindler*** in 1953[38] and was first marketed as a drug to treat trigeminal neuralgia in the 1960s. Later its antiepileptic effect was discovered and it was marketed as an antiepileptic drug in the 1970s.[39] Valproic acid was marketed in the late 1970s following a serendipitous discovery in 1963, when it was used as a solvent for a number of other compounds that were being screened for anticonvulsant activity.[40] During the last two decades, several new drugs have been licensed for the treatment of epilepsy including felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide, stiripentol, clobazam, vigabatrin, and lacosamide. In addition, new formulations of older drugs have also been marketed including fosphenytoin, a pro-drug of phenytoin, and a sustained-release preparation of carbamazepine. In current times research is not only focused on chemical compounds, but also on implantable antiepileptic devices, which are under investigation.[41]

LIMITATION OF AEDs:

Currently available antiepileptic drugs have limited efficacy and their negative properties limit their use and cause difficulties in patient management. Antiepileptic drugs can provide only symptomatic relief, these drugs suppress seizures and have no effect on the epileptogenesis, which is a process that converts the normal circuitry of the brain into a hyperexcitable one,

often after an injury. The long term use of antiepileptic drugs is limited due to their adverse effects, withdrawal symptoms, deleterious interactions with other drugs and economic burden, especially in developing countries.

Unexpected visual field defects have been observed in patients taking vigabatrin a few years after its introduction to the market[42] and in a high number of individuals felbamate unexpectedly caused aplastic anemia, hepatitis and hepatic failure, which were not observed during clinical trials with this drug. [43] Phethenylate was withdrawn because it was producing hepatic necrosis, benzchlor-propamide demonstrated toxic effects with long-term use in animals, and aminoglutethimide was linked to the high incidence of goiter.[37] Allergic rashes occur in approximately 5% of patients with the use of ethosuximide[44]. The older antiepileptic drugs exhibit more serious side effects than newer antiepileptic drugs. The main limitation of phenobarbital is its tendency to alter cognition, mood, and behaviour. With phenytoin and carbamazepine treatment vestibulocerebellar symptoms, such as ataxia, diplopia, nystagmus, and vertigo, are common. Ethosuximide most commonly causes gastro-intestinal symptoms, drowsiness, and headache.

Table 2: There are following other several drugs which have severe side effects.

DRUGS	CLINICAL USES	ADVERSE EFFECTS
Phenobarbital	Partial and generalized seizures (ineffective against AS), status epilepticus	Sedation, lethargy, dysarthria, skin rashes, reduced libido, osteomalacia, cognitive problems, insomnia (in children), distractibility (in children), hyperkinesia (in children), irritability (in children), hepatoxicity, teratogenicity
Phenytoin	Partial seizures, generalized tonic-clonic seizures, status epilepticus, (ineffective against AS and MS)	Ataxia, diplopia, nystagmus, coarsening of facial features gingival hyperplasia, hirsutism, skin rashes, Stevens–Johnson syndrome, Dupuytren's contracture, agranulocytosis, aplastic anemia, hepatoxicity, teratogenicity
Ethosuximide	Absence seizures	Gastrointestinal changes, drowsiness, lethargy, mood changes, headache, visual changes, aplastic anemia, agranulocytosis
Carbamazepine	Partial seizures, generalized tonic-clonic seizures, (ineffective against AS and MS)	Diplopia, dizziness, headache, ataxia, nystagmus, skin rashes, hyponatremia, aplastic anemia, agranulocytosis, weight gain, Stevens–Johnson syndrome, osteomalacia, hepatoxicity, teratogenicity
Benzodiazepines	Status epilepticus, partial and generalized seizures	Sedation, lethargy, drowsiness, dizziness, behavioral disturbances in children, hypersalivation
Valproic acid	Partial and generalized seizures	Tremor, weight gain, dyspepsia, diarrhoea, peripheral edema, pancreatitis, hair loss, thrombocytopenia, agranulocytosis, polycystic ovaries, Stevens–Johnson syndrome, hepatoxicity, teratogenicity
Gabapentin	Adjunct for partial seizures (ineffective against AS and MS)	Drowsiness, dizziness, ataxia, fatigue, hyperactivity (in children), weight gain
Lamotrigine	Adjunct for partial and generalized seizures	Dizziness, sedation, headache, diplopia, ataxia, skin rash, Stevens-Johnson syndrome
Vigabatrin	Infantile spasms, refractory partial seizures (ineffective against AS and MS)	Drowsiness, dizziness, ataxia, tremor, lethargy, insomnia, Irritability and hyperactivity (in children), psychosis and depression, weight gain, visual field defects and blindness
Oxcarbazepine	Partial seizures, generalized tonic-clonic seizures (ineffective against AS and MS)	Drowsiness, dizziness, diplopia, headache, fatigue, GI distress, hyponatremia, skin rash, Stevens-Johnson syndrome
Topiramate	Adjunct for partial and generalized Seizures	Cognitive problems, word finding difficulty, kidney stones, paresthesias, anorexia, weight loss, glaucoma

CHALLENGES TO AEDs DEVELOPMENT:

The development of new drugs is costly and risky. The chances for successful completion of development and approval by the regulatory authorities are less than 10%, even for those drugs which are in Phase 1a stage.[45] The biggest hurdle is our incomplete knowledge of the mechanisms of AEDs resistance[46] which prevents mechanism-driven drug development. Hypothesis of drug resistance is depend on changes in brain uptake of AEDs, structural brain alteration and changes in drug target.[47] Since the discovery of phenytoin in 1938, the development of new AEDs has relied on testing in animals. Animal models with a similarly high predictive value do not exist for other CNS disorders, such as migraine or bipolar disorder and in particular models based on electrically or chemically induced seizures in rodents have been crucial for discovering all the new AEDs since phenytoin. Levetiracetam, although inactive in the standard maximal electroshock and pentylenetetrazole models, was effective in the kindled-rat model, which led to increased interest in the assessment of potential new AEDs in more chronic models (eg, kindling) and in the reintroduced 6 Hz psychomotor activity model.[48] The use of current animal models in the discovery of new AEDs has advantages and disadvantages. The **advantages** include the use of intact rodents as easy models that detect anticonvulsant effects regardless of the mechanisms of action. Maximal electroshock and pentylenetetrazole testing can be used in highthroughput screening, as shown by the **National Institutes of Health Anticonvulsant Screening Program**, which has screened 27 000 potential compounds since 1974.[49] The **disadvantages** relate to the idea that conventional models are likely to identify more of the same new AEDs—eg: drugs that share characteristics with existing drugs, and are unlikely to have an effect on refractory epilepsies. Finally, animals have modest value for predicting human tolerability.

A new AEDs is successful if it has at least one of the following properties: greater efficacy than other drugs, the ability to prevent or delay the onset of epilepsy (epileptogenesis), or at least modify its progression, broad usefulness in non-epileptic CNS disorders, fewer adverse effects than available drugs, and ease of use, such as rapid titration, linear pharmacokinetics, lack of drug interactions, or a longer half-life that enables once or twice daily doses or extended protection if a dose is missed.[50]

RECENTS IN CLINICAL DEVELOPMENT:

More than 20 compounds are at various stages of clinical development. These drugs include with chemical structures that do not resemble existing AEDs, and derivatives of existing drugs that are developed with potentially improved properties.[51]. Some of these compounds are being investigated by medium to large pharmaceutical companies that already have leading products for epilepsy on the market. The large number of drugs currently in clinical trials provides a measure of hope for patients whose epilepsy is not controlled with currently available medication. In the future, this range of antiepileptic drugs will probably increase because of the use of new animal models, discovery of new basic mechanisms of epileptogenesis, acceleration of proof of principle studies in people, and development of new methods of drug delivery.

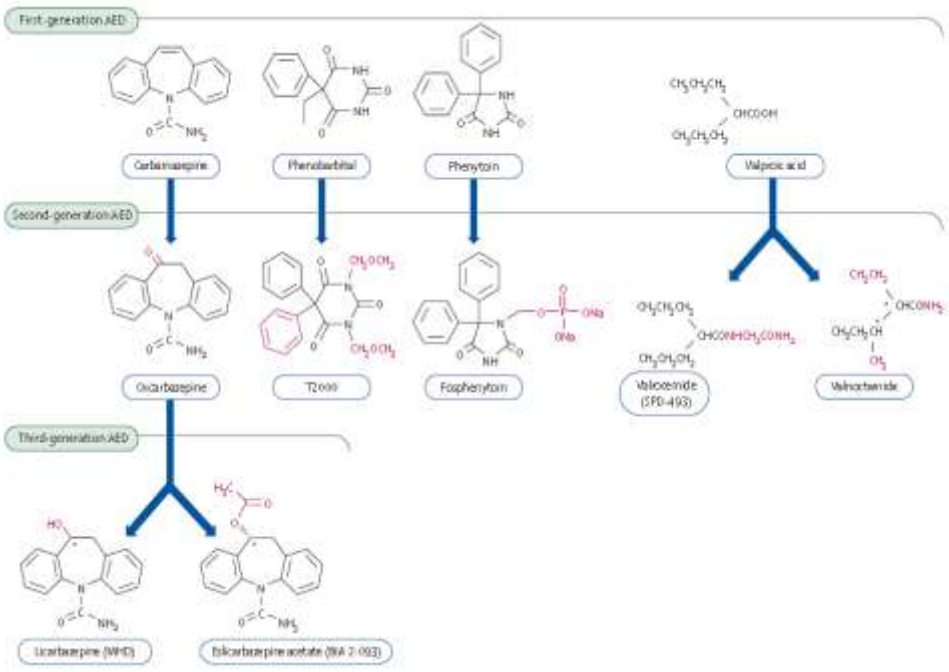

Figure 1: Derivatives of antiepileptic drugs (AEDs) introduced before 1970.

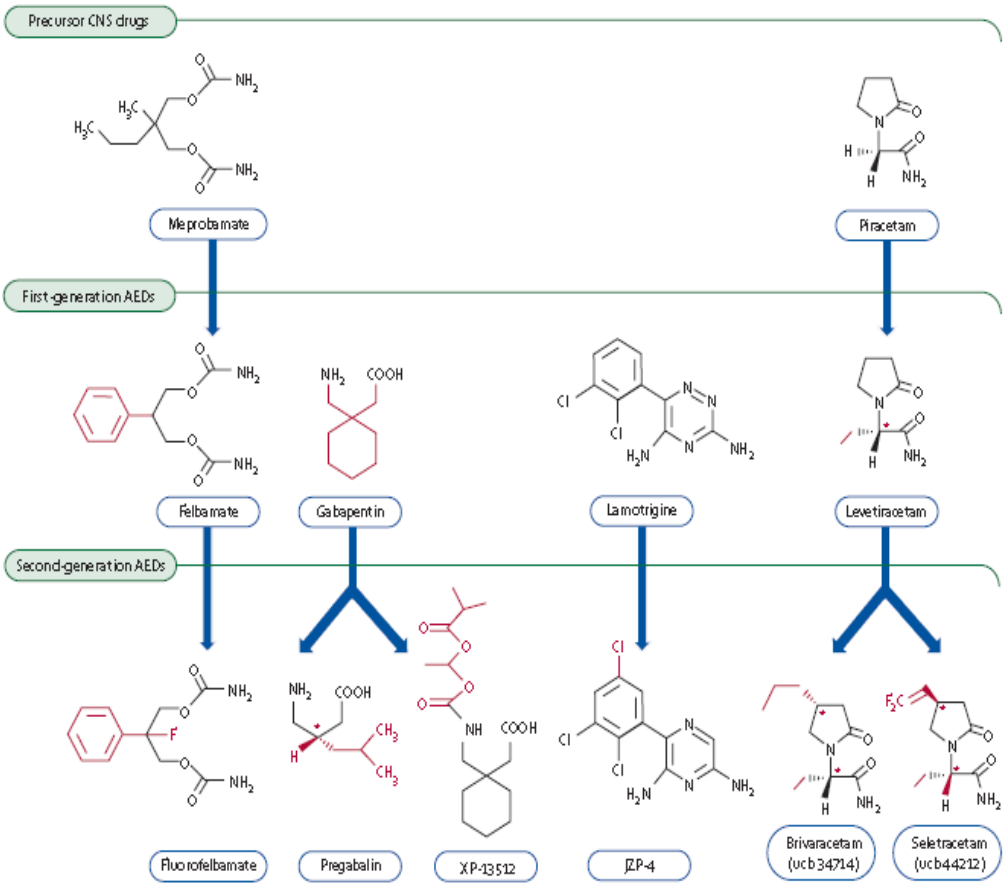

Figure 2: Derivatives of antiepileptic drugs (AEDs) introduced after 1990.

Mechanisms of Action of Antiseizure Drugs:

Major known mechanisms by which antiseizure drugs work:

1. Prolong Inactivation state of voltage-dependent Na+ channels in a use-dependent fashion.

2. Increase the effectiveness of inhibitory GABA transmission via the GABAA receptor.

3. Inhibition of Ca++ currents through T-type Ca++ channels.

4. Inhibition of excitatory glutamate transmission via ionotropic receptors.

1. Prolongation of Na+ channel inactivation state by antiseizure drugs: A, resting state in which Na+ channel activation gate (A) is closed. **B,** Arrival of an action potential causes depolarization and opening of activation gate (A) and Na+ flows into the cell. **C,** As depolarization continues, an inactivation gate (B) moves into the channel. Some antiseizure drugs (black box; e.g., phenytoin) prolong the inactivated state of the channel, presumably by preventing reopening of the inactivation gate.

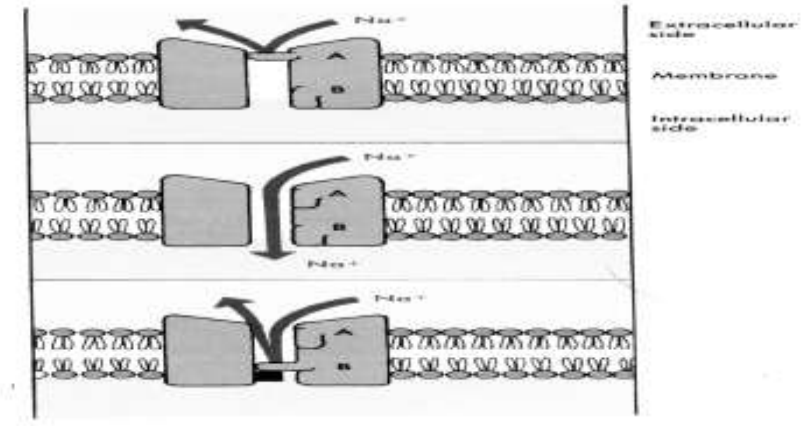

Figure 3: Prolongation of Na+ channel inactivation state by antiseizure drugs

2. Enhancement of GABA transmission by antiseizure drugs: In the presence of the transmitter GABA, the GABAA receptor opens, allowing an influx of Cl^-, which in turn, increases membrane polarization (hyperpolarizes), reducing the likelihood of firing of the neuron. Some antiseizure drugs work by reducing the metabolism of GABA. Others act at the GABAA receptor, enhancing Cl^- influx in response to GABA.

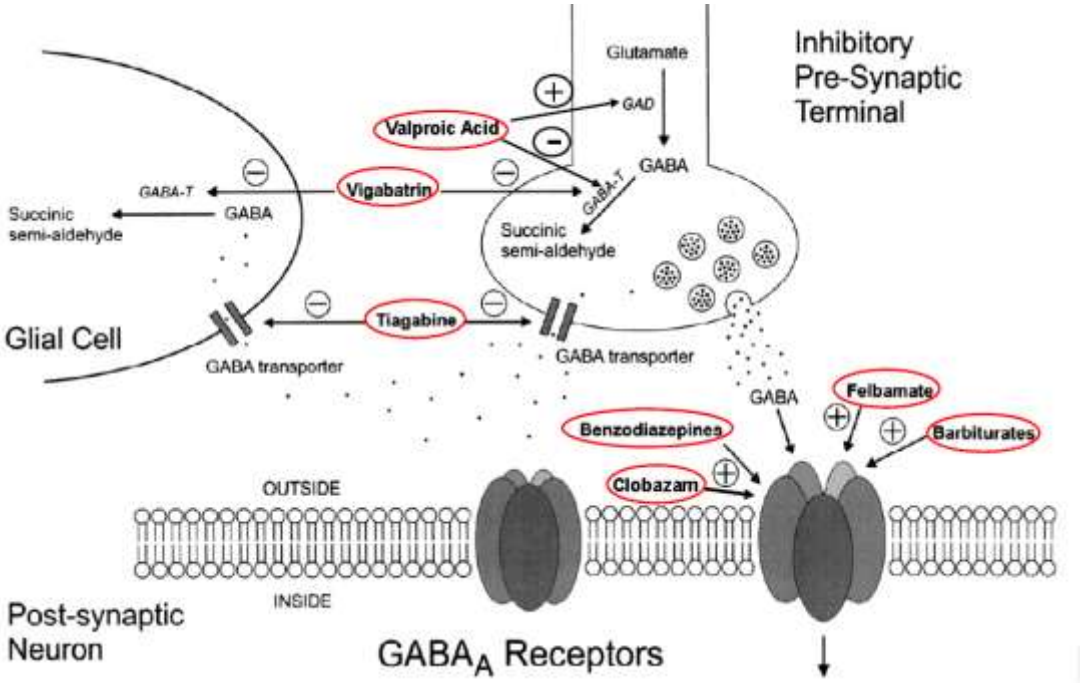

Figure 4: Enhancement of GABA transmission by antiseizure drugs

3. Reduction of current through T-type Ca++ channels by antiseizure drugs: Some drugs reduce the flow of Ca++ through T-type Ca++ channels, thus reducing pacemaker current that underlies the thalamic rhythm in spikes and waves seen in generalized absence seizures.

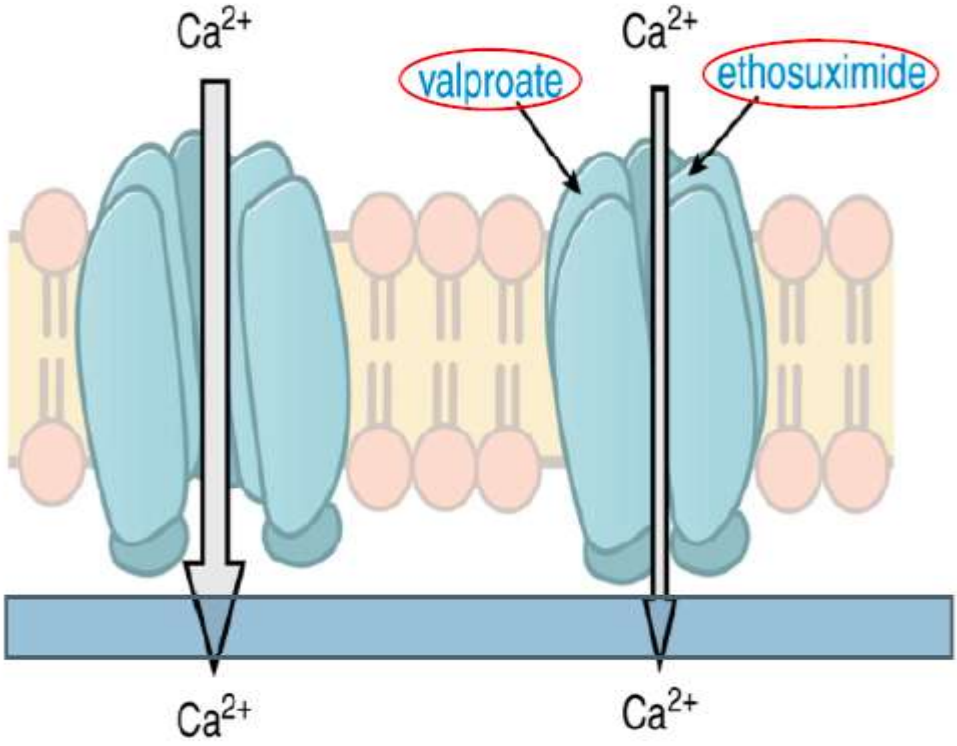

Figure 5: Reduction of current through T-type Ca++ channels

4. Effect of Antiseizure Drugs on Glutamate Receptors: Antiseizure drugs that reduce sodium channel transmission will indirectly affect glutamate transmission by decreasing the amount of transmitter released from the presynaptic terminal. Felbamate and Topiramate are weak antagonists directly on the postsynaptic glutamate receptors.

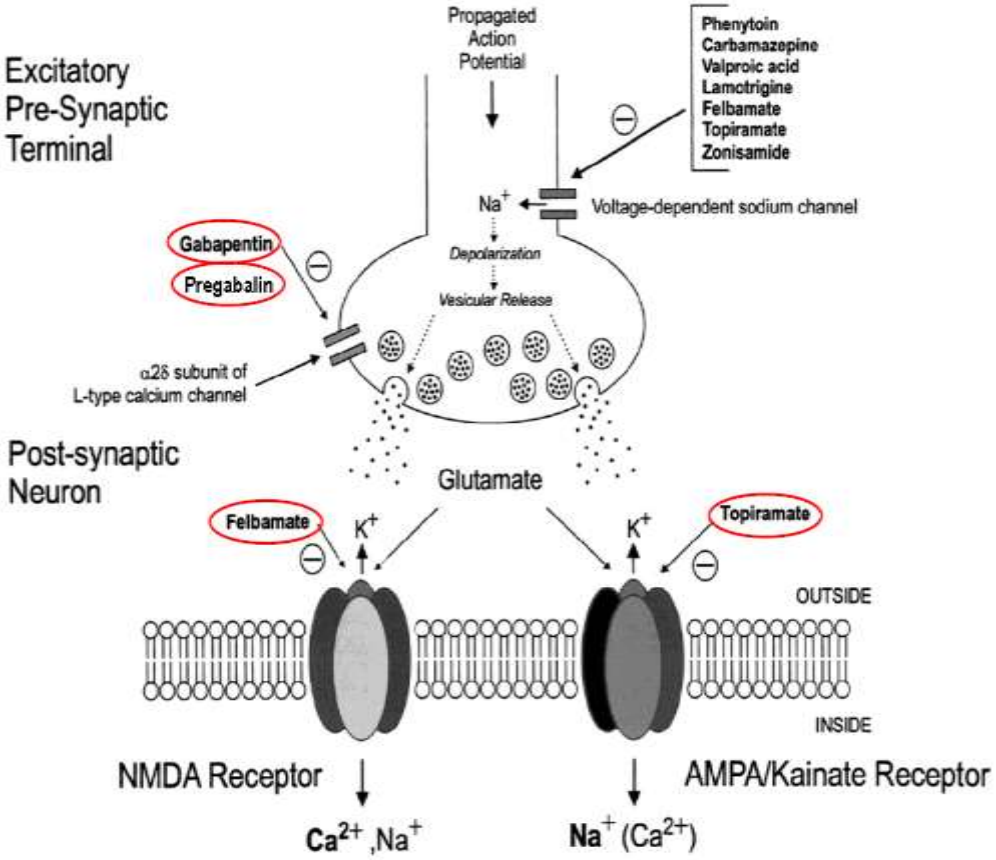

Figure 6: Effect of Antiseizure Drugs on Glutamate Receptors

RESULT & CONCLUSIONS:

In conclusion, despite the huge funding and development of new antiepileptic drugs, 30% of patients are still pharmacoresistant. Currently there is no drug which can prevent epileptogenesis. The treatment of pharmacoresistant patients usually requires polytherapy, therefore these patients are at increased risk of severe side effects and deleterious drug interactions. Hence, there is a need to understand the mechanism of pharmacoresistance and development of new pharmacoresistant animal models which can provide us a new drug with better efficacy and safety profiles than those of older drugs. Any new antiepileptic drug should also be cost effective and display longer duration of action as these properties will improve patient compliance.

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