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Current therapeutic approaches to epilepsy

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Abstract

Epilepsy is one of the most common ailments of man with a prevalence of approximately 1%. It is estimated that 50 millions person's worldwide may have this disorder. Although many are well controlled with available therapies, perhaps one quarter of the total continue to have seizures. Anticonvulsant drugs are the mainstay of epilepsy management and may have to be taken for life. In more than 20% of those affected, chronic in aractable (refraction) epilepsy develops. This necessitates the use of combination therapy. But the use of these drugs in combination is plagued by cognitive impairment and drug interactions with the results that only about 10% of the patients with refractory epilepsy seem to benefit substantially from polypharmacy. The last past two decades has brought many advances to the treatment of epilepsy, including many new pharmacological agents. So substantial data has been collected both chemically as well as pharmacological point of view. Hopefully this will be helpful for Primary care physicians and as well as those involved in epilepsy patients care. Therefore they should be familiar with the new options available.

Key-Words: Epilepsy, Seizures, Anticonvulsant drugs, Polypharmacy

Introduction

The term "epilepsy" refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. The term "seizure" refers to a transient alteration of behaviour due to abnormal excessive, hyper synchronous discharges from an aggregate of CNS neurons.

Seizure can be of following types:

a) Non epileptic - when evoked in a normal brain by the treatment such as electric shock or chemical convulsants.

b) Epileptic - when occur without evident provocation.

The epilepsies are common and frequently devastating disorder, affecting approximately 0.5 to 1% of the population. More than 40 distinct forms of epilepsy have been identified. The incidence increases again, epilepsy begins before the age of 18 in over 75% population. Seizure, the characteristic event in epilepsy is associated with the episodic high frequency discharges of impulses by a group of neurons in the brain. What starts as local abnormal discharges may then spread to other areas of the brain. The site of primary discharge and extent of its spread determines the symptoms that are produced, which range from a brief lapse of attention to a full blown convulsive fit lasting for several minutes.

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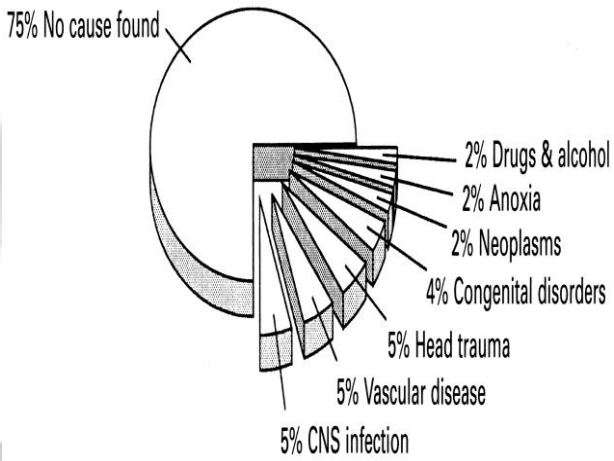
The particular symptoms produced depend on the function of the region of the brain that is affected. Thus involvement of the hypothalamus causes peripheral autonomic discharges and involvement of the reticular formation in the upper brain stem that leads to loss of consciousness[1].

Aetiology

Usually there is no recognizable cause (idiopathic), although it may be develop as a consequence of various kinds of brain damage, such as trauma, infection or tumour growths[2].



Classification of Epileptic Seizures

Epilepsy is classified in several ways:

1. Clinical events (usually seizure type).

2. Electro encephalographic changes (EEG).
3. Aetiology
4. Pathophsiology
5. Anatomy
6. Age

The widely adopted method is the classification of seizures type in which only EEG data is taken into account. This scheme was introduced in 1969 by international league against epilepsy (ILAE) and was revised in 1981[1-3].

I. Generalized seizures[2]	II. Partial seizures [2]	III. Unclassified epileptic seizures
A. Tonic–clonic seizures (grand mal) B. Tonic seizures C. Clonic seizures D. Absence seizure (petitmal) E. Myoclonic seizure F. Atonic seizures (astatic)	A. Simple partial seizures i) With motor signs ii) With somatosensory or special sensory hallucination iii) With automatic symptoms and signs iv) With Psychic symptoms B. Complex partial Seizures i) Simple partial onset followed by impairement of conciousness. ii) With impaired conciousness on onset C. Partial seizures evolving to secondary generalized seizures.	

Basic mechanisms of seizures initiation and propagation

Partial seizure activity can begin in a very discrete region of cortex and then spread to neighbouring regions i.e., there is a seizure initiation phase and a seizure propagation phase. Studies of experimental models of these phases suggest that the initiation phase is characterized by two concurrent events in aggregate neurons.

1. High frequency burst of action potential and
2. Hypersynchronization

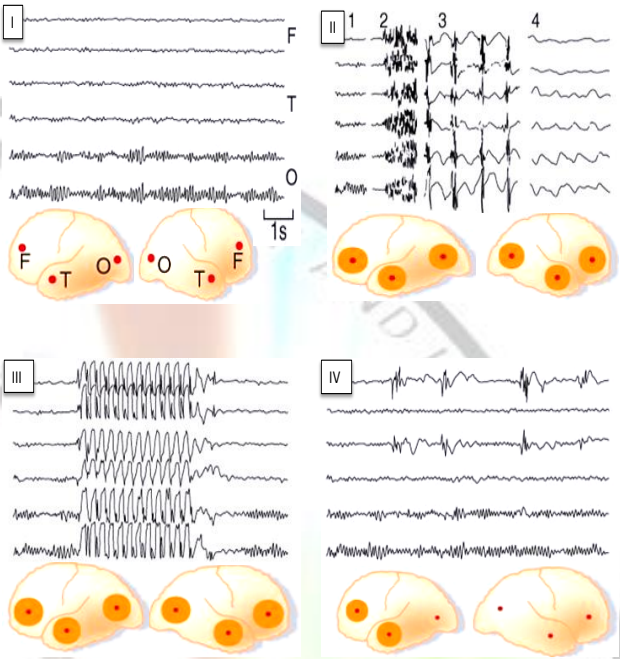


Fig. 1: Types of epileptic seizures. I. Normal; II. Generalized tonic-clonic seizures; III. Absence seizure; IV. Partial seizure.

The bursting is caused by a relatively long lasting depolarization of the neuronal membrane due to influx of extracellular calcium (Ca^{2+}), which leads to the pening of voltage dependent sodium (Na^{2+}) channel: influx of sodium and generation of repetitive action potentials. This is followed by a hyperpolarizing after potential mediated by GABA receptors of potassium channel depending on the cell type.

The synchronized bursts from a sufficient number of neuro result in a so called spike discharge on the EEG. Repetitive discharges of neurons lead to the following

- An increase in extracellular K^+, which blunts the activity of hyperpolarization and depolarizes neighbouring neurons.
- Accumulation of Ca^{2+} in presynaptic terminals, leading to enhance neurotransmitter release.
- Depolarization induced activation of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca^{2+}influx and neuronal activation.

The recruitment of a sufficient number of neurons leads to a loss of the surrounding inhibition and propagation of seizure activity into contiguous areas via local cortical connection and to more distant areas via long commissural pathways such as the corpus callosum.

Epileptogenesis

Epileptogenesis refers to the transformation of normal neurons network into one that is chronically hyperexcitable. For example, there is often a delay of month to year between an initial injury such as trauma, stroke or infection and the first seizure. The injury appears to initiate a process that gradually lowers the seizure threshold in the effected region until a spontaneous seizure occurs. Pathologic studies of the hippocampus from patients with temporal lobe epilepsy (MTLE) are related to structural change in neuronal networks. For example many patients with MTLE syndrome have a highly selective loss of neurons within the dentate gyrus. In response, to the loss of neurons, there is recognition or "spouting" of surviving neurons in a way that affects the excitability of the network. Thus an initial injury such as head injury may lead to a very focal, confined region of structural change that causes local hyperexcitability.

The local hyperexcitability leads to further structure change that evolves over time unit the focal lesion produces clinically evident seizures.

Genetic cause of epilepsy

The genetic causes of a few epilepsy syndromes have recently been discovered. They are:

- ✓ Myoclonic epilepsy with ragged red fibres (MERRF) syndrome is associated with a mutation of mitochondrial lysine.
- ✓ Mutation in the cystation B give may cause another form of progressive myoclonus epilepsy.
- ✓ Mutation with gene encoding the B4 subunit of the acetyl choline receptor appears responsible for a frontal lobe epilepsy syndrome.

Treatment of epilepsy

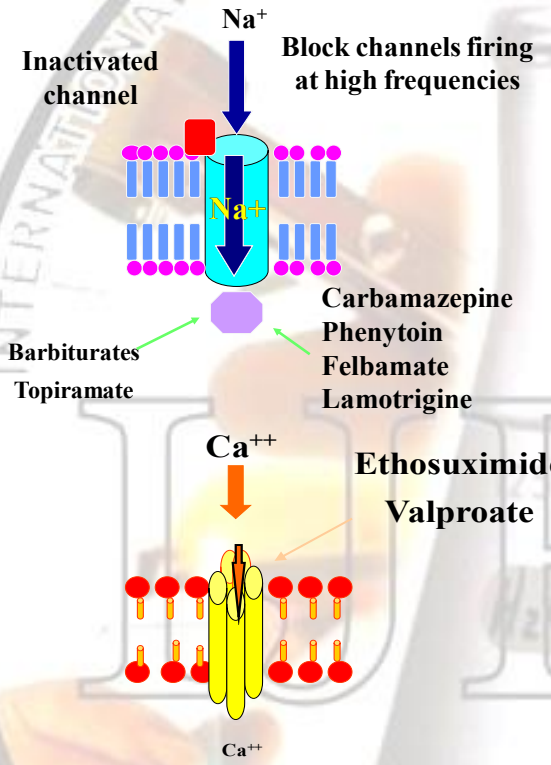
Antiepileptics are agents used medically to control the epilepsy; these are the mainstay of epilepsy management.

Classification[3,6,7,8]

Drugs	**Types of seizures Used**
1. BARBITURATES	
• Phenobarbital	Generalised tonic-clonic seizures
• Mephobarbital	Generalised tonic-clonic seizures
• Primidone	Generalised tonic-clonic seizure
2. HYDANTOINS	
• Phenytoin	Complex partial seizure
• Mephytoin	Generalised Tonic-clonic Seizures
• Ethotoin	Generalised Tonic-clonic Seizures
3. IMINOSTILBENES	
• Carbamazepine	Generalised Tonic-clonic Seizures
• Oxcarbazepine	Generalised Tonic-clonic Seizures
4. OXAZOLIDINEDIONES	
• Trimethadione	Absence Seizures
• Paramethadione	Absence Seizures
5. SUCCINIMIDES	
• Ethosuximide	Generalised Tonic-clonic Seizures
• Phensuximide	Generalised Tonic-clonic Seizures
6. ALIPHATIC CARBOXYLIC ACID	
• Valproic Acid	Generalised Tonic-clonic Seizures
• Divalproex	Generalised Tonic-clonic Seizures
7. BENZODIAZEPINES	
• Clonazepam	Absence Seizures
• Diazepam	Absence Seizures
• Lorazepam	Partial and generalised tonic clonic, absence seizure
8. NEWER DRUGS	
• Lamotrigine	Absence seizure
• Gabapentin	Absence Seizures
• Levetiracetam	Status Epilepticus
• Tiagabine	Absence seizures,Myoclonic Seizures
• Felbamate	adjuvant in partial and secondarily generalised seizures
• Topiramate	adjuvant in partial and secondarily generalised seizures
• Zonisamide	Refractory Partial Epilepsy
• Viagabatrin	Partial and Generalised Tonic Clonic Seizure
	Lennox Gastaut Syndrome
	Refractory Partial Epilepsy, Lennox Gastaut Syndrome
	Refractory Partial Epilepsy
	Partial Epilepsy

Mechanisms of action of Anticonvulsant Drugs [1,2,4]

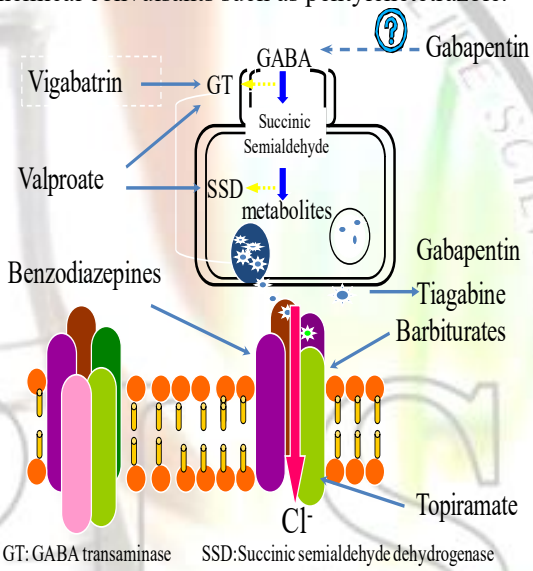
It should perhaps not be Surprising that there might be several mechanisms whereby antiepileptic drugs exert their affects. As mention above in mechanisms of imitation of seizures and propagation epileptic bursts consist of Na^+ dependent action potentials as well as Ca^{++} dependent depolarizing potential. It is now established that inhibition of sodium channels appears to be major component of the mechanism of action of several anticonvulsant drugs such as Phenytion, carbamazepine, oxcarbazepine and lamotrigine.



Reduction in the flow of Ca^{++} through T - type Ca^{++} channels in thalamus

Much current interest is also centred on the role of calcium channel since the depolarization associated with burst firing is mediated by the activation of calcium channel. The anti absence seizures like ethosuximide appears to exert its effect by inhibiting the T-type calcium channels.

The important role of synapses in mediating communication among neurons in the brain suggested that defective synaptic function might lead to a seizure. That is, a reduction of inhibitory synaptic activity or enhancement of excitatory synaptic activity might be expected to trigger a seizure; pharmacological studies of seizures supported this point. The neurotransmitters mediating the bulk of synaptic transmission in the mammalian brain are amino acids, with ϒ-aminobutyric acid (GABA) and glutamate being the principal inhibitory and excitatory neurotransmitters, respectively. Pharmacological studies also revealed that Antagonist of the $GABA_A$ receptor or Agonists of different glutamate-receptor subtypes (NMDA, AMPA, or Kainic Acid) trigger seizures in experimental animals *in vivo*. In contrast pharmacological agents that enhance GABA-mediated synaptic inhibition suppress seizures in diverse models. Glutamate-receptor antagonists also inhibit seizures in diverse models, including seizures evoked by electroshock and chemical convulsants such as pentylenetetrazole.



Several currently available anticonvulsant drugs act to facilitate the action of GABA. Clinically relevant concentaration of benzodiazepines and barbiturates enhance $GABA_A$ receptor mediated inhibition through distinct action on $GABA_A$ receptor.

Viagabatrin an anti-seizure drug is thought to exert its action by irreversibly inhibiting GABA transaminase, an enzyme that degrades GABA and thereby increasing the GABA concentration in the brain.

Another mechanism of enhancing GABA-mediated synaptic inhibition is thought to underlie the antiseizure mechanism of tiagabine. It inhibits the GABA transporter, GAT-1, and reduces neuronal and glial uptake of GABA.

Antiepileptic drugs may therefore suppress activity by any one or combination of the following mechanisms.

Act by inhibiting sodium channels e.g. Phenytoin, carbamazepine, oxcarbazepine.

- Inhibition of T-type calcium channel e.g. Ethosuximide, Valproic acid.
- Enhancement of inhibitory transmitters such as GABA e.g. Benzodiazepines, Barbiturates.

- Inhibition of Exitatory neurotransmitters such as Glutamate and Aspartate.

1. BARBITURATES:[3,4]

The anticonvulsant activity of barbiturates not related to sedation.The SAR of barbiturates show maximum activity when phenyl group at 5 position act by producing GABA like activity ,increases the conductance of chloride ions and reducing calcium dependant release of neurotransmitters .They are clinically useful for Generalised Tonic-clonic Seizures

2. HYDANTOINS:[3,4]

These are the compounds similar to cyclic ureides and barbiturates .They decrease resting fluxes of sodium ions as well as sodium currents that flow during action potentials and also decrease calcium ions influx during depolarization .They are most effective in Grand mal epilepsy.

3. IMINOSTILBENES[4]:

Carbamazepine and oxcarbazepine are related chemically to the tricyclic antidepressants. They are derivatives of iminostilbenes with a carbamyl group at the 5 position. This moiety is essential for potent antiseizure activity. They appear to act by slowing of the rate of recovery of voltage-activated Na^+ channels from inactivation. They are useful in patients with generalized tonic-clonic and both simple and complex partial seizures.

4. OXAZOLIDINEDIONES[4]:

These are compounds isoelectrically related to the hydantoins by substitution of oxygen for nitrogen atom .The alkyl substitution at C-5 is important for anticonvulsant activity. Its highly protective against PTZ induced convulsions in animals. They are clinically useful for Absence seizures.

5. SUCCINIMIDES [1,2,4]:

The screening of aliphatic and heterocyclic amides revealed high anticonvulsant activity among series of alpha n-substituted derivatives of succinimides. These drugs reduce low threshold Ca^{2+} currents in thalamic neurons. The thalamus plays an important role in generation of 3-Hz spike-and-wave rhythms typical of absence seizures. These are effective in control of petit mal epilepsy.

6. ALIPHATIC CARBOXYLIC ACIDS[4]:

Valproic Acid:

Chemically Valproic acid (*n*-dipropylacetic acid) is a simple branched-chain carboxylic acid. The action is similar to that of both phenytoin and carbamazepine and appears to be mediated by a prolonged recovery of voltage-activated Na^+ channels from inactivation. It also produces small reductions of the low-threshold (T) Ca^{2+} current that leads to limit sustained repetitive firing; this effect on T currents is similar to that of ethosuximide in thalamic neurons. Together, these actions of limiting sustained repetitive firing and reducing T currents may contribute to the effectiveness of valproic acid against partial and tonic-clonic seizures and absence seizures, respectively.

7. BENZODIAZEPINES[3]:

The benzodiazepines are employed clinically primarily as sedative-antianxiety drugs, but a large number of benzodiazepines have broad antiseizure properties. But only few have been approved for the long-term treatment of certain types of seizures. Diazepam and Lorazepam have well-defined roles in the management of status epilepticus. The antiseizure actions of the benzodiazepines occur at non-sedating doses, result in large part from their ability to enhance GABA-mediated synaptic inhibition.

8. NEWER DRUGS:

Lamotrigine[1,2]:

Chemically Lamotrigine is a phenyltriazine derivative. Lamotrigine suppresses tonic hindlimb extension in the maximal electroshock model and partial and secondarily generalized seizures in the kindling model, but does not inhibit clonic motor seizures induced by pentylenetetrazol. Mechanisms similar to those of phenytoin and carbamazepine, it blocks sustained repetitive firing of neurons and delays the recovery from inactivation of recombinant Na^+ channels.

Gabapentin[1]:

Chemically it consists of a GABA molecule covalently bound to a lipophilic cyclohexane ring. It inhibits tonic hindlimb extension in the electroshock seizure model and also inhibits clonic seizures induced by pentylenetetrazol. Its efficacy in both these tests parallels that of valproic acid and distinguishes it from phenytoin and carbamazepine. The anticonvulsant mechanism of action of gabapentin is unknown. The poorly suggested mechanism show that it may act by promoting nonvesicular release of GABA. Gabapentin is effective for partial seizures, with and without secondary generalization, when used in addition to other antiseizure drugs.

Levetiracetam[11]:

Chemically it is a pyrrolidine derivative. Levetiracetam exhibits a novel pharmacological profile. It inhibits partial and secondarily generalized tonic-clonic seizures in the kindling model, yet it is ineffective against maximum electroshock- and pentylenetetrazol-induced seizures. The mechanism by which levetiracetam exerts these antiseizure effects is unknown.

It is effective for refractory partial seizures.

Tiagabine[1,2]:
It is a derivative of nipecotic acid. Tiagabine inhibits the GABA transporter, GAT-1, and thereby reduces GABA uptake into neurons and glia. Tiagabine inhibits maximum electroshock seizures and both limbic and secondarily generalized tonic-clonic seizures in the kindling model this indicates its efficacy against partial and tonic-clonic seizures.

Felbamate [11]:
Chemically it is a dicarbamate which is effective in both the maximal electroshock and pentylenetetrazol seizure models. Clinically relevant concentrations of felbamate inhibit NMDA-evoked responses and potentiate GABA-evoked responses. But it poorly controlled partial and secondarily generalized seizures.

Topiramate[1,2]:
It is a sulfamate-substituted monosaccharide. Topiramate reduces voltage-gated Na^+ currents. In addition, topiramate activates a hyperpolarizing K^+ current, enhances postsynaptic $GABA_A$-receptor currents, and also limits activation of the AMPA-kainate-subtype(s) of glutamate receptor. Topiramate inhibits maximal electroshock and pentylenetetrazol-induced seizures as well as partial and secondarily generalized tonic-clonic seizures in the kindling model. It is equivalent to valproate and carbamazepine in children and adults with newly diagnosed partial and primary generalized epilepsy. It also effective as amonotherapy for refractory partial epilepsy and refractory generalized tonic-clonic seizures.

Zonisamide[1,2] :
Zonisamide is a sulfonamide derivative it inhibits the T-type Ca^{2+} currents. In addition, zonisamide inhibits the sustained, repetitive firing of neurons, by prolonging the inactivated state of voltage-gated Na^+ channels like phenytoin and carbamazepine. It is effective in refractory partial seizures.

Viagabatrin[11]:
It is relatively irreversible inhibitors of GABA-Transaminase (GABA-T), the major enzyme responsible for the metabolism of GABA in CNS. As a result of inhibition of GABA-T, there is an increase of concentration of GABA in brain as a result there is an inhibitory neurotransmission. It is mainly effective in partial seizures.

Conclusion
Even with the introduction of newer drugs, remaining more than thirty percent of patients is still need of an effective antiepileptic drug to control their seizures. Additional all presently Antiepileptic drugs only used as prophylactically, they do not cure or prevent the disease progression into refractory epilepsy. So, newer compounds are needed to cure the disease with better understanding of mechanisms involved in epilepsy and also to solve the problems of development of resistant of drugs.

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