

Recent advances in the management of epilepsy: A review

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Abstract

Epilepsy is a complex disorder affecting brain function having a variety of contributing factors. The genetic predisposition plays a key role in the genesis of epilepsy. The already existing antiepileptic drugs (AEDs) provide effective control of majority of patients with different types of seizures. In some refractory cases and in those patients who can not tolerate the conventional AEDs, there is an urgent need to provide relief by controlling the seizures adequately. Various newer approaches in the rational management of seizures have been evolved during the recent years, based on different mechanisms of action and side effects profile. A brief account of these newer treatment modalities have been incorporated in this review in order to enlighten the readers about the possible beneficial effect of this regimen vis a vis the limitations of such use.

Keywords: Neurotransmitter imbalance, defective gene, newer antiepileptic drugs, plasma levels, newer approaches.

It has now been well established that epilepsy is not a single disorder¹ but a group of disorders of central nervous system characterized by paroxysmal cerebral dysrhythmia manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movement (convulsions), sensory or psychiatric phenomena; when a person has two or more seizures, he is considered to have epilepsy. It is a common neurological disorder affecting about 0.5% of the population², in which cluster of neurons sometime signal abnormally. During a seizure, neurons may fire as many as 500 times a second, compared to the normal rate of about 80 times a second.

Various hypotheses have been put forward for the genesis of epilepsy:

1. Abnormality in brain wiring: may occur during brain development leading to abnormal neuronal connections.
2. Imbalance of neurotransmitter: The spread of seizure activity may be mediated either by increase of excitatory neurotransmitter (mainly glutamate) or by decrease of activity of inhibitory neurotransmitters like GABA (Gamma- aminobutyric acid and possibly glycine).
3. Disruption of cell membrane surrounding neuron: important for molecules to move in and out of membranes and how cell nourishes and repair the membrane.

4. BDNF: (Brain derived neurotrophic factor): activates its receptor in the hippocampus during epileptogenesis.

Causes of epilepsy

About 40% of patients with epilepsy have a genetic component towards its aetiology³.

Genetic factors:

More than 500 genes are involved in epilepsy and persons susceptibility to seizures may be triggered by following factors:

1. defective gene for ion channels
2. progressive myoclonus epilepsy → cystatin B protein gene missing
3. Lafora body disease → gene that helps break carbohydrate is missing
4. genes mediating resistance to various antiepileptic drugs (AEDs).

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The knowledge of genetics has significantly helped in classifying epilepsy into specific types or syndromes according to their pattern of inheritance⁴:

- a. Mendelian disorder- Where a single locus is responsible with a detectable structural or metabolic abnormality of the brain. Various diverse genes have been identified in progressive myoclonic epilepsies like EPM1 (Unverricht Lundborg disease) EPM2 (lafora body disease) and neuronal ceroid lipofuscinosis (CLN1, CLN2, CLN3, CLN5 & CLN8)
- b. Non-Mendelian disorder- where multiple gene and other environmental factors are responsible with identification of mutant genes encoding alpha 4 subunit of neuronal nicotinic acetylcholine receptor (nAChR, CHRNA4), voltage-gated potassium channel (KCNQ2, KCNQ3) and sodium channel (SCN1B). The majority of familial epilepsies display a complex non-mendelian pattern of inheritance.
- c. Idiopathic generalized epilepsies (IGE) like childhood absence epilepsy, juvenile absence epilepsy and juvenile myoclonic epilepsy.
- d. Benign familial neonatal convulsion (BFNC) is a rare autosomal dominant inherited idiopathic generalized epilepsy.
- e. Childhood absence seizure (CAE) commonly begins between 4-14 years of age and the exact genetic locus has not been identified.
- f. Juvenile myoclonic epilepsy (JME) usually occurs after 10 years of age with early morning myoclonic jerks.
- g. Generalized epilepsy with febrile seizure plus (GEF+) is a genetic epilepsy syndrome which includes febrile seizures and generalized tonic-clonic seizures.
- h. X-linked infantile spasm occurs only in male infants around 2-6 months of age.
- i. Partial/ Focal epilepsy- Non genetic
- j. Benign partial epilepsy of childhood.

Various disorders

Various disorders like brain tumors, alcoholism, Alzheimer's disease, strokes, meningitis, hydrocephalus, cerebral palsy, may precipitate epilepsies. About 32% of all cases of newly developed epilepsy in elderly people are due to cerebrovascular disease.

Head injury

Head injury constitutes an important contributing factor for epilepsy.

Prenatal injury and development problems:

About 2.0% of seizures in children are due to cerebral palsy or other neurological abnormalities.

Poisoning

Poisoning with Lead, Carbon monoxide antidepressants etc. and lack of sleep, stress may precipitate epilepsy.

Treatment modalities

Currently available treatment controls 80% of patients by drugs and surgery and 20% have intractable seizures, where at times, local anaesthetic (lidocaine) or even general anaesthesia may be necessary in highly resistant cases.

Classification of antiepileptic drugs (AEDs):

1. Barbiturates: Phenobarbitone, Mephobarbitone
2. Deoxy barbiturate: Primidone
3. Hydantoin: Phenytoin
4. Iminostilbene: Carbamazepine
5. Succinimide: Ethosuximide
6. Aliphatic carboxylic acid: Valproic acid
7. Benzodiazepines: Clonazepam, Clobazam, Diazepam
8. Newer drugs: Lamotrigine, Gabapentin, Vigabatrin, Felbamate, Topiramate, Tiagabine, Zonisamide, Levitiracetam
9. Miscellaneous: Trimethadione, Phenacimide etc.

Since long it was assumed that to treat epilepsy in its totality, a single drug would be enough and in 1857, Bromide was introduced for the first time for the control of epilepsy. Later on in 1912, Phenobarbital saw the light of the day as an important member of AED family, and then in 1938, Phenytoin, a structurally related drug to barbiturate was discovered. All these drugs (except Bromide) are being used very commonly to provide effective seizure control and phenytoin still plays a major role in the management of epilepsy⁵. Later on, the introduction of carbamazepine and lamotrigine have opened up new avenues in the management of epilepsy. The latest surge of newer AEDs during the last decade have seen the emergence of drugs like gabapentin, vigabatrin, topiramate, tiagabine, oxycarbazepine, zonisamide and levitiracetam⁶.

Various mechanisms have been put forward which primarily deals with the inhibition of abnormal

unsynchronous high frequency neuronal discharge by a group of neurons in the brain and its spread to other areas of the brain: be it, the stabilizing effect on excitable cell membranes resulting in increase in seizure threshold by drugs which reduce Na^+ conductance and reduce Ca^{2+} influx or by inhibition of the spread of seizure activity² by blocking synaptic transmission mediated by an increase in the activity of the principle inhibitory neurotransmitter GABA and also glycine, thereby increasing membrane permeability to chloride ion which reduces cell excitability. The blockade of NMDA (N-methyl-D-aspartate) receptors via the glycine binding sites and inhibition of glutamate, the excitatory neurotransmitter, may also be responsible for attenuation of spread of seizure activity. The inhibition of noradrenaline and 5-hydroxytryptamine and increased uptake of dopamine are also the likely effect of some of the AEDs.

The antiseizure properties of valproic acid (sodium valproate) were discovered by chance when it was employed as a vehicle for other compounds used for screening of antiseizure activity. Sodium valproate has been found to be an effective drug for a wide range of seizure disorders. Chemically unrelated to any other class of antiepileptic drugs, sodium valproate, a simple mono- carboxylic acid, is particularly useful in certain types of infantile epilepsy where its low toxicity and lack of sedative action are important. It is also effective in adolescents in whom grandmal and petitmal co-exists since valproate is effective in both. It is also a mood stabilizer and used in bipolar depressive illness. It is effective in the treatment of absence, myoclonic, partial and tonic- clonic seizures. Initially it is administered daily in a dose of 15 mg/kg body weight, gradually increased at weekly intervals by 5-10 mg/kg/day to a maximum daily dose of 60 mg/kg. It significantly increases GABA content of the brain by inhibiting GABA transaminase and succinic semialdehyde dehydrogenase. Though sodium valproate is relatively free of unwanted effects, it may cause thinning and curling of hairs in about 10% of patients. Hepatotoxicity is a more serious side effect and it may cause spinabifida and other neural

tube defects when given to pregnant women; folate supplementation (0.4 mg/day) has been recommended to all women of child bearing age to reduce the likelihood of such defects.⁶

General principles of management of Epilepsy

Early initiation of treatment (following recurrent seizures) with AEDs almost always proves to be effective and improves prognosis. Initially one drug regimen should be started unless status epilepticus exists, to achieve therapeutic benefit with careful monitoring of the dosage and saliva or plasma drug concentration if possible. To minimize dose related adverse effects, addition of a second drug is advisable when the first drug fails to control the seizures. The multi-drug therapy should be started at a reduced dose of each drug with careful monitoring. It should be remembered while selecting the multi-drug regimen that the combination acts by well defined mechanisms like either by promoting Na^+ channel activation and /or by enhancing GABA mediated synaptic inhibition and the possibility of drug- drug interactions. The alternative line of approach should continue till the seizure is controlled. Abrupt withdrawal of any AED should be discouraged (esp. barbiturates and benzodiazepines) as they may precipitate status epilepticus. If a patient is seizures free for 3-4 years, gradual withdrawal of drugs (over a period of 3-6 months) is advocated. To increase the patients compliance, drugs are best administered in single or twice daily dose. Many AEDs are quite long acting with a relatively low plasma clearance and greater half lives (>12 hrs.). The therapeutic index being low, these drugs exhibit toxicity. Dose increments are made gradually at two-weekly intervals to achieve the minimum effective dose. Routine monitoring of plasma and saliva drug concentration is mandatory with concomitant renal or hepatic disease, in old age, during pregnancy or specially when sodium valproate or phenytoin is used. A small increment in phenytoin's dose may lead to toxicity due to its dose dependent kinetics (zero order kinetics). The therapeutic efficacy of a drug and/or the appearance of toxicity should be assessed by monitoring the plasma and saliva drug concentrations.

Effective plasma levels of some of the commonly used AEDs⁷ have been given below (Table -1)

Table 1: Effective plasma level

Drugs	Effective level (µg/ml)	High effective level (µg/ml)	Toxic level (µg/ml)
Carbamazepine	4-12	7	>8
Primidone	5-15	10	<12
Phenytoin	10-20	18	>20
Phenobarbital	10-40	35	>40
Ethosuximide	50-100	80	>100
Valproate	50-100	80	>100

Pregnancy, lactation and AEDs

Pregnancy and seizure disorder can affect each other and at times become harmful to the developing foetus due to anoxia and metabolic disorder. Folic acid supplements should be advised to patients on AEDs (phenobarbital and phenytoin), deficiency of which may cause neural tube defects. Similarly, pregnant mothers on AED therapy should be given prophylactic oral vitamin K₁ supplement (10 mg/day) during the last few weeks of pregnancy to avoid the danger of postpartum haemorrhage and neonatal intracerebral haemorrhage. Almost all the AEDs (carbamazepine being the safest)² cross the placental barrier and are excreted in breast milk causing sedation and poor suckling by the breast fed baby. Increased frequency of malformation at birth (known as anticonvulsant embryopathy) is also another problem in mothers taking AEDs, specially phenytoin or phenobarbital. In children suffering from epilepsy a single drug regimen with minimal doses should be initiated to avoid any complications. Febrile convulsions in children does not necessarily always precipitate epilepsy and should be treated early with paracetamol and rectal diazepam. Prolong use of phenytoin or phenobarbital may affect the cognitive development of the child.

Treatment of status epilepticus

Status epilepticus (SE) is a neurological emergency where rapid control of behavioural and electrical seizure activity is mandatory because the longer the episode of SE remains untreated, most of the drugs become refractory and the control is more difficult resulting in possible permanent brain damage. Intravenous lorazepam (4 mg) is now the preferred initial choice, may be repeated after 10 minutes, if necessary. Alternatively, Clonazepam 1 mg i.v. or Diazepam 10-20 mg i.v. may be tried. Since Diazepam is more likely to cause hypotension and respiratory depression and its effect is short lasting (about 20 minutes), either Phenytoin (15-18 mg / kg i.v.) or Phenobarbitone (10-20 mg/kg i.v.) may be considered. In refractory cases, Thiopental or Profol

or Midazolam may be preferred with full intensive care support system. Magnesium sulphate (4 gm i. v.) infusion for 24 hrs. after the last seizure, may be a better option than either Phenytoin⁸ or Diazepam for the treatment of seizure disorder of eclampsia. Some of the AEDs (Phenytoin, Carbamazepine, Barbiturates, Topiramate, Oxcarbazepine) may cause contraceptive failure (when used with oral contraceptive pills) by inducing hepatic microsomal enzymes. In such cases, the dose of oestrogen can be increased (at least upto 50 µg/day) to achieve reasonably satisfactory contraception. However, drugs like sodium valproate and lamotrigine do not cause enzyme induction and contraceptive failure.

Newer antiepileptic drugs (AEDs)

A short account of newer antiepileptic drugs have been outlined below

1. Lamotrigine⁹: Initially developed as an anti- folate agent based upon incorrect idea that by reducing folate, seizures can be controlled; it has a broader spectrum of anti-seizure action, possibly by inhibiting synaptic release of glutamate by acting at Na⁺ channel themselves. Completely absorbed orally plasma half-life ranging from 24 to 35 hrs and once daily dose between 100-300 mg can be used. Metabolised primarily by glucuronidation. Addition of Valproate markedly increases plasma concentration of lamotrigine. Effective as monotherapy or add-on therapy of partial and secondarily generalized tonic-clonic seizures in adults and Lennox-Gastaut syndrome (a disorder of childhood characterized by multiple seizure types with mental retardation and refractoriness to anti-seizure medication), also it is effective in juvenile myoclonic epilepsy and absence seizures. Adverse effects include drowsiness, dizziness, diplopia, headache and hypersensitivity reaction.

2. Gabapentin: It is effective in partial and grandmal seizures and also in neuropathic pain. It is a GABA analogue which increases its release by inhibiting GABA uptake. It is fairly well absorbed orally, half life ranges between 5-8 hrs, administered 2-3 times a day, total dose not exceeding 2.4 gm/day. Adverse effects include tremors, ataxia, drowsiness and dizziness.
3. Vigabatrin: It is useful in the treatment of partial and to some extent in grandmal or infantile seizures, but it worsens absence and myoclonic seizures. It prevents the inactivation of GABA by inhibiting GABA-aminotransferase. It is well absorbed orally and its half life is 6-8 hrs., administered in twice daily dosage of 500 mg each, may be increased upto 2-3 gm/day. Adverse effects include drowsiness, dizziness, weight gain and rarely agitation, mental confusion and psychosis. This drug should not be used in pre-existing mental disease; visual defects (irreversible tunnel vision) has been reported on long term use of this drug.
4. Felbamate: It is effective mainly in partial seizures. It is believed to block NMDA receptors via glycine binding sites. It is absorbed orally and have a long half life (20 hrs). It increases plasma level of phenytoin and sodium valproate and decreases that of carbamazepine. The use of this drug is limited as it causes aplastic anaemia and hepatitis.
5. Topiramate: Partial and grandmal seizures are controlled by this drugs and also have some effect on absence seizures. This drug appears to have multiple actions including blockade of voltage-gated sodium channels, potentiation of GABA activity and inhibition of Kainite (KA) effect on AMPA (alpha- amino-3 hydroxy-5 methyl-isoxazole-4-propionate) receptors; both KA and AMPA receptors are activated to cause excitation of CNS where glutamate is the principle transmitter⁷. Therapeutic spectrum of Topiramate resembles Phenytoin with less side effects. It has been reported to be teratogenic in animals, so contraindicated in women in child bearing age. It is also effective in both adults and children with refractory partial seizures with or without secondary generalized tonic- clonic seizures in patients with Lennox- Gastaut syndrome. It is quite useful in infantile spasm also. This drug is rapidly absorbed when used orally and its half-life is between 20-30 hrs. It is administered in a dose range of 200-600 mg/day. Common adverse effects include drowsiness, dizziness, mental clouding, anxiety, cognitive slowing and rarely urolithiasis.
6. Tiagabine: A derivative of nipecotic acid, tiagabine is used as an add on drug for partial seizures which acts by inhibiting neuronal and glial uptake of GABA. It is very well absorbed orally with nearly 100% bioavailability. It has half-life of 5-8 hrs. and used in doses ranging from 16 to 56 mg four times a day. It is a well tolerated drug with minor dose- related adverse effects like nervousness, dizziness, drowsiness, tremors and depression. Psychosis or ataxia may require withdrawal of the drug.
7. Zonisamide: It is a sulphonamide derivative which mainly appears to act on the sodium channel and also on voltage- dependent calcium channel. It is effective on different types of seizures like partial, grandmal, infantile and myoclonus. It is well absorbed orally with a long half-life of 1-3 days. It is used in dosage ranging from 100-600 mg /day. Adverse effects include drowsiness, ataxia and cognitive impairment. Potentially serious skin rashes may also occur.
8. Levetiracetam: It is a piracetam (nootropic agent) analogue whose mode of action remains unclear. Most probably is acts through modulation of GABA receptors and also through Ca²⁺ and K⁺ channels. It is mainly used for the treatment of partial seizures though it has a potentially broader spectrum of use. It is completely absorbed after oral administration with a half-life of 6-8 hrs. and dosage ranging from 0.5 to 1 gm twice daily. Adverse effects include drowsiness, asthenia and somnolence.

Some other AEDs of potential therapeutic benefit and newer approaches in the management of epilepsy

1. Stripentol- derived from alcohol used in partial and absence seizures
2. Retigabine- possibly acts through K⁺ channels
3. Remacemide¹⁰- NMDA receptor modulator
4. Talampanel- AMPA receptor antagonist
5. Pregabalin- related to Gabapentin
6. Delivering drugs directly to the part of the brain from where seizures originate-sodium valproate in fatty capsule.
7. Transporter proteins- many drugs need these to get into the brain.

8. Melatonin- might reduce seizures in some children.
9. Diet – unusual diet called "Ketogenic diet" that helps body to breakdown fats instead of carbohydrates.
10. Vagus nerve stimulation¹¹ (VNS) was approved by US FDA in 1997 for epileptic patients (older than 12 years of age) not controlled by standard medication. It is a battery- powered device, surgically implanted under the skin of chest and attached to vagus nerve in lower part of the neck. It delivers short bursts of electrical energy to brain via vagus nerve. On an average, it reduces short term seizure frequency by 20-40% with an approximately longterm decrease in mean seizure frequency of 40-50% and the dose of the antiepileptic medication can be further reduced in those patients who can not tolerate these drugs. Patients who suffer from complex partial seizures or generalized seizures with loss of consciousness not responding to standard anticonvulsant medication and patients who can not undergo brain surgery are considered good candidates for VNS. It also may be recommended as a treatment for photosensitive epilepsy and epilepsy resulting from head injury. Zabara¹² hypothesized that VNS had two distinct anti-epileptic mechanism of action: a) a direct inhibition terminating the beginning or ongoing seizure and (b) a long lasting inhibition which increased with continued periods of stimulation to prevent seizures. Investigators have suggested that VNS possibly increases seizure threshold by causing widespread release of GABA and glycine in the brain. Adverse effects like hoarseness or voice changes, throat discomfort resulting difficulty in swallowing, cough or dyspnoea are mild which appears during stimulation, diminishes over time. About the suitability of VNS in the management of epilepsy, it may be described as a long-lasting, hassle-free and on-demand therapy, with no interactions and potential life threatening adverse effects. Moreover, the reduction of depressive symptoms in patients with epilepsy by VNS¹³ and its mood stabilizing effect appears to be an added advantage.

Finally, the continued search and discovery of newer antiepileptic drugs during the last decade has not only

failed to revolutionize the approach of the management of a complex disorder like epilepsy, none of these agents has been shown to be superior to the standard drugs like phenytoin, carbamazepine or sodium valproate. An estimated 1% of the general population has epilepsy and close to 30% of these patients, the epilepsy is intractable to medications; many others have their seizures controlled at the expense of unacceptable adverse effects from pharmacotherapy. Before vagus nerve stimulation was available, the only non- pharmacologic treatment option for refractory epilepsy was surgery. However, not all patients with refractory epilepsy are candidates for surgery. Child patients with intractable epilepsy may have a progressive disorder that is medically, physically and socially disabling. Surgical resection of the epileptogenic zone or lesional pathology, or both, may significantly reduce seizure tendency in selected patients. Favourable candidates for focal cortical resection include individuals with medical temporal lobe epilepsy and partial seizures related to primary brain tumor or vascular anomalies¹⁴. The objective of pre-surgical investigations, dominated by scalp-recorded video electroencephalography and magnetic resonance imaging is the localization of the epileptogenic focus. Two methods of exploration are available: (a) the combination of subdural and intracerebral electrode placement through craniotomy and (b) the stereotactic placement of intracerebral depth electrodes (stereo – EEG). The choice of either of these two methods depend on child's age (3 months to 10 years) and on the topography of the epileptogenic focus. Surgery can be either palliative, with the purpose of reducing the intensity and/or the frequency of a certain seizure type or curative, aiming at a suppression of the epileptogenic focus through a resective or disconnective surgical procedure. reports suggest that initiation of surgical treatment at an early stage significantly improves the quality of life, seizure free period and acceptable socialization¹⁵.The pharmacogenetic approach, however, looks at how the response to antiepileptic drugs may be genetically determined and its could also help to identify those who might respond better to a particular drug without experiencing adverse effects. The genetic information helps in accurate diagnosis, informative patient counseling and formulating the disease preventive strategy.⁴ In the search of an ideal antiseizure drug that should suppress all types of seizures without causing much unwanted adverse effects, more recently introduced drugs have some distinct advantage¹⁶ of fewer drug interaction problem; but the hallmark of successful management of epilepsy is the rigidly advocated

regularity of medication with full patient cooperation and compliance.

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