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A Review on the Cognitive Impairment caused by Anti-epileptics and their Management

Nivitha M[1], Narayanan J[2,*] and Chitra V[3]

[1]Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District-603203, Tamilnadu, India.

[2*]Assistant Professor, Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District-603203, Tamilnadu, India.

[3]Dean and Professor & Head, Department of Pharmacology, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu District-603203, Tamilnadu, India.

Abstract

Epilepsy is a multifaceted disorder defined by unprovoked seizures that affects people of all ages. It is divided as per the type of seizures as epilepsy and epilepsy syndrome. There are four main types of epilepsy: focal, generalized, and combined generalized and focal, and unknown. The pathophysiology of epilepsy consists of two major factors and they are hyper-excitability and hyper-synchrony. The drugs involved in the treatment of Grand mal and partial seizures act by blocking the activity of neurotrophic factors, N-methyl D-aspartate (NMDA) receptors, voltage gated channel blockage of sodium and potassium. Commonly seen side effects or negative effects of Anti-epileptic Drugs (AED) are decrease in reaction speed, information processing speed, and concentration. The newer antiepileptic drugs show lesser cognitive side effects when compare to older drugs. Cognitive impairment caused by AEDs in children is more when compared to its effect in adult. The management of cognitive impairment due to AEDs includes constant monitoring of cognition with reference to the changes observed in an individual as a result of AEDs. Nootropics, also known as "smart drugs," are compounds that have been in development over three decades and are likely the first to be used to treat cognitive deficits. It is a diverse group of compounds with varying chemical compositions and biological functions that are intended to improve learning and memory or to compensate for natural or induced cognitive impairments. This review covers the cognitive impairment associated with the intake of AEDs.

Keywords: Alternative medicine, Anti- epileptic drugs, Cognitive impairment, Herbal medcines, Nootropics.

Introduction

Epilepsy is a multifaceted disorder defined by unprovoked seizures that affects people of all ages. Epilepsy also involves cognitive and psychiatric challenges. Epilepsy is defined as the “abnormal firing or excitation of neurons.[1] Prevalence of epilepsy is more in men than women. Study on incidence of epilepsy based on age group shows that elders are affected than younger people.[2,3] Seizures can be caused due to various factors and there are genetic influence, head trauma, brain defects, infectious diseases, brain injury, and developmental disorders. Genetic influence includes ion-channel mutation epilepsy, familial nocturnal frontal lobe epilepsy, benign familial neonatal convulsions, and infantile convulsion syndrome.[4]

Classification of Epilepsy

Epilepsy is classified based on the seizure type, epilepsy, and, epilepsy syndrome. There are four main types of epilepsy: focal, generalized, and combined generalized and focal, and unknown. Focal epilepsy is characterized by focal onset seizures.

The focal onset seizure is limited to one hemisphere occurring within the network. Sub-cortical structure is the origin for focal onset seizure. The impressions of Electroencephalogram (EEG) findings for focal epilepsy are focal sharp waves and focal interictal slowing. Focal epilepsies may be unifocal, multifocal or hemispheric.

Generalized onset seizures are seen in patients with generalized epilepsy. Generalized seizures occur at bilaterally originated networks like cortical and sub-cortical structures.

They are further classified as motor onset and non-motor onset. Motor onset is further divided into tonic-clonic, tonic, atonic, myoclonic, myoclonic-atonic, and epileptic spasm. In tonic-clonic seizure the patient is unconscious and it is bilateral. The episode lasts for few seconds or minutes. This is followed by rhythmic bilateral jerking. In generalized tonic seizure we can observe bilaterally increased tone of limbs lasting for seconds to minutes.This type of seizure mostly occurs at night. Sudden loss of muscle tone or drop attack occurs in generalized atonic seizure. This type is mostly seen in intellectually impaired patients. Myoclonic seizure is characterized by series of jerks with partially retained awareness.

There are four types of non-motor onset seizures: typical absence, atypical absence, myoclonic absence, and absence with eyelid myoclonia. Typical absence generalized seizure occurs with abrupt onset and offset of impaired awareness. Clonic movements are observed in eyelids, chin, head, eyebrows.Atypical absence seizures generally have less abrupt onset and offset of loss of awareness. Myoclonic jerks and loss of muscle tone are the main features of this type of seizure. Bilateral myoclonic jerks are seen in myoclonic absence seizures. The jerks are mostly bilateral. It can also be unilateral or asymmetric. The jerks are mostly observed in shoulder and arms. In the absence with eyelid myoclonia type of generalized seizure upward deviation of eyeballs with eyelid jerks which are very fast and rhythmic are observed.

The aetiology of epilepsy can be structural, infectious, genetic, immune system, metabolic factors and also can be unknown. Structural abnormalities can increase the risk of occurrence of an epileptic episode. Identification of structural lesion using Magnetic resonance imaging (MRI) studies may help us in assessing the dysfunction cortical development. Family history of an autosomal dominant disorder is an important factor that causes epilepsy and it is considered to be a major genetic aetiological factor. Infection can also cause epilepsy. Congenital infections like Zika virus, cytomegalovirus, panencephalitis are some of the examples for infectious aetiology. Immune disorders and metabolic disorders can also cause epilepsy.[5–7]

Pathophysiology of Epilepsy

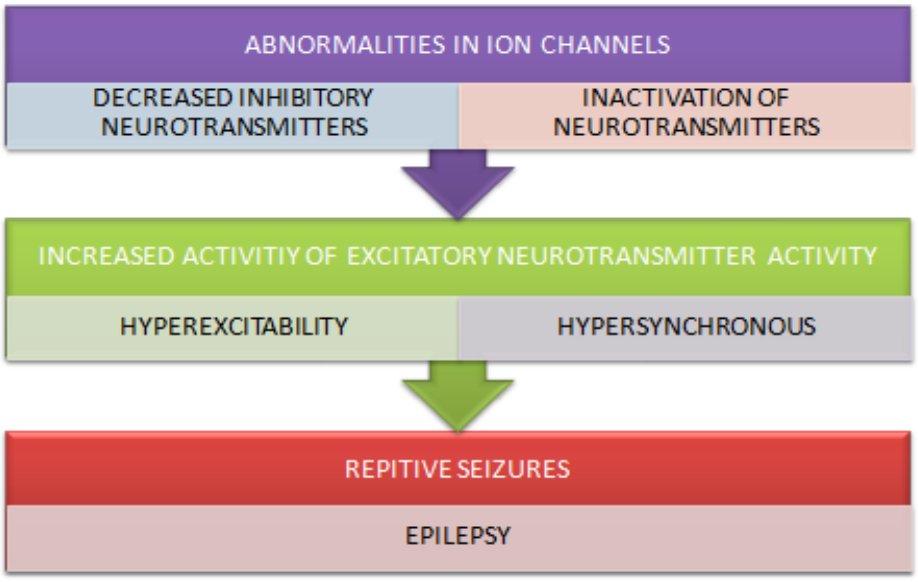

Figure 1 Pathophysiology of Epilepsy

Abnormal neuronal firing

The pathophysiology of epilepsy consists of two major factors and they are hyper-excitability and hyper-synchrony. Hyper-excitability is the over responsiveness of the neurons or abnormal responsiveness of neurons to an excitatory input. This process leads to hyper-synchrony where the neighbouring neurons also involve in abnormal responsiveness.

Role of channels and receptor in abnormal epileptic firing

There are various receptors and channels that play a role in epilepsy pathophysiology. Voltage- gated Sodium (Na^+) channel may cause repetitive action potential firing. Voltage-gated potassium(K^+) channel causes repetitive action polarization.[8]

Mechanism involved in hyper-excitability

Alteration in neuronal membrane ion channels

Pathophysiology of epilepsy involves the dysfunction of voltage gated Ligand channels and Ligand gated ion channels. They contribute to both acquired and genetic epilepsies.

Voltage gated sodium channels

Voltage gated sodium channels are responsible for action potential. This action potential is important for neuronal conduction to take place. Their abnormal or dysfunction is a major cause for febrile seizures, benign neonatal familial seizures.[9] Initiation and propagation of neuronal firing is carried out by voltage gated sodium channel. Dysfunction or imbalance in voltage gated sodium current leads to prolonged state of depolarisation. This results in increased or amplified response by the neurons to synaptic input and enhancing its repetitive firing capability.[10]

Voltage gated potassium channels

Benign neonatal epilepsy and episodic ataxia type 1are caused due to the abnormal functioning of voltage gated potassium channel. Voltage gated potassium channel plays a major role in repolarization and hyperpolarisation. These two are followed by paroxysmal depolarisation shift. Mutation of voltage gated potassium channel leads to misconduct of neuronal impulse.[9]

Voltage gated calcium channels

The release of neurotransmitters is regulated by calcium channel. They also play a major role in sustained depolarization of phase of Paroxysmal Depolarization Shift (PDS). Juvenile myoclonic epilepsy and the absence-like patterns are observed when there is a mutation in voltage gated calcium channel.[9]

Voltage gated chloride channels

Voltage gated Cl^- channel plays a major role in Gamma-aminobutyric acid (GABA) transmission. They are involved in rapid post-PDS hyperpolarisation. Juvenile myoclonic epilepsies, epilepsy with grand mal seizures on awakening or juvenile absence epilepsy are related to the mutation in Voltage gated Cl^- channel. [9]

Modification of second messaging system

The absence attack activation of N-methyl D-aspartate(NMDA)receptor leads to increased entry of calcium ions into the cell. The activation of NMDA receptor is due to the inhibition of GABA-ergic inhibition. Calcium entry affects the activation of secondary messenger cascade. The cascade makes the short-lived electrophysiological process to long-lasting intracellular process.[11]

Biochemical modification in receptors

While studying the biochemistry of epilepsy through MRI, abnormal or altered concentration and values of cerebral metabolites in patients with epilepsy and convulsive seizures were observed. GABA value was prominently high in hippocampus and thalamus in temporal epilepsy. Disturbance in glutamate value in the frontal cortex and brain lesion are identified in idiopathic generalized epilepsy. The abnormality in GABA plays a major role in hyper-excitability.[12]

Neurotransmitter release and vesicle trafficking alteration

Imbalance in glutamate and GABA results in irreversible neuronal damage and these two neurotransmitters play a major role in the pathophysiology of epilepsy. Nicotinic receptor is majorly present in hippocampus and cortical neurons.[13]

Change in extra cellular ion concentration

Table 1 Mechanism involved in hyper excitability[14]

IONS	CHANGES IN EXTRACELLULAR ION CONCENTRATION
POTASSIUM	Epileptogenic changes (**in fig 2**) lead to an increase in the extracellular accumulation of K + during physiological activity,which triggers the occurence of a seizure and a further increase in potassium ions. It leads to prolonged depolarisation,firing action potentials, and releasing more K^+ into the extracellular space. This uncontrolled positive feedback loop is believed to stop when depolarization is so severe that voltage-gated Na^+ channels are inactivated and neurons are unable to trigger action potentials, a condition known as depolarization block. The initiation, maintenance and termination of seizure episode depend on the accumulation of extracellular potassium ions.
SODIUM	Voltage-gated sodium channels play an essential role in the generation and propagation of action potentials, and dysfunctions caused by mutations can induce erratic neuronal activity. Increase in sodium ions results in intense neural activity and activation of NMDA receptors. This process is accompanied by epileptic seizures.
CALCIUM	During an epileptic episode there is increased influx of calcium ions via voltage gated calcium channels and NMDA receptors. Rapid accumulation of calcium ions (intra-cellular) combined with high levels of glutamate release is observed during seizure.
CHLORIDE	Chloride ions are responsible for inhibition of fast synaptic transmission. It has a critical influence on the neuronal activity. There is increased chloride ions during clonic seizures and accumulation of chloride ions determines the termination of epileptic episode.
BICARBONATES AND HYDROGEN	Hydrogen and bicarbonates play a major role in cell function and regulation. Their effect is on pH. The pH has its effect on protein folding and enzymatic activity. Cell processes like cell division, metabolism, apoptosis and

	migration is maintained by cellular pH. pH also has its control on neural cell excitability and synaptic transmission.

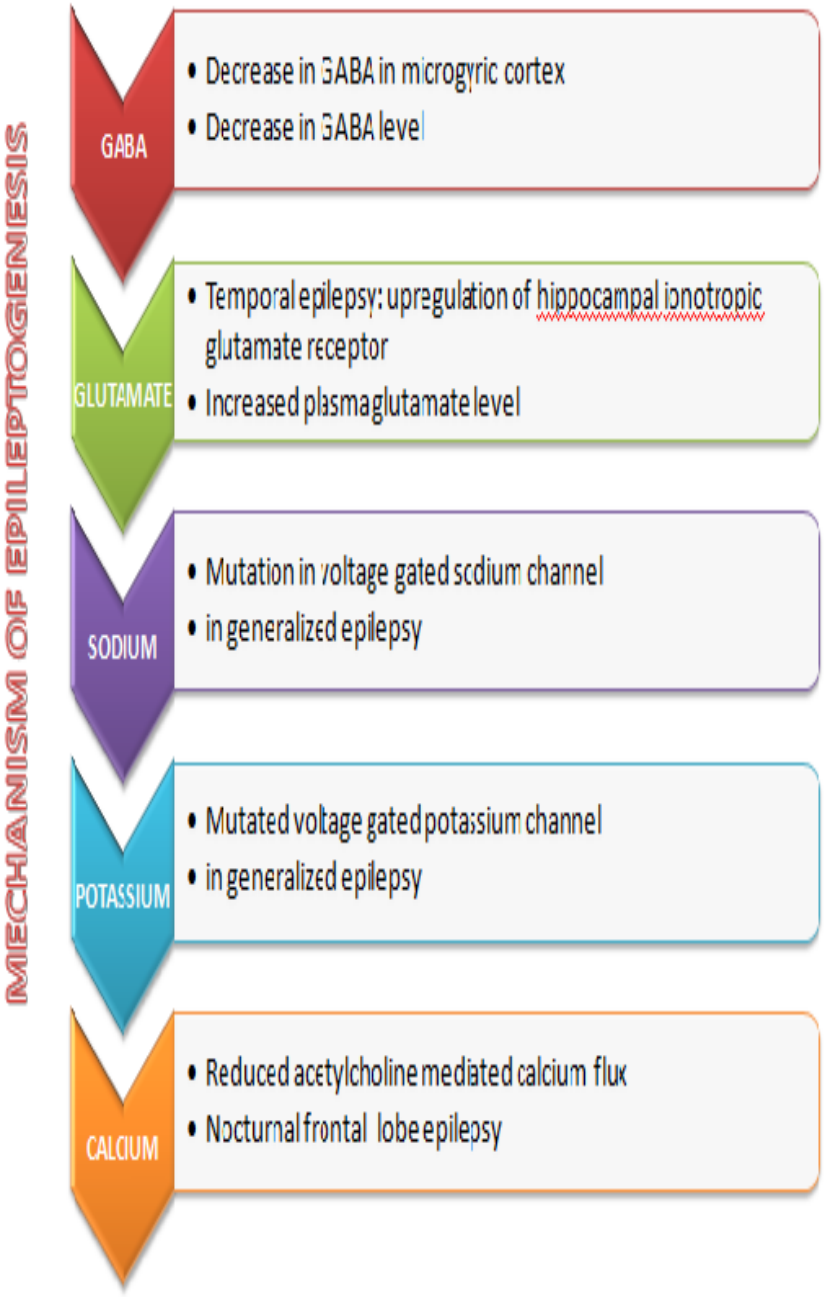

Figure 2 Epileptogenesis mechanism

Anti-Epileptic Drugs

The anti-epileptic drugs work by three main mechanisms. The drugs provide anti-epileptic action by enhancing the action of GABA, sodium channel inhibition and inhibition of calcium channel. The others mechanisms by which drugs provide anti-epileptic action include glutamate release inhibition and glutamate receptor blockade.

They are classified based on their basic mode of action

1. Drugs acting on Sodium ion Channels:Phenytoin,Carbamazepine,Topiramate,Valproic acid
2. Drugs acting on Calcium ion Channels : Ethosuximide, Valproic acid
3. Drugs that inhibit transmission of Excitatory Amino acid(EAA):Felbamate,Topiramate.
4. Drugs enhancing transmission of GABA :Diazepam, Clonazepam, Phenobarbital,Valproic acid, Gabapentin,Vigabatrin,Topiramate, Felbamate.

Anti- epileptic drugs are classified into three generations- first, second and third. The first-generation anti-epileptic drugs are commonly used. They are Phenytoin, Phenobarbital, Carbamazepine, Valproicacid, Zonisamide and Clobazam.The second generation drugs Gabapetin, Topiramate, Lamotrigine, Levetiracetam, Rufinamide,Vigabatrin,Oxcarbazepine and Perampanel. The third generation drugs include Lacosamide and Eslicarbazepine acetate.

Newer Antiepileptic Drugs

Gabapentin,Topiramate,Lamotrigine, Levetiracetam**,** Rufinamide, Vigabatrin, Oxcarbazepine, Perampanel.[15]

Herbal Medicines for Epilepsy Treatment

The use of herbal medicines as alternatives to allopathic medicine in the treatment of epilepsy is highly prevalent. Although the herbal formulations are found to be effective, they seem to possess insufficient evidence to support the high efficacy and aspects concerning toxicity.[16] The complications that occur as a result of the use of anti- epileptic drugs and the control of seizures are managed using the herbal medicines and they are the most commonly approached alternatives.[17] The herbal medicines chosen for the treatment involves effects on control of seizures, reduction of complications and improving general overall health.[17]

The Anti- epileptic compounds that have a plant origin are listed below.[18]

Table 2 Anti- epileptic compounds with plant origin

COMPOUNDS			
Withania somnifera	Valeriana officinalis	Centella asiatica	Bunium persicum
Trichosanthes dioica	Pimpinella anisum	Curcumin	Phytol
Ficus platyphylla	Panax ginseng	Vitexin	Zizyphus jujuba
Nigella sativa oil	Cyperus rotundus	Mentha pulegium	Narinjin
Psidium guajava	Zhumeria majdae	Turmeric	Curcumol
Zingiber officinale	Angelica archangelica	Anacyclus pyrethrum	Quercetin
Feretia apodanthera	Rosmarinus officinalis	Ocimum basilicum	Emblica officinalis

Mechanism of action of Drugs:

The drugs involved in the treatment of Grand mal and partial seizures follow any of the following mechanisms:

1. These drugs work by blocking the voltage- dependent sodium channels during frequencies of high firing.
2. NMDA/AMPA receptors blockade
3. Voltage-gated N-type Ca channel blockade
4. Drugs bind selectively to synaptic vesicular protein
5. Neurotrophic factors effect blockade

The drugs used in the treatment of petite mal seizures work by inhibiting the T-type Calcium channel.[19]

Adverse Drug Reactions:

The anti-epileptic drugs can often result in several adverse events, some of which are irreversible and serious. They are majorly grouped as:

Table 3 Adverse events

Toxicity due to overuse	Chronic toxicity
Clinically presented by Nystagmus Blurred vision Ataxia Lethargy Central Nervous System depression In case of very high doses, results in cardiovascular collapse and coma	Gingival hyperplasia Facial features coarsening Megaloblastic anemia Vitamin K deficiency Vitamin D deficiency Hirsutism Hyperglycemia

Other adverse events

1. Drowsiness
2. Slurred speech
3. Headache
4. Dipliopia
5. Ataxia
6. Vertigo

Idiosyncratic reactions - mostly seen in patients that are under treatment for trigeminal neuralgia

1. Leukopenia
2. aplastic anaemia
3. Systemic Lupus Erythematosus(SLE)
4. blood dyscrasias
5. hepatitis.[20]

The side effects of the drug mainly depend on the treatment duration, dose of the medication, type of therapy etc. they mainly occur as a result of high dosing and overtime the body gets adjusted to the medication and its dose.[21]

Various studies are conducted to study the effect of the plant compounds that provide Anti-epileptic action. These include testing the drugs on laboratory animals after the induction of epilepsy through any

or all of the following methods. The animals are segregated into batches and epilepsy is induced in each of the batches via various methods like MES(Maximal electroshock seizure), PTZ(pentylenetetrazole) seizure test, pilocarpine and kainite test, chemical kindling model etc.[22]

Pathology of cognitive impairment due to Anti- epileptic drugs

Cognitive impairment is frequently observed during the beginning stage of epilepsy and before the administration of anti-epileptic medication. Antiepileptic drugs (AEDs) can influence cognitive function by reducing neuronal excitability or increasing inhibitory neurotransmission. It is said that any AED can cause cognitive decline if used long enough. Deficits in attention, memory, and executive functions can be detected in the early onset of epilepsy. Commonly seen anti epileptic side effects or negative effects are decrease in reaction speed, information processing speed, and concentration.[23]

The aetiology and type of seizures ,seizure prevalence and time span,age at which seizure begins, acquirement of brain abrasion prior to the seizure onset,repeated seizures causing brain injury, heredity, psychology and social behaviour ,treatment and surgery of epilepsy can all have a negative impact on cognition. Everyone of these interconnected factors contribute to cognitive deficits in a complex way. AEDs have effects that are dose dependant on cognitive functions which can be exacerbated by the multiple use of AEDs. Since AEDs are frequently chosen depending upon the traditional measures of effectiveness of treatment, such as therapeutic efficacy, as well as their deleterious neurocognitive side effects, their effects on cognition are especially significant.Cognitive adverse effects induced by AED is a key issue for patients receiving treatment for epilepsy. Children's growing neurological systems may be more susceptible to the long-term implications of AED-induced cognitive loss, thus it's especially vital to recognise and reduce the cognitive effects of AEDs.[24]

Table 4 Cognitive complications of epilepsy syndrome

EPILEPSY SYNDROME	CORE PATHOPHYSIOLOGY	CORE COGNITIVEDEFICIT
Temporal lobe epilepsy	Hippocampus and mesial temporal lobe	Anterograde memory
Frontal lobe epilepsy	Frontal lobe	Executive function
Benign epilepsy with centrotemporal lobe	Sylvian and rolandic regions	Language abilities
Absence epilepsy	Thalamocortical network	Attention
Juvenile myoclonic epilepsy	Frontothalamic network	Executive function

Older anticonvulsant drugs like carbamazepine, Valproic acid, and phenytoin have comparatively lesser cognitive side effects than newer anticonvulsant drugs.[23]

Studies suggest that administration of Phenobarbital to children with epilepsy have low Intelligent quotient(IQ) level.[25–27] Compared to valproate and carbamazepine, phenobarbital has worse cognitive side effects. A study shows that carbamazepine has a negative cognitive effect than levetiracetam and lamotrigine but better than phenytoin.[28–30] Topiramate causes slow reactions, reduced language skills, and reduced working memory.[31]

Benzodiazepines like clobazam, clonazepam, diazepam, and lorazepam are used as anticonvulsants drugs. They also affect the cognition of the patient with epilepsy widely. Side-effects seen while giving benzodiazepines are fatigue, sedation, drowsiness, and concentration disorders.[23]

Effect of anti-epileptic drugs in cognition

Neuropsychological studies suggest that attention, memory, and information processing speed are majorly affected by antiepileptic drugs. The newer antiepileptic drugs show lesser cognitive side effects when compare to older drugs.

Phenobarbital and Primidone

Lower IQ is observed in children with epilepsy while taking Phenobarbital. Effect of Phenobarbital in cognition is more compared to valproate and carbamazepine. Attentional and memory difficulties in children are observed during administration of primidone. But these changes are reversible when the drug is discontinued.[32]

Phenytoin

Concentration disturbance, memory, mental speed, and visuomotor dysfunction are the major side-effects of taking phenytoin. These side-effects depend on the dose of phenytoin administration. Drug withdrawal improves motor coordination, memory.[32]

Carbamazepine

Carbamazepine is given for partial seizures in adults. Information processing speed and attention are also majorly affected due to administration of carbamazepine. The changes are mostly irreversible. Even after discontinuation of carbamazepine arithmetic performance, faster motor skills are not regained. After one month of time the finger tapping rate, impaired movement time, reaction time are observed again.[32]

Sodium valproate and Ethosuximide

A study suggests that task assessing coordination, memory, concentration, mental flexibility is affected by sodium valproate. Minority group of patients may also develop Parkinsonism associated with memory problems and psychomotor slowing. Ethosuximide shows no major side effect in cognition and also improves cognition.[32]

Clobazam

Intelligence, memory, attention, psychomotor speed, and impulsivity are similar to that of carbamazepine.[32]

Zonisamide

One retrospective study suggests that 35.0% memory loss and 27.0% attentional problems were observed while taking zonisamide.4.0%-12.0% of other cognitive problems in children were also observed. Minor group of patients had cognition deficit after one year of treatment. Poor performance in tasks involving attention, memory and verbal fluency were seen. The adverse effects caused by zonisamide were dose-related.[32]

Pregablin

In a study conducted in 2009 showed 2.0% cognitive dysfunction in patients taking Pregablin. The cognitive side effects include deterioration in verbal and visual episodic memory.[32]

Topiramate

Topiramate has its effect on memory and language skill. Cognitive adverse effects are observed after one year of treatment. Withdrawal of Topiramate shows improvement in attention, language skill, thinking, memory, verbal fluency, psychomotor activity, movement coordination. When compared to adults children taking Topiramate experienced cognitive adverse effects.But the side effects are reversible with discontinuation.[32]

Negative cognitive effect of Anti- epileptic drugs in children

Topiramate and Zonisamide are said to cause cognitive impairment in children. The side effects of these two drugs are word-finding disorders, cognitive slow-down, and memory working disorders.[31] Administration of Valproic acid, carbamazepine, and oxcarbamazepine to children can cause decrease information processing speed, deficit in language skills, verbal learning issues, memory processes.[33] Cognitive impairment due to consumption of anti-epileptic drugs in children is more when compared to its effect in adult. Performance in school and the potential development during childhood and adolescence is greatly affected by the cognitive impairment caused by anti- epileptic drugs which has to be viewed seriously.[23]

Valproic acid during pregnancy

Taking Valproic acid during pregnancy will affect the intellectual ability of the unborn child. Administration of Valproic acid in higher doses to the pregnant patient has a major impact on the IQ of the unborn child. This effect is irreversible and undesirable which directly affects the unborn child rather than the pregnant mother. Valproic acid also causes autism disorder. Pregnant women, women of child bearing age must avoid taking Valproic acid for treating epilepsy.[34–37]

Valproic acid was the most common drug prescribed to treat epilepsy.Among patients taking carbamazepine and Valproic acid memory and attention deficit was commonly observed during the study.[38]

Phenytoin in epilepsy

Phenytoin is considered to be the first line drug of choice for the treatment of epilepsy and it mainly improves the condition of generalized seizures, partial seizures and also status epilepticus and it does not impair the neurological function significantly. However, phenytoin tends to cause peripheral neuropathy, psychosis, gingival hyperplasia, hydantoin syndrome in new born babies, purple glove syndrome, cardiovascular collapse, decreased bone mineral content, locomotor dysfunction etc.[39]

Management of cognitive impairment occurring due to anti- epileptic drugs

The drugs used for the management of epilepsy have several positive effects on cognition and control of seizures, but more frequently these drugs impart unappreciated adverse effects which include newer problems with cognition and behaviour. Sometimes, they tend to aggravate the existing neurological and psychological impairments.[32,40]

Generally, the adverse effects of the drug increase with increase in drug load or higher doses. As the drug attains higher concentrations in serum, the drug tends to produce adverse effects.[41–44] Uptitration is another risk factor that is proposed.[45]

The domains of attention and functions of execution are impaired by the anti-epileptic drugs.[46] Higher brain functions can also be affected. The adverse effects of anti- epileptic drugs are reversible in most cases and usually resolve on discontinuation of the drug or sometimes after reduction of dose.[47] Cognitive

impairment and neuropsychological disturbances cause a negative effect in everyday life and decreases the overall quality of life. Also, the anti- epileptic drugs are retained for a long time.

The adverse effects can be directly managed by titrating the rates, choosing lower doses but ensuring they are effective, choosing the drug after the consideration of the pharmacokinetics. Considering the pharmacodynamic interactions and restricting the polytherapy and by making combination and selection of the anti- epileptic drugs based on the behavioral pattern and cognitive effects.

Despite the various methods to manage the side effects, the adverse effects can never be ruled out. Therefore, the management should be addressed on everyday basis during clinical practice. The key to this is to enhance the awareness about the potential adverse effects that particularly affect cognition. The patient and the care givers are priorly informed about the side effects of the anti- epileptic drugs. This helps in the acceptance of side effects that actually occur and also improves the number of follow- up visits which results in alleviating the side effects.

The management of cognitive impairment due to anti- epileptic drugs includes constant monitoring of cognition with reference to the changes observed in an individual as a result of anti- epileptic drugs. The treatment involves two assessments, the initial baseline therapeutic management and the follow-up sessions after the final target dose has been reached.[46] Some evidences state that systematic screening with any of the scales can potentially aid in the treatment and choice of drug, thereby reducing the adverse effects.[48]

Another approach that is suggested is the use of cognition- enhancing pharmacological agents like nootropics. On economically considering the use of nootropics, it is the last choice for use and keeping in mind the earlier stated negative effect on cognition, it is the choice of last resort.[49]

Cognitive training also does the needful in management of cognitive impairment caused due to the use of anti-epileptic drugs. Newer anti- epileptic drugs have been developed and introduced and these drugs seem to have positive or neutral effects on impaired cognition.[49]

The newly developed anti-epileptic drugs do not provide any advantage over traditional drugs in terms of efficacy nor the acute adverse effects produced by the drugs.[45–47] On administration of the newer anti-epileptic drugs, there were fewer and lesser side effects compared to traditional drugs. Also, the severity of the interaction of these drugs with other drugs has declined to a great level.[48,50–52] The newer anti-epileptic drugs have lesser teratogenic effect and they also have milder effects on the physical status of the patient like secretion of hormones, lipid and bone metabolism.[53]

Lamotrigine and levetiracetam have the lowest teratogenicity among the new drugs developed for epilepsy. Articles state that the newly developed drugs also tend to produce favorable outcomes.[54] These drugs bind to unique sites; the binding sites of the drugs are listed below.

1. Levetiracetam binds to synaptic vesicle 2
2. Perampanel binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA receptor)
3. Lacosamide binds to collapsing response mediated protein-2 (CRMP2).[51]

Nootropics used for cognitive impairment

Nootropics, also known as "smart drugs," are compounds that have been in development over three decades and are likely the first to be used to treat cognitive deficits. Both memory acquisition and retention showed improvement without affecting the anticonvulsant effect. It is a diverse group of compounds with varying chemical compositions and biological functions that are intended to improve

learning and memory or to compensate for natural or induced cognitive impairments. Nootropics also postpone the aging of "normal" brain, but they may also improve "normal" brain activity.
The molecular mechanism of action of nootropics is not entirely understood, but some of these drugs's pharmacological actions include

1. An increase in acetylcholine concentration due to the cholinergic network's functional activation.
2. Oxidative catabolism is stimulated hence metabolism of the brain is enhanced
3. Adenosine tri-phosphate(ATP)/ Adenosine di-phosphate(ADP) ratio and Cyclic adenosine monophosphate (cAMP) levels rise.
4. Phospholipid metabolism and protein production are improved.
5. Increased oxygen and glucose use in the presence of slowed brain metabolism.
6. Increased perfusion in the local area.
7. Changes in the ion fluxes.[55]

Nootropic drugs

1. CNS STIMULANTS:- Amphetamine, Methyl phenidate, Eugeroics ,Caeffine ,Nicotine.
2. RACETAMS:- Piracetam, Oxiracetam, Phenyl piracetam ,Aniracetam
3. CHOLINERGICS:- Citicoline,Choline bitartrate, α-Glycerylphosphorylcholine
4. MISCELLANEOUS:Tolcapone,Levodopa,Atomoxeline,Desipramine,Nicergoline, Integrated stress response inhibitor(ISRIB)
5. HERBS:-Bacopa monnieri, Panax ginseng, Ginkgo biloba, Salvia officinalis, Centella asiatica.

Conclusion

Synthetic and Natural Anti Epileptic drugs have been given to treat various seizures such as focal, generalized, combined generalized and focal and unknown for many years.Although these drugs potentially control seizures they adversely cause cognitive impairment even in children with epilepsy. Hence, Nootropic drugs which facilitate learning and memory can be given to patients including children to reduce cognitive impairment along with Anti epileptic drugs.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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