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CURRENT TRETMENT OF EPILEPSY: STATE OF ART

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ABSTRACT

Epilepsy is one of the most common serious neurological disorders. Epilepsy is one of the neurological disorders of the brain in which an individual experiences chronic abnormal bursts of electrical discharge in the brain. They are various types of epilepsy that are Simple partial seizure, Complex partial seizures, generalized seizure tonic clonic seizure, Absence seizures, atonic seizures, myoclonic seizures and infantile spas. The cause of convulsions must be clearly understood through some precise observation. Epileptic attack can be caused by biochemical insults to the brain, such as hypoglycemia, anoxia, hypocalcaemia, hyperventilation, water intoxication and sudden withdrawal of certain drugs such as barbiturates or alcohol. Antiepileptic drugs or anticonvulsant drugs or antiseizure are diverse group of pharmaceuticals aid in the treatment of epileptic seizures. Antiepileptic drugs or anticonvulsant drugs or antiseizure are diverse group of pharmaceuticals aid in the treatment of epileptic seizures. Phenytoin is one of the older genemiceion AEDs. AEDs suppress the rapid and excessive firing of neurons during seizures. This articles explains that types of epilepsy, mechanism of action of AEDs, and treatment of epilepsy.

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INTRODUCTION

Epilepsy is one of the most common neurological disorders of the brain in which an individual experiences chronic abnormal bursts of electrical discharge in the brain. About 50 million people worldwide have epilepsy and 90% of them are from developing countries and making it second to stroke as one of the most common serious neurologic disorders[1]. Moreover from various studies worldwide, approximately 0.5% of the population is reported to be affected by active epilepsy [2, 3].

Epileptic seizures are caused parts of the brain eliciting abnormal electrical activity. The region of seizure genemiceing tissue, or the epileptogenic focus, can be due to structural abnormalities that disrupt normal neural circuitry. These abnormalities may be genetic, caused by head injury, infection, stroke or tumor [4].In the past several years, our understanding of epilepsy has increased in several respects. It is a common chronic neurological disorder in which the balance between cerebral excitability and inhibition is tipped toward uncontrolled excitability and characterized by recurrent unprovoked seizures[5]. There is now clear evidence that there are distinct differences between the immature and mature brain in the pathophysiology and consequences of seizures [6,7.]

Epilepsy is a chronic disorder of the brain which affects people in every country of the world. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. Epilepsy increases a person's risk of premature death by about two to three times compared to the general population and it is characterized by recurrent seizures- which are physical reactions to sudden, usually brief, excessive electrical discharges in a group of brain cells. Different parts of the brain can be the site of such discharges. Epilepsy is also remarkably more uniformly distributed around the world. There is no racial, geographical or social class boundary it occurs in both the sexes, at all ages especially in childhood, adolescence and increasingly in aging population.

Epidemiological data of epilepsy

Epilepsy is one of the most common serious neurological disorders. It is estimated that there are 55 lacks persons with epilepsy in India, 20 lacks in USA and 3 lacks in UK [8]. Each year 120 per 100,000 people in the United States come to medical attention because of a newly recognized seizure. At least 8% of the general population will have at least one seizure and not have epilepsy. The mice of recurrence of a first unprovoked seizure within 5 years ranges between 23% and 80%.6 The age adjusted incidence of epilepsy is 44 per 100,000 people in a year. Each year about 125,000 new epilepsy cases occur; of these, 30 % are in people younger than age 18 at the time of diagnosis. The relatively high frequency of epilepsy in the elderly is now being recognized. At least 10 % of patients in long- term care facilities are taking at least one antiepileptic drugs [9.]

Definition of epilepsy:

The term epilepsy is derived from the Latin and Greek word seizures or to seize up on. This implies that epilepsy is ancient disorders indeed in all civilizations it can traced as far back as medical records exist.

Epileptic seizures refer to a transient altemiceion of behavior due to disordered, synchronous and rhythmic firing of populations of brain neurons [10.]

Types of epilepsy:

Simple partial seizures:

It lasts for 1-2 minutes often secondary. Convulsions are formed to a group of muscles or localized sensory disturbances depending on the area of the cortex involved in the seizure, without the loss of consciousness.

Complex partial seizures:

It is called temporal lobe epilepsy, attacks of bizarre and confused behavior and purposeless movements, emotional changes lasting 1-2 minutes along with impairment of consciousness.

Generlized seizure tonic clonic seizure:

It lasts for 1-2 minutes. The usual sequence is aura, cry, tonic spasm of all the muscles, unconsciousness, jerking followed by prolonged sleep and depression of all CNS functions.

Types	Description
I. Partial Seizures (seizures begin locally)	A. Simple (without impairment of consciousness) 1. with motor symptoms. 2. with special sensory or soma to Sensory symptoms. 3. with psychic symptoms B. Complex (with impairment of consciousness) 1. Simple partial onset followed by impairment of consciousness with or without automatisms. 2. Impaired consciousness at onset – with or without automatisms. C. Secondarily Generalized (partial onset evolving to generalized tonic clonic seizures)
II. Generalized seizures (bilaterally symmetrical and without local onset)	
III. Unclassified Seizures	
IV. Status epileptics	

Absence seizures:
Prevalent in children. Momentary loss of consciousness, little bilateral jerking, Patient freezes and stares in one direction**.**

Atonic seizures:
Unconsciousness with relaxation of all muscle due to excessive inhibitory discharges and patient may fall.

Myoclonic seizures:
Shock like momentary contraction of muscles of a limb or the whole body.

Infantile spas:
Seen in infants, probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deteriomiceion.[12]

Causes of epilepsy*:*

Approximately 1% of the world's population has epilepsy, the second most common neurological disorder after stroke. The cause of convulsions must be clearly understood through some precise observations. The type of seizure depends on the site of the focus in the brain. Epileptic attack can be caused by biochemical insults to the brain, such as hypoglycemia, anoxia, hypocalcaemia, hyperventilation, water intoxication and sudden withdrawal of certain drugs such as barbiturates or alcohol. Epilepsy can also be caused by previous active pathology, such as birth trauma to the brain, during or following meningitis, trauma to the skull and brain later in life, cerebral abscesses, cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage. Further analysis shows that the blockade of post-synaptic gamma-amino butyric acid receptors or an inhibition of GABA synthesis is the principal origin of brain discharge.[28]

Treatment of Epilepsy:

Antiepileptic drugs or anticonvulsant drugs or anti seizure are diverse group of pharmaceuticals aid in the treatment of epileptic seizures. AEDs are also increasingly being used in the treatment of bipolar disorder, also act as mood stabilizers and for the treatment of neuropathic pain. AEDs suppress the rapid and excessive firing of neurons during seizures. AEDs also prevent the spread ofu the seizures within the brain.[14]

Mechanisms of action of AEDs

AEDs protect against seizures through interactions with a variety of cellular targets.

The actions on these targets can be categorized into four broad groups:

(1) Modulation of voltage-gated ion channels (mainly sodium and also calcium channels);

(2) Effects on GABA systems, including enhancement of synaptic inhibition on GABA-A.

(3) Inhibition of synaptic excitation mediated by iono-tropic glutamate receptors; and

(4) Direct effects on synaptic release machinery.

The ultimate effects of these interactions are to modify the bursting properties of neurons and to reduce synchronization in localized neuronal ensembles. In addition, AEDs inhibit the spread of abnormal firing to distant sites.

Some seizures, including typical generalized absence seizures, are believed to result from thalamocortical synchronization. AEDs effective in these seizure types interfere with the rhythm-genemiceing mechanisms that underlie the synchronized activity in the thalamocortical circuit.[14]

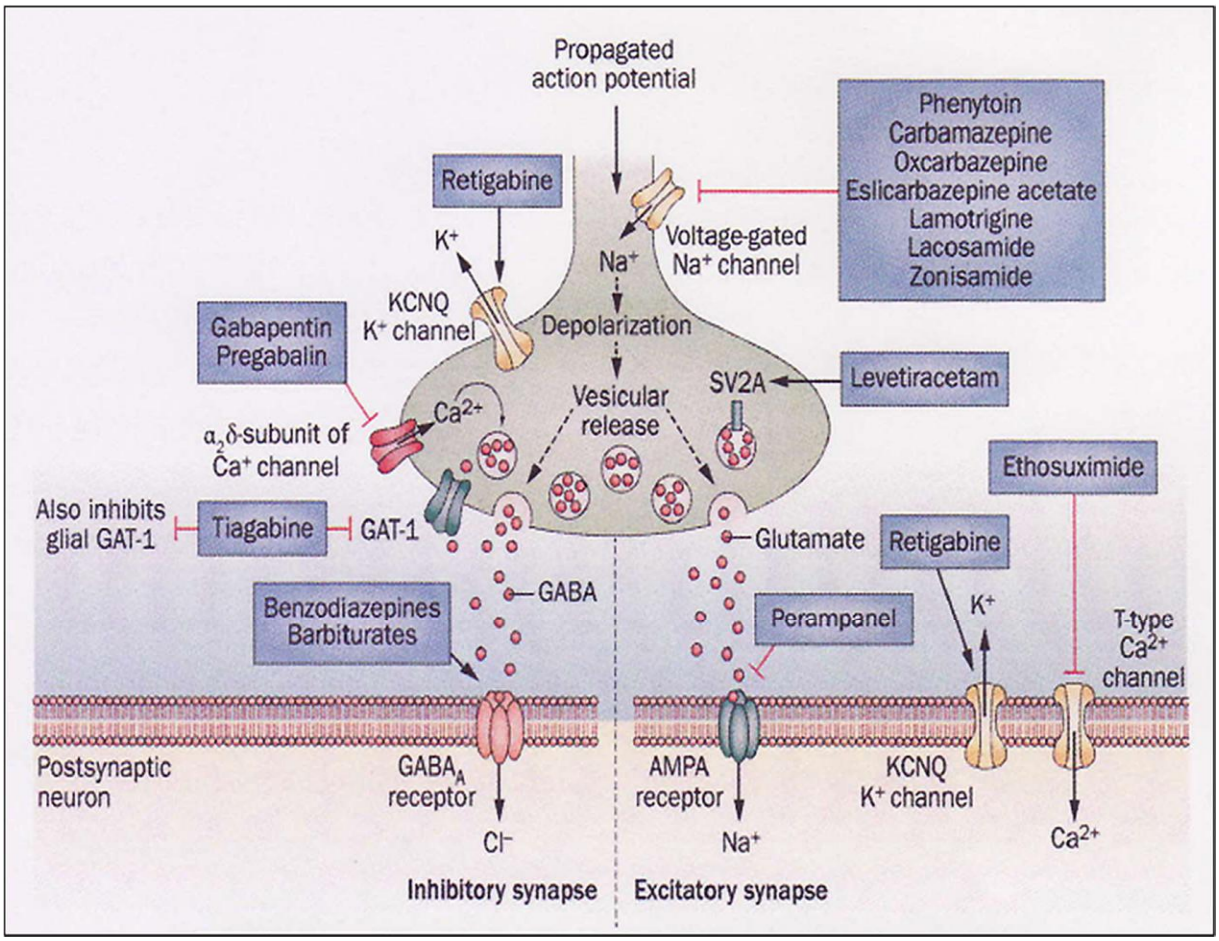

Fig-1: Modulation of voltage-activated sodium channels -Löscher and Schmidt, Nature Reviews Neurology 2012.

Several AEDs are believed to act largely through modulation of the gating of voltage-activated sodium channels, although effects on other targets including voltage-activated calcium channels may play a role in their seizure protection. These include Phenytoin, Lamotrigine, Carbamazepine, oxcarbazepine, and zonisamide. Other AEDs that may act, at least in part, through effects on sodium channels include felbamate, topiramate, and valproate.

Sodium channel blocking AEDs inhibit high-frequency repetitive spike firing, which is believed to occur during the spread of seizure activity, without affecting ordinary ongoing neural activity. This accounts for their relatively mild effects on normal brain function. At ordinary hyperpolarized membrane potentials, clinically relevant concentmiceions of sodium channel-blocking AEDs block sodium channels only weakly. However, upon membrane depolarization, the degree of block markedly increases.

The state-dependent block produced by AEDs that act on voltage-activated sodium channels results from preferential binding of the drugs to inactivated conformations of the channel. These agents act mainly on action potential firing; the drugs do not directly alter excitatory or inhibitory synaptic responses. However, a critical downstream action of AEDs that acts on voltage activated sodium channels may be to reduce action potential–dependent neurotransmitter release, particularly that dependent upon prolonged high-frequency firing as occurs during epileptic discharges. Interestingly, such drugs seem to have a preferential action on glutamate release and only weakly affect GABA release, possibly as a result of differences in excitation–contraction coupling in glutamatergic and GABA ergic neurons.

Voltage-activated sodium channel block also may reduce the propagation of action potentials from the soma into dendrites and may reduce the dendritic amplification of synaptic potentials. Together, these actions inhibit the spread of epileptic-form activity. Blockade of non in activating sodium currents that arise from alternate gating of the same channels responsible for fast sodium currents and influence initiation and maintenance of epileptic-form activity may also contribute to AED effects. Enhanced persistent sodium currents are associated with epilepsy in some forms of the ‘‘generalized epilepsy with febrile seizures plus’’ syndrome .[16]

NEUROTRANSMITTERS AND CALCIUM CHANNELS

GABA Systems:

The GABA system is the second key target for AEDs. Drugs that block GABA-A receptors are well known to induce seizures, and subunit mutations have been associated with inherited epilepsy syndromes [17, 18]. AEDs can interact with GABA systems either through direct effect on postsynaptic GABA receptors or by altering the cellular disposition of GABA. Benzodiazepines are examples of drugs that act on postsynaptic GABA receptors. They are specific for ionotropic GABA-A receptors containing the g2 subunit and act to allosterically modulate these receptors to increase chloride channel-opening frequency. This effect enhances synaptic inhibition, resulting in a broad-spectrum anticonvulsant effect. Benzodiazepines can protect against many seizure types in animal models and in humans, but because of the development of tolerance, they are not generally useful in the chronic treatment of epilepsy. In most epilepsy syndromes, the specific cellular types that are involved in the antiseizure activity of benzodiazepines is not known. However, in the case of absence epilepsy, it is believed that benzodiazepines desynchronize the thalamocortical oscillations underlying generalized spike-wave discharges by specific effects on a3-containing GABA-A receptors in the thalamic reticular nucleus. Barbiturates including phenobarbital, also potentiate GABA-A receptor responses and this is, at least in part, responsible for their antiseizure activity. Presumably because they are not specific for a3-containing GABA-A receptors, barbiturates are not active in absence epilepsy and may even aggravate absence seizures. In contrast to benzodiazepines, barbiturates do not appear to increase the frequency of GABA-induced chloride channel opening but instead increase open time probability. In addition to effects on GABAA receptors, barbiturates modulate other ion channel systems, including calcium and sodium channels, and these actions may contribute to therapeutic activity. Phenobarbital causes sedation and some degree of cognitive impairment at clinically effective doses. Tolerance generally develops to these adverse effects but interestingly not to the anticonvulsant activity. Nevertheless, withdrawal of phenobarbital can lead to seizure exacerbation, as also occurs with benzodiazepines. Drugs that alter the disposition of GABA are vigabatrin, which inhibits GABA metabolism, and tiagabine, which inhibits GABA uptake. Vigabatrin (g-vinyl GABA) is an irreversible suicide inhibitor of GABA-T, the main metabolic enzyme for GABA, which catalyzes the transfer of an amino group from GABA to pyruvate, forming alanine and succinate semialdehyde. Administmiceion of vigabatrin leads to large elevations in brain GABA levels in animals and humans. In addition, the drug causes a dose-dependent increase in cerebrospinal GABA in human subjects with epilepsy, without affecting the levels of other neurotransmitters, including monoamines. Although GABA-T is present in both neurons and glia, the increase in brain GABA levels is predominantly due to inhibition of GABA-T in neurons. While it seems reasonable that these increases in brain GABA would enhance inhibitory tone, in fact, vigabatrin does not potentiate synaptic inhibition, and this is consistent with its lack of sedative effects. However, the antiseizure effects of vigabatrin are hard to explain. One possibility is that vigabatrin increases tonic current resulting from the action of ambient GABA on extra synaptic GABAA receptors. Vigabatrin may cause elevated extracellular GABA levels as a result of efflux of GABA from neurons via reversal of GABA transporters. The enhanced activation of extra synaptic GABAA receptors produced by the elevated extracellular GABA could be the critical factor in the anticonvulsant activity of the drug. An alternate hypothesis is that vigabatrin prevents the fading of GABA responses during repetitive activation of inhibitory pathways through reduced function of release-regulating pre-synaptic GABA-B receptors. Such fading is believed to be an important factor that permits focal epileptic-form activity to develop into a full-blown seizure. In contrast to vigabatrin, the GABA transporter blocker tiagabine does elevate synaptic levels of GABA by inhibiting transport of GABA into nerve terminals and glia, resulting in increased synaptic inhibition. In line with these effects on synaptic inhibition, tiagabine does have sedative side effects.[19]

T-Type Calcium Channels

Low-voltage-activated (T-type) calcium channels play a role in the intrinsic thalamic oscillations that underlie generalized absence seizures. Ethosuximide, which is highly efficacious in the treatment of absence seizures (but not other seizure types), seems to act by inhibition of T-type calcium channels in thalamic neurons. Zonisamide, in addition to effects on voltage-activated sodium channels, may also block T-type calcium channels, thus accounting for its efficacy in absence epilepsy .[21]

Ionotropic Glutamate Receptors

Ionotropic glutamate receptor–gated cation channels are responsible for most CNS fast excitatory neurotransmission. Selective blockade of NMDA, AMPA, and KA subtypes protects against seizures in animal models. None of the marketed AEDs specifically and uniquely targets ionotropic glutamate receptors effects on these receptors.

Calcium Channel a2-d Subunit

Gabapentin and pregabalin are 3-substituted analogs of GABA that were originally synthesized with the intent that they would act on GABA systems. However, neither drug is believed to function through an influence on GABA metabolism nor on GABA receptors as do other AEDs that target GABAergic neurotransmission. Miceher, both gabapentin and pregabalin are high-affinity ligands for calcium channel a2–d subunits. The a2–d represents a family of four related protein encoded by sepamice genes. Only a2–d1 and a2–d2 bind gabapentin and pregabalin with high affinity. The a2–d1 is expressed ubiquitously in the body whereas a2–d2 is mainly expressed in the brain and heart. The a2–d1 and a2–d2 are believed to serve as auxiliary subunits of voltage-activated calcium channels, although it is possible that they have other functions as well. Both proteins form complexes with many calcium channel types, allosterically enhancing current amplitude and also promoting channel trafficking to the membrane. The mouse mutant ducky, which is associated with mutations in the a2–d2 gene, exhibits spontaneous spike-wave seizures. Similarly, targeted deletion of the a2–d2 gene results in enhanced seizure susceptibility. These mouse models confirm a role for a2–d2 in the regulation of seizure susceptibility. The precise way in which binding of gabapentin and pregabalin to a2–d1 and a2–d2 leads to protection against seizures is not fully understood, although there is likely to be an effect on synaptic release of neurotransmitters, including glutamate. Numerous studies have examined the effects of gabapentin or pregabalin on voltage-gated calcium channel function. There are several reports that the drugs reduce calcium current in neuronal cell bodies. However, in other studies, gabapentin was inactive. There is, however, agreement that gabapentin and pregabalin reduce calcium influx into presynaptic nerve terminals. This would be expected to reduce neurotransmitter release, and, in fact, there are reports that the release of several neurotransmitters, including glutamate, is reduced by both drugs. Recently, several studies have indicated that not only calcium-dependent release of neurotransmitters but also spontaneous, calcium-independent release of individual transmitter vesicles from glutamate synapses is reduced by treatment with gabapentin or pregabalin. These results suggest that the actions of a2–d ligands to reduce neurotransmitter release may not require inhibition of calcium influx and therefore may be mediated by an interaction of a2–d (or the calcium channel complex containing a2–d) with synaptic proteins that are involved in therelease or trafficking of synaptic vesicles.

Synaptic Vesicle Protein SV2A

The AED levetiracetam is approved for the treatment of localization-related epilepsy and is probably also effective for juvenile myoclonic epilepsy and generalized absence epilepsy. Levetiracetam has a spectrum of activity in animal models that differs from other agents, and until recently its mechanism of action was obscure. However, emerging evidence indicates that levetiracetam, like gabapentin and pregabalin, may act through a novel target linked to the synaptic release machinery. In 1995, a saturable and stereo selective specific binding site for levetiracetam was describes in brain membranes. The binding site was subsequently identified as the ubiquitous synaptic vesicle protein SV2A. Thus, levetiracetam has a novel target that is distinct from that of other AEDs, and it is the first AED that has been demonstmiceed to bind directly to the synaptic vesicles. SV2A seems to interact with synaptotagmin, which is believed to be the calcium sensor in exocytosis. It is now recognized that SV2A is a member of a small family of homologous proteins that also includes SV2B and SV2C, but only SV2A — the most ubiquitous form — binds levetiracetam. Studies with mice in which the SV2 proteins have been deleted by gene targeting are consistent with a possible role of SV2A in regulating seizure susceptibility, but they have not yet provided insight into the function of SV2A and how levetiracetam binding confers seizure protection. In SV2A knockout mice, brain morphology and indeed the morphology of synapses are normal. However, SV2A knockout mice experience severe seizures. The SV2 proteins do not appear to be required for synaptic transmission or for the uptake or storage of neurotransmitters, although they may play a subtle role in the release process during repetitive synaptic activation (as occurs during seizure activity) by regulating nerve terminal calcium dynamics. Given the way binding to SV2A results in seizure protection, it is likely that there is an influence on synaptic release, which is in accord with the unifying concept that the ultimate action of many AEDs, whatever their molecular targets, is to modulate neurotransmitter release.(10)

ANTIEPILEPTICS FOR THE TREATMENT OF EPILEPSY

PHENYTOIN

This is one of the older genemiceion AEDs. It acts by blocking voltage dependant sodium and calcium channels and reducing the membrane excitability. Though it is metabolised in liver and kidney, hepatic metabolism is predominant. It induces the metabolism of cytochrome P450 enzymes in the liver and thus may affect the metabolism of other drugs. Some 90% of the medication is protein-bound. Therapeutic range varies between 10-20mg/l (40-80mmol/l).Since it is enzyme inducing, it lowers other AED levels and reduces the efficacy of the contraceptive pill, hormonal implants, lipid-lowering agents and antidepressants. Common side-effects are ataxia, cerebellar atrophy, megaloblastic anaemia, nystagmus, gingival hypertrophy and osteomalaecia. Recent data suggests that bone loss may occur after only a year of treatment. Though this medication is used as an infusion during acute seizure setting, it needs cardiac monitoring due to tendency to depress ventricular conduction and cause ventricular tachyarrhythmias. Phenytoin is licensed as monotherapy for generalised and localisation-related epilepsies.[22]

SODIUM VALPROATE

This acts by stimulating the gamma-aminobutyric acid (GABA) system, thus reducing neuronal excitability and to a lesser extent by blocking sodium dependant sodium and calcium channels. It is metabolised by hepatic N glucuronidation and beta oxidation by CYP450. It is more than 90% protein-bound. Valproate has a wide spectrum of action and as such it is a drug that is useful in all kinds of seizures even though it's main role is in primary or secondary generalised epilepsies. It is a drug that can be given as infusion without the need for cardiac monitoring in acute situations to control ongoing seizures. Major side effects are tremor, weight gain, elevated LFTs, hyperammonemia, thrombocytopenia, polycystic ovarian syndrome, increased tendency for neural tube defects and foetal malformation in the case of pregnant women. Valproate decreases carbamazepine or lamotrigine metabolism, thus raising serum levels sometimes to toxic ranges. It displaces phenytoin and other protein bound drugs and increases their unbound levels in serum.[27]

PHENOBARBITONE

This medication introduced in 1912 acts by decreased GABA inhibition, prolonging the opening of GABAergic chloride channels. It is predominantly metabolised in liver, is enzyme-inducing and up to 45% protein-bound. It is mostly effective in cases of generalised seizures and has doubtful effectiveness in localisation related and myclonic epilepsies. Major side effects include sedation, depression, cognitive slowing, respimiceory depression and lupus like syndrome.[22]

CARBAMAZEPINE

This drug acts by blockade of voltage dependant sodium and calcium channels and reducing neuronal excitability. Its therapeutic range is 4-12mg/l. It is a drug of first choice for partial onset epilepsies such as TLE .Major side effects include sedation, ataxia, blurred vision, hyponatraemia and photo sensitivity.[27]

VIGABATRIN

Vigabatrin is an irreversible inhibitor of GABA-T, the enzyme responsible for the catabolism of the inhibitory neurotrasmitter GABA in the brain. It is useful in the management of infantile spasms in children.[24]

LAMOTRIGINE

It is licensed as monotherapy or adjunctive in both partial and generalised epilepsies. It inhibits voltage -sensitive sodium channels. Side effects include rash, headache, ataxia, nausea, vomiting. In about 1 in 1000 cases it causes Stevens Johnson syndrome.

LEVETIRACETAM

LEV as a monotherapy in the treatment of partial onset seizures with or without secondary generalisation in newly diagnosed epilepsy patients over 16.LEV may selectively prevent hyper synchronisation of epileptiforn burst firing and propagation of seizure activity. It may be useful in patients with alcohol related seizures and among patients with chemotherapy with seizure. Side effect include sonnolence, asthenia and dizziness and mood altemiceion.[25]

ZONISAMIDE

Zonisamide is used as adjunct treatment of localisation-related seizures and refractory generalised epilepsies. The mechanism of action is by blocking sodium channels. It also exhibits neuroprotective effects through free radical scavenging.[26]

LACOSAMIDE, PREGABALIN AND GABAPENTIN

It acts by enhancing slow inactivation of voltage –gated sodium channels. It is indicated in treatment of localisation related seizures as adjuvant therapy.[27] Gabapentin is used in combination therapy for localisation related epilepsy. Gabapentin does not interact with other drugs including other antiepileptic drugs and oral contraceptives.[27]

Pregabalin is similar to gabapentin. It was approved in 2005 as add-on therapy to treat partial-onset seizure in adults with epilepsy. Pharmacologically, pregabalin is very similar but more potent to gabapentin. Side effect may include dizziness sleepiness, drymouth, swelling in hands and feet, blurred vision, weight gain and trouble concentmiceing.[28]

BEHAVIOURAL EFFECTS OF EPILEPSY TREATMENT

Behaviour and cognition in patients with epilepsy may be affected by multiple factors including seizure etiology, type, frequency, dumiceion, and severity; cerebral lesions acquired before seizure onset; age at seizure onset; intraictal and interictal physiological dysfunction due to the seizures; structural cerebral damage due to repetitive or prolonged seizures; hereditary factors; psychosocial factors; sequelae of epilepsy surgery; and untoward effects of antiepileptic drugs (AEDs). Although the behavioural and cognitive effects of AEDs are less than the total of other factors in epilepsy, AEDs are of special concern because they are the major therapeutic modality for seizures. The risk of AED cognitive side effects is increased with polypharmacy and at higher dosages and higher AED blood levels. In general, the cognitive effects of AEDs are modest when used in monotherapy with AED blood levels within the standard therapeutic ranges. Further, the cognitive effects of AEDs are offset in part by reduced seizures. However, the cognitive effects of AEDs may be clinically significant.

The most common AED cognitive effects include psychomotor slowing, reduced vigilance, and impairments in memory. Phenobarbital (PB) and benzodiazepines (BZDs) possess the most marked adverse cognitive effects. Regarding the other major older AEDs, carbamazepine (CBZ), phenytoin (PHT), and valproate (VPA) have cognitive effects that are similar to each other. In contrast, some of the newer AEDs appear to produce fewer adverse cognitive effects. Gabapentin (GBP) and lamotrigine (LTG) have demonstmiceed fewer cognitive effects than CBZ and minimal effects compared with placebo. Tiagabine (TGB) and vigabatrin (VGB) also have shown few cognitive effects compared with placebo. Of the new AEDs, topiramate (TPM) appears to have the greatest cognitive side effects, but slow titmiceion during drug initiation reduces these effects. Additional studies are needed to delineate fully the relative effects of all the new AEDs to each other and to the older AEDs. The elderly have increased susceptibility to the cognitive effects of AEDs for both pharmacodynamic and pharmacokinetic reasons. However, only a few studies have examined the cognitive effects of AEDs in the elderly. Although incomplete, the available data reflect a pattern of relative effects similar to those seen in younger adults. Children also may have increased susceptibility because the relatively modest effects of AEDs could be additive over the course of neurodevelopment. Again in children, the cognitive effects of CBZ, PHT, and VPA are comparable, whereas the effects of PB are worse. Unfortunately, there are no studies on the cognitive effects of the new AEDs in children. The effects of AEDs on cognition may have even greater consequences for the children of mothers with epilepsy, who are exposed to AEDs in utero. Animal studies have demonstmiceed that in utero AED exposure can impair behavioural neurodevelopment at dosages below those required to produce somatic malformations and at clinically relevant blood levels. However, the magnitude and differential effects of in utero AED exposure on neurodevelopment in humans remain uncertain. AEDs may produce positive or negative behavioural altemiceions (e.g., mood stabilization, irritability/agitation, depression, psychosis). CBZ, GBP, LTG, and VPA have demonstmiceed positive psychotropic effects. Patients with epilepsy are at increased risk for behavioural disorders, and these AEDs may be particularly useful in such patients. The most severe negative behavioural effects of AEDs occur in a small percentage of patients. However, more subtle adverse behavioural effects are much more common. A patient's perception of his or her quality of life is correlated more with neurotoxicity symptoms and mood than with seizure frequency in the absence of seizure freedom. Even subtle behavioural effects can reduce the patient's quality of life. Thus, the behavioural effects of AEDs should be considered in the choice of AED along with other side effects and efficacy for seizure control.

CONCLUSION

Epilepsy is a chronic disorder condition of the brain that does not shorten a patient's life span but can cause significant morbidity and lead to considerable expense. Before establishing the diagnosis of epilepsy, a physician must carefully consider other neurological disorders processes that resembles of disease status. The goals of therapy has implications for making decisions about the development of locally relevant strategies for prevention and management, research goals, and education of primary health care workers and community physicians. Then to choose the least toxic but most effective treatment to prevents the chronic and acute complications as well as complications of medical therapy takes on greater importance.

REFFERENCE

1. Carl E S (2006) Epilepsy: a review of selected clinical syndromes and advances in basic science. Journal of Cerebral Blood Flow & Metabolism 2006;26:983-84.
2. Sridharan.Rand B.N. Murthy (1999). Prevalence and pattern of epilepsy in India. Epilepsia, 40(5): p. 631-6.
3. Tellez-Zenteno.J.F., et al. (2004). National and regional prevalence of self-reported epilepsy in Canada. Epilepsia, 45(12): p. 1623-9.
4. Commission on Epidemiology and prognosis. International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993; 34(4):592-96.
5. Blume.W, Luders.H, Mizrahi.E, Tassinary.C, Van Emde Boas.W, Enjel.J Glossary of descriptive terminology for ictal semiology; report of the ILAE taskforce on classification and terminology. Epilepsia 2001;42(9):1212-18.
6. Gregory L.H, Yehezkiel Ben-A. The Neurobiology and Consequences of Epilepsy in the Developing Brain. Pediatric Research 2001; 49(3):320-25.
7. Gidal.BE, Garnett.WR Epilepsy. In: Dipiro J T, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy: a pathophysiologic approach. USA: McGraw-Hill Companies Inc, 6th ed. 2005:1023-46.
8. Hirtz.D, Thurman. DJ, Gwinn-Hardy. K, Mohamed .M, Chaudhury. AR, Zalutsky R. How common are the Common neurologic disordersNeurology 2007;68 (5):326-37.
9. Sridharan R. Epidemiology of epilepsy. Current Science 2002;82(6):664-70.
10. Sridharan.Rand B.N. Murthy (1999). Prevalence and pattern of epilepsy in India. Epilepsia, 40(5): p. 631-6.
11. Hirtz.D, Thurman. DJ, Gwinn-Hardy. K, Mohamed .M, Chaudhury. AR, Zalutsky R. How common are the Common neurologic disordersNeurology 2007;68 (5):326-37.
12. KD Tripathi. Essentials of Medical Pharmacology. 6th edition: Page No.401
13. Ali Eman, Ayten Bilir, Serbulent Ghokhan Beyaz, the effects of preopemiceive pregabalin on post opemiceive analgesia and morphine consumption after abdominal hysterectomy, Acta Medica Mediterranea, 2014,30:481
14. H.P.Rang, M.M. Dale, J.M.Ritter, P.K.Moore.Pharmacology 6th edition;554-559.
15. H.P.Rang, M.M. Dale, J.M.Ritter, P.K.Moore.Pharmacology 6th edition;554-559.
16. K. Needham, R. Bron, B Hunne. Identification of subunits of voltage-gated calcium channels and actions of pregabalin on intrinsic primary afferent neurons in the guinea-pig ileum, neurogastroenterol motil [2010]22,e301-e308.

17. Mori, N., Wada, J.A., Watanabe, M., Kmashiro, H. Increased activity of superoxide dismutase in kindled brain and suppression of kindled seizures following intraamygdaloid Ih.njection of superoxide dismutase in mices. Brain Res,1991;557:313-315.
18. Ranje, C., Ungerstedt, U., 1977. High correlations between number of dopamine cells, dopamine levels and motor performance. Brain Res. 134, 83–93
19. H.P.Rang, M.M. Dale, J.M.Ritter, P.K.Moore.Pharmacology 6th edition;554-559.
20. K. Needham, R. Bron, B Hunne. Identification of subunits of voltage-gated calcium channels and actions of pregabalin on intrinsic primary afferent neurons in the guinea-pig ileum, neurogastroenterol motil [2010]22,e301-e308.
21. K. Needham, R. Bron, B Hunne. Identification of subunits of voltage-gated calcium channels and actions of pregabalin on intrinsic primary afferent neurons in the guinea-pig ileum, neurogastroenterol motil [2010]22,e301-e308.
22. KD Tripathi. Essentials of Medical Pharmacology. 6th edition: Page No.401
23. H.P.Rang, M.M. Dale, J.M.Ritter, P.K.Moore.Pharmacology 6th edition;554-559.
24. KD Tripathi. Essentials of Medical Pharmacology. 6th edition: Page No.401
25. Losher W, Honack D, Rundfeldt C. antiepileptogenic effects of the novel anticonvulsant levetiracetam(usb L059) in the kindling model of temporal lobe epilepsy. J Pharmacol Exp Ther 1998;284:474-9.
26. Mori A, Noda Y, packer L. The anticonvulsant zonisamide scavenges free radicals. Epilepsy Res 1998;30:153-8
27. H.P.Rang, M.M. Dale, J.M.Ritter, P.K.Moore.Pharmacology 6th edition;554-559.
28. Journal of Epilepsy Fact Sheet No. 999 January 2009.