Review Article

Epilepsy: Current Perspective

Mendhi S M*, Suralkar A A, Chitlange S S, Mane P B, Gairola N, Sharma A N
Department of Pharmacology, Padm. Dr. D. Y. Patil Institute of Pharmaceutical Sciences & Research, Pimpri, Pune, India.
***Corresponding author's E-mail:** sachin24mendhi@gmail.com

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ABSTRACT

Epilepsy is the name for a group of chronic neurological disorder characterized by recurrent epileptic seizures. It is responsible for an enormous amount of suffering, affecting some 50 million people of all ages, especially in childhood, adolescence and the ageing population. The suffering caused by the disease is both physical and psychosocial, bringing a huge burden to people with epilepsy, their families and society at large. Nearly 90% of the people with epilepsy are found in developing regions. Epilepsy is almost always treated using antiepileptic drugs. Recent studies in both developed and developing countries have shown that up to 70% of epilepsy cases can be successfully treated, yet about three fourths of affected people in developing countries do not get the proper treatment what they need. People with epilepsy and their families can suffer from stigma and discrimination in many parts of the world. Epilepsy increases a person's risk of premature death by about two to three times compared to the general population. So there is need to treat or cure this disorder & important to study about epilepsy. The present review summarizes information about epilepsy and the brief Summary of antiepileptic drugs with producing their side effects which is helpful for researchers. Also described the pharmacological management of eclampsia and pre-eclampsia.

Keywords: Epilepsy, Seizures, Antiepileptic Drugs, Eclampsia, Pre-eclampsia

INTRODUCTION

The word "Epilepsy" is derived from Greek word meaning "a condition of being overcome, seized or attacked." The word "Epilepsy" means nothing more than the tendency to have seizures. The brain is highly complex & sensitive organ. It controls and regulates all our actions, movements, sensations, thoughts and emotions. It is the seat of memory, and it regulates involuntary inner workings of the body such as function of the heart and the lungs. The brain cells work together, communicating by means of electric signals.[1] Occasionally there is an abnormal electrical discharge from a group of cells, and the result is seizure. The types of seizure depend upon the part of brain where the abnormal electrical discharge arises.

Seizures result from an electrochemical disorder in the brain. Brain cells use chemical reactions to produce electrical discharges. Each brain cell either excites or inhibits other brain cells with its discharges. When the balance of excitation and inhibition in a region of brain is moved too far in the direction of excitation, then a seizure can result.[2]

The type of seizure depends upon several factors. One of the most important factors is where in the brain the abnormal electrical discharge occurs. Figure given below shows the four lobes of the brain (frontal, temporal, parietal and occipital) and where key regions of the brain are located. Strength and sensation are laid out along the border of the frontal and parietal lobes, with strength more toward the front (frontal) and skin sensation more toward the back (parietal) of the strip. Moving laterally and down the brain are control areas for trunk, arm, hand, fingers, face, lips, and tongue, with tongue most laterally and inferiorly on the motor strip.

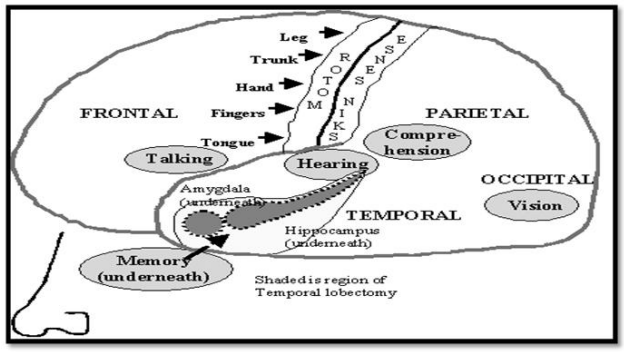


Figure 1: Brain Regions

The progression of electrical activity during a seizure can march through this area activating each muscle group in sequence over seconds to minutes. A talking center, called Broca's area, is located in the left frontal lobe in front of the motor strip, and a speech comprehension area called Wernicke's area in the left temporal-parietal region for most right-handers. Speech centers may be on the right or both sides for left-handers. Visual perception is governed from the posterior poles of the occipital lobes. In general, brain functions are crossed: the left side of the brain receives information from, and gives information to, the right side of the body, and vice versa.[3]

The undersurface of the temporal lobe is particularly prone to have seizures. The temporal lobes include the parts of the brain most commonly involved in adult epilepsy. Such temporal structures are given Greek names, such as "amygdala" (almond) and "hippocampus" (sea-horse). The amygdala and hippocampus are targets

for surgical removal in surgery for epilepsy. These structures are also involved in expression of emotionality and in ability to form memories. In simple terms, if an abnormal electrical discharge originates in motor cortex the patient will experience a motor seizure; if in sensory cortex: a sensory perception; if in visual cortex lights, flashes, or jagged lines. Seizures in deep temporal lobe structures present with arrest of activi-ties, loss of memory or awareness, and automatic (robot-like) behavior. If a seizure spreads to all regions of brain, then a tonic-clonic (grand mal) seizure results, with loss of consciousness, stiffening and jerking.[4]

Before discussing the details of seizures and epilepsy, it is worth making the point that epilepsy is common. Because of the social stigma of this disease, many people with epilepsy do not make it publically known.

Epilepsy

Epilepsy is defined as a condition characterized by *recurrent* (two or more) epileptic seizures, unprovoked by any immediate identified cause.[5]

Prevalence

Prevalent epilepsy is defined as a diagnosis of epilepsy (recurrent unprovoked seizures) at some point prior to the prevalence period or date. An active prevalence case is one that continues to experience the burden of epilepsy based either on recency of seizure (generally in the year prior to the prevalence date or within 5 years of the prevalence date, depending on the study) and/or recency of anti-seizure medication use. Point prevalence reflects the number of cases of active epilepsy on prevalence day, divided by the total population under study on that prevalence day.[6]

Incidence

Incidence of epilepsy is defined as the number of new cases of epilepsy over a specified time period.

Age-adjustment

Since the incidence and prevalence of epilepsy vary with age, overall population incidence and prevalence cannot be compared unless the age structures of the populations are identical.[7]

Etiology

Broad etiologic categories included idiopathic, symptomatic, and cryptogenic (ILAE, 1989). Idiopathic epilepsies are assumed to have a genetic basis and generally have onset during childhood. Symptomatic epilepsies typically follow an identified brain insult. For cryptogenic epilepsies, the cause of the epilepsy is unknown but many presume that a cause could be identified with sufficient investigation.[8]

By definition, one seizure does not make epilepsy, nor does a small series of seizures that have an immediate precipitating factor, for example, alcohol withdrawal seizures. The seizures must be spontaneous and recurrent to represent epilepsy.

SEIZURE CLASSIFICATION

Simplified international classification of seizures:

A. Partial Seizures (Focal, start in one place)

1. Simple (no loss of consciousness/memory)

- Sensory
- Motor

2. Sensory-Motor

- Psychic (abnl thoughts / perceptions)
- Autonomic (Heat, flushing, GI)
- Complex (loss of consciousness / memory)
- With or without aura (warning)
- With or without automatisms

B. Secondarily generalized (spreads)

1. Generalized

- Absence, typical or atypical (petit mal)

2. Tonic-Clonic (grand mal)

- Myoclonic
- Atonic
- Tonic

3. Unclassifiable

A. Partial Seizures

Partial seizures are further divided into simple partial seizures with no alteration of consciousness or memory, or complex partial seizures with alteration of consciousness or memory. Simple partial seizures can be motor seizures with twitching, abnormal sensations, abnormal visions, sounds or smells, and distortions of perception. Seizure activity can spread to the autonomic nervous system, resulting in flushing, tingling, or nausea. All such simple partial seizures will be in clear consciousness and with full recall on the part of the patient. If the patient becomes con-fused or cannot remember what is happening during the seizure, then the seizure is classified as a complex partial seizure.

Complex Partial Seizures

Complex partial seizures previously were called "psychomotor seizures", "temporal lobe seizures" or "limbic seizures". These words are all synonyms. Complex partial seizures may have an aura, which is a warning for the seizure, typically a familiar feeling (déjà vu), nausea, heat or tingling, or distortion of sensory perceptions.

About half of the patients do not have any remembered aura. During the complex partial seizure patients may fumble or perform automatic fragments of activity such

as lip smacking, picking at their clothes, walking around aimlessly, or saying nonsense phrases over and over again. These purposeless activities are called automatisms. About 75% of people with complex partial seizures have automatisms. Those who do not simply stop, stare and blank out for a few seconds to minutes.[9]

B. Generalized Seizures

Generalized seizures are divided into several categories as listed below.

1. Absence Seizures

Absence seizures previously were called petit mal seizures. Absence seizures usually have onset in childhood, but they can persist into adulthood. Absence seizures present with staring spells lasting several seconds, sometimes in con-junction with eyelid fluttering or head nodding. These seizures can be difficult to distinguish from complex partial seizures that also may result in staring. Absence seizures usually are briefer and permit quicker recovery. The EEG also helps to distinguish an absence from a complex partial seizure (see below).[10]

2. Tonic-Clonic Seizures

Generalized tonic-clonic seizures previously were called grand mal seizures. These seizures start with sudden loss of consciousness and tonic activity (stiffening) followed by clonic activity (rhythmic jerking) of the limbs. The patients eyes will roll up at the beginning of the seizure and the patient will typically emit a cry, not because of pain, but because of contraction of the respiratory muscles against a closed throat. Generalized tonic-clonic seizures usually last one to three minutes. The seizure itself is called an ictus. After the seizure, the patient is "post ictal sluggish, sleepy and confused, variably for hours. Any seizure can have a post ictal period.

3. Secondarily Generalized Seizures

Seizures that begin focally can spread to the entire brain, in which case a tonic-clonic seizure ensues. It is important, however, to distinguish those that are true grand mal, generalized from the start, from those that start focally and secondarily generalize. Secondarily generalized seizures arise from a part of the brain that is focally abnormal. Drugs used to treat primarily and secondarily generalized tonic-clonic seizures are different. Patients with secondarily generalized tonic-clonic seizures may be candidates for curative epilepsy surgery ; whereas, primarily generalized tonic-clonic seizures are not surgical candidates, because there is no seizure origin site (focus) to remove.

4. Atonic Seizures

Atonic seizures are epileptic drop attacks. Atonic seizures typically occur in children or adults with wide-spread brain injuries. People with atonic seizures suddenly become limp and may fall to the ground. Football helmets are sometimes required to protect against serious injuries.

5. Myoclonic Seizures

Myoclonic seizure is a brief un-sustained jerk or series of jerks, less organized than the rhythmic jerks seen during a generalized tonic-clonic seizure. Other specialized seizure types occasionally are encountered.

6. Tonic Seizures

Tonic seizures involve stiffening of muscles as the primary seizure manifestation. Arms or legs may extend forward or up into the air. Consciousness may or may not be lost. By definition, the clonic (jerking) phase is absent. Classification can be difficult, because stiffening is a feature of many complex partial seizures. Tonic seizures, however, are much less common than are complex partial or tonic-clonic seizures.

7. Mixed Seizure Types

Patients can have more than one seizure type. One seizure type may progress into another as the electrical activity spreads throughout the brain. A typical progression is from a simple partial seizure, to a complex partial seizure (when the patient becomes confused), to a secondarily generalized tonic-clonic seizure (when the electrical activity has spread throughout the entire brain). The brain has control mechanisms to keep seizures localized. Antiepileptic medications enhance the ability of the brain to limit spread of a seizure.[11]

Common types

Complex partial seizures account for about 40% of all seizure types in adults. Simple partial seizures ac-count for about 20%, primary generalized tonic-clonic seizures about 20%, absence about 10% and other seizure types for 10%. In a pediatric population, absence seizures occupy a greater proportion.

Other types of Seizures

1. Benign rolandic epilepsy is an epileptic syndrome occurring in young children that is age limited (You stop having seizures in ten year) Salivation, twitching of mouth or upper extremity on one side are typical manifestations. Seizures occur almost nocturnally

2. Juvenile myoclonic epilepsy is epilepsy characterized by onset in childhood or adolescence and is associative with extremity jerking and generalized tonic clonic seizures ('grand mal') within an hour or two of wakening from sleep. Seizures that may be precipitated by sleep deprivation, alcohol intake or coffee (strange) tend to occur in the morning.

3. Status epilepticus is the term used to describe recurrent seizures without recovery of consciousness between attacks. This is medical emergency and can be life threatening or cause brain damage. Immediate action to get the necessary medical care treatment should be taken.

4. Pseudo- Seizures (Psychogenic- seizures) are quite common and can occur in people who have, or do not

have epilepsy. The attacks are triggered by a conscious or unconscious desire for more care and attention. The seizures start with rapid breathing, triggered by mental stress, anxiety, or pain. As the person breath rapidly, they buildup carbondioxide in their body & change their chemistry. This can cause symptoms like seizures: prickling in the face, hands, & feet, stiffening, trembling etc. The appropriate treatment for pseudoseizures is to calm down the patient and start them breathing at normal rate. Treatment also involves investigating the mental & emotional factors that led to pseudo seizures.

5. Other seizure term includes Atonic (Drop attacks), Myoclonic, Infantile spasms, Nocturnal, Photosensitive, Visual, Musicogenic, Jacksonian, Sensory, Bilateral myclonus, Atkinetic, Autonomic, Prolonged seizures and Ictal state.[12]

Signs and symptoms

Characteristics of seizures vary and depend on where in the brain the disturbance first starts, and how far it spreads. Temporary symptoms can occur, such as loss of awareness or consciousness, and disturbances of movement, sensation (including vision, hearing and taste), mood or mental function. People with seizures tend to have more physical problems (such as fractures and bruising), higher rates of other diseases or psychosocial issues.[13]

Rates of disease

The estimated proportion of the general population with active epilepsy (i.e. continuing seizures or the need for treatment) at a given time is between 4 to 10 per 1,000 peoples. However, some studies in developing countries suggest that the proportion is between 6 to 10 per 1,000. Around 50 million people in the world have epilepsy. In developed countries, annual new cases are between 40 to 70 per 100,000 people in the general population. In developing countries, this figure is often close to twice as high due to the higher risk of experiencing conditions that can lead to permanent brain damage. Close to 90% of epilepsy cases worldwide are found in developing regions.[14]

Causes

The most common type - for six out of ten people with the disorder is called idiopathic epilepsy and has no known cause. Epilepsy with a known cause is called secondary epilepsy, or symptomatic epilepsy. The cause could be brain damage from a loss of oxygen or trauma during birth, a severe blow to the head, a stroke that starves the brain of oxygen, an infection of the brain such as meningitis, or a brain tumor.

Risk factors

- Head trauma, central nervous system infections and tumors are associated with secondary epilepsy.
- For the younger population, perinatal complications, congenital, developmental and genetic conditions are associated with epilepsy.
- Cerebrovascular disease conditions that affect the brain and its blood supply are the most common risk factor in the elderly.
- A family history of epilepsy seems to increase the influence of other risk factors.[15]

Tests for Epilepsy / Diagnosis

The most important diagnostic test in epilepsy is a careful history, taking detailed information on the nature of the patient's episodes. To an experienced clinician, the events should sound like seizures. The physician will then perform a physical and neurological examination looking for evidence of brain injury that might give a clue as to the cause and location of the seizure focus. In epilepsy, how-ever, the history is usually more important than the physical examination.

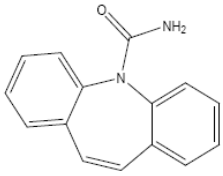
Blood tests will be done to look for infectious or chemical causes of seizures, such as low blood sugar, low blood calcium, low oxygen, kidney failure or liver failure, or drugs or toxins in the blood. Blood tests are also important as a baseline if antiepileptic medications are to be used, since they indicate baseline normality of white blood counts, red blood counts, platelets, liver and kidney function.[16] The physician may get an x-ray of the brain to see if there is an underlying structural cause of the seizures such as tumor, blood clot, or abnormal blood vessels, abscess, old stroke, or other structural causes. A magnetic resonance imaging (MRI) scan is more detailed and useful for seizure diagnosis than is the older CT scan, but individual doctors may choose one over the other. If there is any question of infectious meningitis causing the seizure, then a physician may perform a lumbar puncture (spinal tap) to rule out this condition.

The electroencephalogram (EEG) has special importance in the diagnosis of epilepsy. The EEG measures electrical activity of the brain. Normal brain electrical patterns can be recognized by experienced electroencephalographers.[17] During a seizure the brain shows a high voltage rhythmical pattern of activity, which is a little different for each seizure type. The abnormal electricity appears in a certain region of the brain which can give a clue to what part of the brain has the seizure focus, or place of origin. The EEG can also help classify the type of seizures.[18] EEGs would not be very useful if they required recording during a seizure. Fortunately for diagnosis, 50-80% of individuals have some abnormal EEG patterns, called spikes, in between seizures. These are brief high voltage discharges in the EEG which may mark a tendency for seizures and a place where seizures originate. Patients do not have much in the way of symptoms from spikes be-cause they are so brief. Such spikes are also called interictal spikes, because interictal means between seizures. Absence (petit mal) seizures

have a pattern known as spike-waves with spikes and after going slow waves.[19,20]

ANTIEPILEPTIC DRUGS

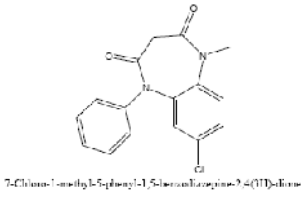
1. Carbamazepine:



5H-dibenzo[b,f]azepine-5-carboxamide
(Carbamazepine)

Carbamazepine is indicated for partial seizures and generalized tonic-clonic seizures. Carbamazepine is likely to act by preventing repetitive firing in depolarized neurons, via a blockade of Na+ channels. Carbamazepine should be introduced in low dosage (100-200 mg daily) to allow tolerance to develop to its CNS side effects. The dose can then be increased in 12 weekly increments of 100-200 mg/day to a maintenance amount that completely controls the seizure disorder.[21] Diplopia, headache, dizziness, nausea and vomiting are the commonest side effects of carbamazepine, some of which may be due to its active metabolite 10,11 epoxicarbazepine. Carbamazepine can cause a range of idiosyncratic reactions, the most common of which is a skin rash, occurring in up to 10% of patients. Rarely, it may cause more severe skin eruptions including erythema multiforme and Stevens-Johnson syndrome. Reversible mild leucopenia often occurs but does not require discontinuation of therapy unless accompanied by evidence of infection or if the cell count is well below 2 x 109/L. Blood dyscrasias and toxic hepatitis occur very rarely.[22] Drugs affected include sodium valproate, ethosuximide, corticosteroids, anticoagulants, antipsychotics and cyclosporine. Drugs that inhibit carbamazepine metabolism and which may result in toxicity include phenytoin, cimetidine, danazol, dextropropoxyphene, diltiazem, erythromycin, isoniazid, verapamil and viloxazine. The substantial variation in carbamazepine concentrations in any given individual over the course of the day as much as 100% with twice-daily dosing using the regular release formulations makes the interpretation of levels problematical. In most patients, the dosage can be titrated adequately on clinical criteria alone. Exceptions include patients with learning disabilities, those in whom adherence to treatment is suspect and those taking a cocktail of AEDs likely to interact with each other.[23]

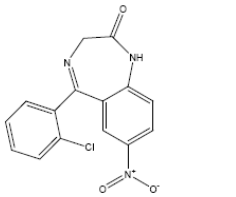
2. Clobazam:



(Clobazam)

Clobazam is a useful adjunctive drug in refractory epilepsy although the majority of responders will develop tolerance to its antiepileptic action. Nevertheless, a useful proportion (up to 2030%) will become and stay seizure-free in the long term. There is some evidence that intermittent use of clobazam reduces the likelihood of tolerance. Short-term administration, e.g. 10-20 mg daily for 3-7 days, can be useful in women with catamenial seizures and as 'cover' for special events such as holidays, weddings and surgery. A single dose of 20-30 mg can have a prophylactic action if taken immediately after the first seizure in patients who suffer regular clusters of complex partial or secondary generalized seizures. Clobazam's structure differs from that of other benzodiazepines, and this may account for its lesser propensity to cause sedation. Nevertheless, tiredness, irritability and depression are commonly reported.

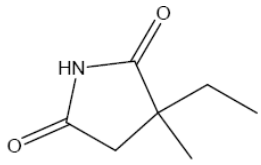
3. Clonazepam:



5-(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepin-2-one
(Clonazepam)

Clonazepam has efficacy against absences, myoclonic jerks and tonic-clonic seizures. Sedation and tolerance, however, substantially reduce its usefulness. Few patients respond well to this drug, and nearly 50% will have an exacerbation of seizures when it is withdrawn. Accordingly, clonazepam now has a limited role in the management of epilepsy, possibly limited to refractory myoclonic seizures. Like other benzodiazepines, clonazepam should only be prescribed as a last resort in patients with learning difficulties.

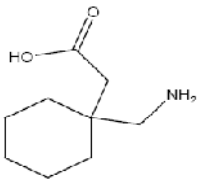
4. Ethosuximide:



3-ethyl-3-methyl-pyrrolidine-2,5-dione
(Ethosuximide)

Ethosuximide is only indicated in the treatment of absence seizures. It acts by reducing calcium conductance in thalamic neurones. Slow introduction is sensible to minimize the development of gastrointestinal and CNS side effects. In children over six years, 500 mg daily is a reasonable starting dose, with further increments as necessary to a maximum of 1-2 g per day. The dose can be increased every 2-4 weeks according to clinical need. Side effects usually involve the gastrointestinal tract (nausea, vomiting, abdominal pain) or CNS (lethargy, dizziness, and ataxia). Blood dyscrasias have been reported rarely.

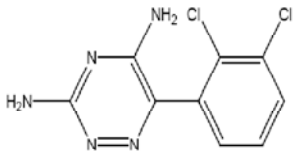
5. Gabapentin:



2-[1-(aminomethyl)cyclohexyl]acetic acid
(Gabapentin)

Gabapentin may occasionally be useful as a second-line treatment of partial seizures. It is of no use in other seizure types. The mode of action of gabapentin is unknown. It interacts with a specific high-affinity binding site in the brain that has not yet been identified functionally. It appears, however, to be associated with a leucine transporter system across neuronal cell membranes and may increase intracellular GABA. The initial dose is 300-400 mg/day and the titration rate consists of weekly dose increases up to 1800-2400 mg/day in the first instance. The optimal dose remains to be established: the maximum recommended dose is currently 3600 mg/day but the efficacy of higher doses is presently being investigated. In view of its short elimination half-life a three times daily dosage is recommended. Gabapentin is not metabolized, exhibits no protein binding and does not induce hepatic enzymes. Its potential for drug interaction is small and, to date, no clinically significant interaction with other drugs has been reported. Gabapentin may, therefore, be a useful add-on drug in patients with a high risk of drug interactions. There is no need to measure its plasma concentration as a guide to dosing. Side effects of gabapentin are mainly related to the CNS and these include drowsiness, dizziness, diplopia, ataxia and headaches. It may occasionally worsen seizures, particularly myoclonic seizures. Gabapentin treatment has not been associated with any serious idiosyncratic reaction to date.

6. Lamotrigine:

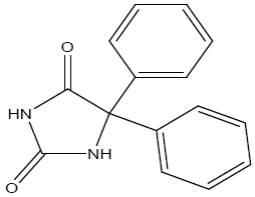


5-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine
(Lamotrigine)

Lamotrigine is a first-line drug for patients with partial seizures and with generalized seizures. Its mode of action is likely to be due to its potential to modulate sodium channels and to block the release of glutamate. The recommended starting dose is 25 mg. This dose is given on alternate days in patients receiving concomitant sodium valproate and daily as monotherapy or in patients receiving other AEDs, with a maximum recommended dose of 400-500 mg/day in two divided doses. Treatment should be slowly titrated upwards over a period of several weeks as too rapid titration may be associated with an increased incidence of adverse events, particularly skin rash.

Lamotrigine does not seem to interact with other concomitantly administered AEDs, although it may increase levels of 10, 11-epoxi-carbazepine, the active metabolite of carbamazepine. Hepatic enzyme inducers, however, increase lamotrigine clearance, reducing its half-life. Hence, higher doses of lamotrigine need to be used with concomitant enzyme inducing drugs such as phenytoin and carbamazepine. Inhibitors of hepatic enzymes, such as sodium valproate, block the metabolism of lamotrigine so that reduced doses of lamotrigine have to be used if both drugs are given together. Oral contraceptives may increase the metabolism of lamotrigine. Headaches, drowsiness, ataxia, diplopia, insomnia, nausea and dizziness are the most commonly reported acute adverse effects of lamotrigine, particularly during dose escalation. A skin rash is the commonest idiosyncratic side effect of this drug and affects up to 5% of patients. The incidence is higher when lamotrigine is used in combination with sodium valproate or if larger initial doses of lamotrigine are used. Rarely, it may cause more severe idiosyncratic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, aplastic anaemia and liver failure.

7. Phenytoin:

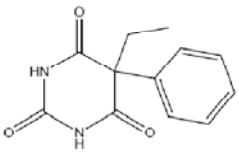


5,5-diphenylimidazolidine-2,4-dione
(Phenytoin)

Phenytoin is a last resort option for partial and tonic-clonic seizures. It is seldom used as a first or second option in view of its toxicity and kinetic profile. It has several pharmacological effects by which it could exert its antiepileptic action, but blockade of Na+ channels appears to be its primary mechanism of action. Phenytoin is one of a handful of drugs that switches from first-order to saturation kinetics at therapeutic dosage. Accordingly, at concentrations around 60 µmol/L, a moderate increment in dose, can produce an unexpectedly large rise in level with accompanying neurotoxicity. Conversely, levels can fall precipitously when the dose is reduced modestly, resulting sometimes in unexpected deterioration in seizure control. The dosage producing the same levels, therefore, varies substantially among different individuals. A starting dose of 5 mg/kg bodyweight will produce levels within the target range of 40-80µmol/L in the majority of patients. Some, however, will saturate at this dose and present with neurotoxicity. Others will require a much higher dose, particularly those with enzyme-induction due to alcohol abuse. Below 20µmol/L, an increment not exceeding 100mg can be tried; patients with phenytoin concentrations above 20–40 could have an increment of 50 mg daily, and if over 40 µmol/L, an increase of 25mg daily. Phenytoin can produce a range of dose-related and idiosyncratic adverse effects

including rash, hepatotoxicity and blood dyscrasias. Reversible cosmetic changes (gum hyperplasia, acne, hirsutism, facial coarsening), although often mild, can be troublesome. Symptoms of neurotoxicity (drowsiness, dysarthria, tremor, ataxia, cognitive difficulties) become increasingly likely with levels above 80µmol/L. The diagnosis of phenytoin toxicity should be made on clinical grounds and not assumed from a high level. The patient will complain of mental slowing and unsteadiness, and neurological examination will reveal cerebellar signs. Permanent cerebellar damage may be a consequence of chronic toxicity, so it is important to examine the patient regularly. In some of these patients, cerebellar atrophy will be apparent on brain imaging, although hard evidence for cause and effect is not readily available. A paradoxical increase in seizure frequency may also occur with marked phenytoin toxicity. Phenytoin is an enzyme inducer and so can accelerate the metabolism of a number of lipid-soluble drugs, including carbamazepine, sodium valproate, ethosuximide, anticoagulants, steroids and cyclosporine. Because its metabolism is saturable, the drug provides a target for drugs such as allopurinol, amiodarone, cimetidine, imipramine and some sulphonamides. Protein binding displacement interactions with AEDs are only clinically relevant when there is concomitant enzyme inhibition, as is the case with the combination of phenytoin and sodium valproate.

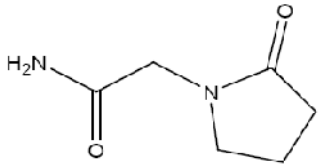
8. Phenobarbital:



5-ethyl-5-phenylpyrimidine-2,4,6(1H,3H,5H)-trione
(Phenobarbital)

Phenobarbital is an established treatment for partial and tonic-clonic seizures but is seldom used nowadays as a first or second option in developed countries because of its potential to cause neurotoxicity. Its antiepileptic effect is likely to be mediated through potentiation of GABA inhibition by binding to a specific site on the GABA receptor. Phenobarbital is an easy drug to use clinically. To minimize sedation, a low dose should be started (30 mg in adolescents and adults), which can be increased gradually (15-30 mg incremental steps) according to clinical requirements. The value of measuring phenobarbital levels is limited, as the concentration associated with optimal seizure control varies considerably. In addition, the development of tolerance to its CNS side effects makes the toxic threshold imprecise. Nevertheless, an unexpectedly low or high concentration may help to make the correct clinical decision in an individual patient. The major problem in the clinical use of phenobarbital is its effect on cognition, mood and behaviour. It can produce fatigue, listlessness and tiredness in adults and insomnia, hyperactivity and aggression in children (and sometimes in the elderly). Subtle impairment of memory, mood and learning capacity can occur in both groups. Depression may be a consequence of long-term administration, and arthritic changes, frozen shoulder, and Dupuytren's contracture can be associated problems. Tolerance develops to the deleterious cognitive effects of the drug but also to its efficacy in some patients. Phenobarbital is an enzyme inducer and can accelerate the metabolism of many lipid-soluble drugs.[22]

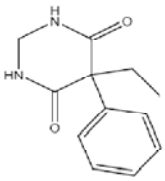
9. Piracetam:



2-oxo-1-pyrrolidineacetamide
(Piracetam)

Piracetam is indicated only as an adjunctive treatment in refractory myoclonus. It has no use in other seizure types. Its mode of action is unknown. The usual starting dose is 7.2 g daily in two or three divided doses, increased weekly by 4.8 g/day according to clinical response. Effective doses are usually between 12 and 24 g/day and this bulk is one of the limiting factors of the use of this drug. Piracetam is generally well tolerated. The commonest side effects are diarrhoea, weight gain, insomnia, and depression. Hyperkinesia has been reported with very high doses. There are no known drug interactions with piracetam.

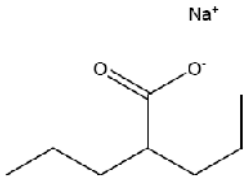
10. Primidone:



(Primidone)

Primidone is metabolized to phenobarbital and its efficacy is similar to that of phenobarbital, but it is not as well tolerated. There is therefore nothing to recommend it over phenobarbital for patients in whom treatment with a barbiturate is contemplated.

11. Sodium valproate: (Valproic acid)

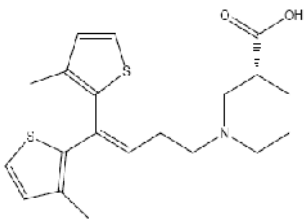


sodium 2-propylpentanoate
(Sodium valproate)

Sodium valproate is a broad spectrum AED effective over the complete range of seizure types, with particular value in the idiopathic generalized epilepsies. It use in women of childbearing potential, however, is problematic in view of its potential terratogenecity. The mechanism of action of sodium valproate is poorly understood. It is likely that

it exerts its antiepileptic effect, at least in part, by a mechanism similar to that of phenytoin and carbamazepine, limiting sustained repetitive firing by an effect on Na^+ channels. Valproate, however, also has GABA ergic properties. The starting dose of sodium valproate for adults and adolescents should be 500 mg/day for one or two weeks, increasing in most patients to 500 mg twice daily. The controlled release formulation can be given once daily. Alterations thereafter should be made according to clinical need. Since the drug can take several weeks to become fully effective, frequent dosage adjustments shortly after initiating therapy may be unwarranted. Because the drug does not exhibit a clear-cut concentration-effect-toxicity relationship and the daily variation in the level at a given dose is wide, routine monitoring is not helpful unless used as a check of adherence to drug therapy. Side effects of sodium valproate include dose-related tremor, weight gain due to appetite stimulation, thinning or loss of hair (usually temporary), and menstrual irregularities including amenorrhoea. Polycystic ovarian syndrome has been reported in some patients. Sedation is an uncommon complaint, although stupor and encephalopathy can occur, albeit rarely, possibly as a consequence of underlying carnitine deficiency. Hepatotoxicity, histologically a microvesicular steatosis similar to that found in Reye's syndrome, affects fewer than one in 20,000 exposed individuals. Children under three years of age receiving AED polypharmacy are the highest risk group. Hyperammonaemia without hepatic damage can be demonstrated in approximately 20% of patients receiving the drug. This is usually transient, but occasionally can present clinically with confusion, nausea and vomiting, and clouding of consciousness. Other sporadic problems include thrombocytopenia and pancreatitis. Valproate is more teratogenic than other commonly used AEDs and this need to be taken into account when treating women of childbearing age. Sodium valproate can inhibit a range of hepatic metabolic processes, including oxidation, conjugation and epoxidation reactions. Targets include other AEDs, particularly phenytoin, phenobarbital, carbamazepine epoxide, and lamotrigine. Aspirin displaces sodium valproate from its binding sites on plasma protein and inhibits its metabolism. Sodium valproate, however, does not interfere with the hormonal components of the oral contraceptive pill.

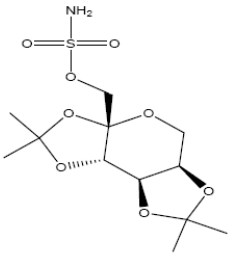
12. Tiagabine:



(R) 1 [4,4 bis(3 methylthiophen 2 yl)but 3 enyl] piperidine 3 carboxylic acid
(Tiagabine)

Tiagabine is a second-line drug for partial seizures with or without secondary generalization. It has no use in any other seizure type. Tiagabine, a nipecotic acid analogue, increases GABA via inhibition of GABA re-uptake in glial cells. The recommended dose is between 30 and 45 mg/day, although higher doses (up to 80 mg/day) have been used. Tiagabine should be started at 10mg/day in two divided doses, and increased by 5-10 mg/day each week up to 30 mg/day in the first instance. Doses above 30 mg/day should be given in three divided doses. Tiagabine does not affect levels of carbamazepine or phenytoin, but may reduce the plasma concentration of valproate by about 10%, which is unlikely to be of clinical importance. Enzyme-inducing AEDs, however, decrease the half-life of tiagabine and patients taking such drugs as concomitant medication may need to take tiagabine three times a day from the beginning of treatment. Side effects are sedation, headache, tiredness and dizziness, Tremor, diarrhoea, irritability, confusion, and depression are seen occasionally. Exacerbations of seizures and cases of non-convulsive status epilepticus have also been reported.[23]

13. Topiramate:

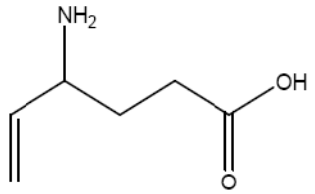


2,3:4,5-Bis-O-(1-methylethylidene)-beta-D-fructopyranose sulfamate
(Topiramate)

Topiramate is licensed as a first-line drug for patients with partial seizures with or without secondary generalization and for generalized seizure disorders. It is a sulphurated fructose and, to date, five possible mechanisms of action have been suggested. It is a strong blocker of voltage-activated sodium channels and has an effect on GABAA receptors. In addition, it blocks the kainate/AMPA type of glutamate receptors, modulates calcium channels and is a weak inhibitor of carbonic anhydrase; it is not clear if this is relevant to its antiepileptic action. Recommended doses are between 75 and 300 mg, although some patients may derive benefit from a dose that is outside this range. The recommended starting dose for most patients is 25 mg once daily, titrating upwards every two weeks in 25 mg/day increments up to 200 mg/day in two divided doses. After that, the dose can be increased by 50 mg each week until seizure control is achieved or side effects develop. Topiramate exhibits linear pharmacokinetics with low levels of protein binding. It has minimal interaction with other AEDs, although hepatic enzyme inducers accelerate its metabolism. Because of this, topiramate doses may need to be adjusted downwards if patients are coming off carbamazepine or phenytoin. Most of the acute and dose-related side effects of topiramate are CNS-related. These include dizziness, drowsiness, headaches, irritability, cognitive slowing and speech impairment. These are usually transient and in some patients seem to be related

to the dose and rate of titration. Paraesthesia and nephrolithiasis have also been reported and are likely to be due to topiramate's carbonic anhydrase inhibitory action. Patients starting topiramate should increase their fluid intake to reduce the risk of kidney stones. Initial weight loss is seen in up to 40% of patients and is usually not problematic. No idiosyncratic side effects have yet been described. Topiramate is teratogenic in some animal models and it is not recommended for use in women of childbearing potential.

14. Vigabatrin:



(RS)-4-aminohex-5-enoic acid

(Vigabatrin)

Vigabatrin is now a last resort treatment for patients with partial seizures. It is, however, still a first-line treatment for infantile spasms, particularly those associated with tuberous sclerosis. It has no use in primary generalized epilepsy and may worsen myoclonic seizures. Tolerance may develop in up to one-third of initial responders. It mode of action is due to increased GABA levels by irreversible inhibition of GABA-aminotransferase. The recommended dose is 1000-2000 mg/day, although doses of up to 4000 mg/day in two divided doses can be used if necessary. Treatment should be started with a low dose (250-500 mg/day), and titrated slowly upwards over a period of several weeks until therapeutic response is achieved. Too rapid titration may be associated with an increased incidence of adverse events. The addition of vigabatrin reduces plasma concentrations of phenytoin. The mechanism is unknown but may be due to decreased phenytoin absorption. Usually this has no clinical significance, but occasionally an increase in phenytoin dose is necessary if seizures increase a few weeks after the introduction of vigabatrin. The corollary of this effect is that plasma phenytoin concentrations rise after the withdrawal of concomitant vigabatrin therapy. Vigabatrin has no other known pharmacokinetic interactions. There is no need to measure the plasma concentration to guide dosing. Sedation, dizziness and headache are the most commonly reported adverse effects, particularly when doses are being increased. Tolerance often develops and the symptoms are frequently self-limiting. These symptoms can usually be avoided by introducing the drug gradually. Allergic skin rashes are extremely rare. Up to 10% of patients taking vigabatrin develop a change in mood, commonly agitation, ill temper and disturbed behaviour, depression or, more rarely, paranoid and psychotic symptoms. Visual field defects have been associated with long-term treatment with vigabatrin in up to 40-50% of patients and this limits the use of the drug to those cases in which potential benefit outweighs risk.[24]

Side effects of established antiepileptic drugs

Carbamazepine: Diplopia, Dizziness, Headache, Nausea, Drowsiness, Neutropenia Hyponatraemia, Hypocalcaemia, Orofacial dyskinesias, Cardiac arrhythmia, Morbilliform Stevens-Johnson Syndrome

Clobazam: Fatigue, Drowsiness, Dizziness, Ataxia, Irritability, Aggression, Psychosis, Hypersalivation, Weight gain, Rash

Clonazepam: Fatigue, Sedation, Drowsiness, Dizziness, Irritability, Aggression, Hyperkinesias, Thrombocytopenia, Rash, Bronchorrhoea

Ethosuximid: Nausea, Anorexia, Vomiting, Agitation, Drowsiness, Headache, Lethargy, Erythema, Aplastic anaemia, Lupus-like syndrome

Gabapentin: Somnolence, Dizziness, Ataxia, Fatigue, Diplopia, Paraesthesia, Amnesia

Lamotrigine: Drowsiness, Diplopia, Headache, Ataxia, Insomnia, Nausea, Vomiting, Aggression, Irritability, Rash, Stevens - Johnson syndrome, Liver failure, Aplastic anemia

Phenobarbital: Fatigue, Listlessness, Tiredness, Depression, Insomnia (Children), Hyperkinesias, Rash, Poor Memory, Macropapular Rash, Hepatotoxicity, Terratogenecity, Necrolysis, Hypocalcaemia

Phenytoin: Nystagmus, Ataxia, Anorexia, Dyspepsia, Neonatal hemorrhage, Megaloblastic anemia, Hyperkinesias (children), Acne, Gum hypertrophy, Hirsutism, Lupus-like syndrome, Hepatotoxicity, Terratogenecity

Piracetam: Diarrhoea, Weight gain, Insomnia, Depression, Agranulocytosis, Folate deficiency

Primidone: Fatigue, Listlessness, Tiredness, Depression, decreased libido, Impotence, Rash, Thrombocytopenia, Osteomalacia, Hypocalcaemia, Terratogenecity

Sodium Valproate: Tremor, Hair loss, Anorexia, Dyspepsia, Alopecia, Hyperammonaemia, Thrombocytopenia, Encephalopathy, Terratogenecity, Drowsiness, Amenorrhea

Tiagabine: Dizziness, Headache, Tremor, Difficulty concentrating, Light-headedness, Asthenia, Abnormal thinking, Increased Nonconvulsive status, Nervousness

Topiramate: Anorexia, Weight loss, Impairment, Impaired speech, Paraesthesia, Kidney stones impaired seizures, Weight gain

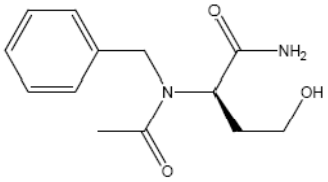
Vigabatrin: Drowsiness, Ataxia, Fatigue, Nystagmus, Diplopia, Irritability, memory, Ataxia, Visual field defects, Tremor, Stupor

New Antiepileptic Drugs

1. Eslicarbazepine acetate:

Eslicarbazepine acetate is a new drug, licensed as an add-on for focal epilepsy, which has similarities to carbamazepine and oxcarbazepine. As such it interacts with voltage-gated sodium channels and this is likely to be its main mode of action. There are no head-to-head comparisions between this drug and oxcarbazepine or carbamazepine but in the randomized clinical trial response was seen in some people that had not responded to carbamazepine or oxcarbazepine. Its tolerability and pharmacokinetic profile are similar to that of oxcarbazepine.

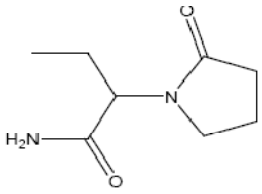
2. Lacosamide:



N2-acetyl-N-benzyl-D-homoserinamide
(Lacosamide)

Lacosamide**,** a functionalized amino-acid, is a second line drug for focal epilepsy in patients over the age of 16 years. Its putative mode of action is not shared with any other currently available AEDs. It is said to enhance the slow inactivation of sodium channels and to modulate collapsing response mediator protein-2 (CRMP-2), although it is not known how this contributes to its antiepileptic action. The recommended doses are between 200 and 400mg/day divided in two doses. It should be started at 50–100 mg/day and increased by 50mg per day every one or two weeks.

3. Levetiracetam:



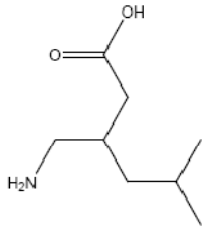
2-(2-oxopyrrolidin-1-yl)butanamide
(Levetiracetam)

Levetiracetam, a piracetam derivative, is a broad-spectrum drug indicated both as a first-line drug and as an add-on drug. No mode of action for levetiracetam has yet been advanced. It has a binding site in the brain for which the natural ligand is the synaptic vesicle protein SV2A although it is not known if this is related to its mode of action. The recommended doses are between 1000 and 3000 mg/day divided into two doses although some people respond to doses outside this range. Levetiracetam should be started at 500 mg/day divided into two doses and increased by 250-500 mg/day every week up to 1000-1500 mg/day in the first instance. Levetiracetam is well tolerated overall and no idiosyncratic side effects have yet been described. Somnolence, dizziness, asthenia, ataxia, insomnia, behavioral problems (particularly irritability, usually of a transient nature) are the most common side effects. No definite pharmacokinetic interactions have yet been identified, but there are reports of potential pharmacodynamic interactions with carbamazepine and phenytoin.

4. Oxcarbazepine:

Oxcarbazepine, the 10-keto analogue of carbamazepine, has a similar mechanism of action to carbamazepine. Its indications are very similar to those of carbamazepine; it is effective in partial seizures with or without secondary generalization and may worsen absences and myoclonic seizures. The recommended doses are between 600 and 2400 mg/day divided into two doses. Oxcarbazepine should be started at 300 mg/day and increased by 300 mg/day each week, up to 900 mg/day in the first instance. Oxcarbazepine weakly induces hepatic enzymes, and so is likely to have fewer drug interactions than carbamazepine. A high dose of the oral contraceptive pill is advised to give protection against pregnancy. Oxcarbazepine exhibits less autoinduction than carbamazepine. Its safety profile is very similar to that of carbamazepine apart from hyponatraemia, which is more pronounced with oxcarbazepine, and allergic skin reactions which are less common. Cross-sensitivity is seen in less than one-third of patients hypersensitive to carbamazepine. There are indications of terratogenecity in animal models, particularly at high doses, and caution should be used in humans.

5. Pregabalin:

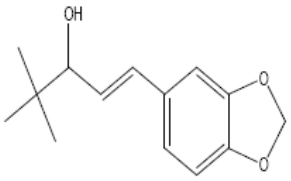


3-(aminomethyl)-5-methylhexanoic acid
(Pregabalin)

Pregabalin has been licensed for the adjunctive treatment of refractory focal epilepsy. It is closely related to gabapentin, it is also a structural analogue of the neurotransmitter GABA that does not seem to affect transmitter response. It modulates calcium channels by binding to a subunit of Ca+ and this action is thought to be the basis of its antiepileptic mechanism. The recommended doses are between 150 and 600 mg divided into two doses, although some people may respond to doses outside this range. Pregabalin would normally be started at 50 or 75 mg bid and increased in incremental steps of 50 mg every two weeks up to 600 mg according to clinical need. Pregabalin is available in 25, 50, 75, 100, 150, 200 and 300 mg tablets. Overall pregabalin is well tolerated and so far no idiosyncratic side effects have been described. Dizziness, drowsiness, ataxia, tremor and diplopia are the most common side

effects. Weight gain, particularly with higher doses, seems to be a chronic side effect of this medication. No pharmacokinetic interactions have yet been identified. In addition to its use in epilepsy, pregabalin has also been indicated for neuropathic pain and there are studies to suggest that it might be useful in generalized anxiety disorders.

6. Stiripentol:



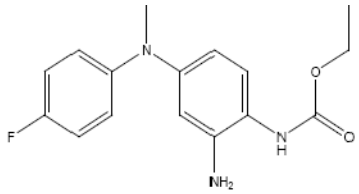
(RS)-(E)-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol

Caution: Stereochemical terms discarded: rs

(Stiripentol)

Stiripentol is licensed as an orphan drug for severe myoclonic epilepsy of infancy (SMEI) when used in conjunction with sodium valproate and clobazam. It is an aromatic alcohol and is unrelated to any other AED. Its mode of action is unknown.

7. Retigabine:

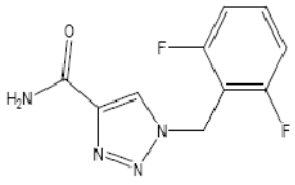


ethyl N-[2-amino-4-[(4-fluorophenyl)methylamino]phenyl]carbamate

(Retigabine)

Retigabine has just been licensed as add-on for focal epilepsy. It is the first drug licensed which acts as a modulator of potassium channels. Effective dose is likely to be somewhere between 600 and 1200 mg a day. The commonest emerging treatment side effects during the clinical trial development programme were CNS-related and drowsiness, dizziness, slurred speech, ataxia, tremor and diplopia. It also seems to cause urinary tract infection in some people. No clinical significant pharmacokinetic interaction has yet been seen. [25]

8. Rufinamide:

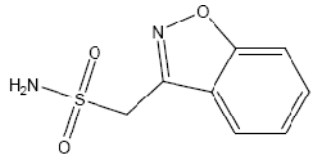


1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide

(Rufinamide)

Rufinamide is licensed as an orphan drug for the Lennox-Gastaut spectrum when used as an adjunctive. It is a triazole derivative and is unrelated to any other AED. Its mode of action is unknown.

9. Zonisamide:



benzo[d]isoxazol-3-ylmethanesulfonamide

(Zonisamide)

Zonisamide, a sulphonamide analogue which inhibits carbonic anhydrase, is a potent blocker of the spread of epileptic discharges. This effect is believed to be mediated through action at voltage-sensitive sodium channels. It is used as a second-line drug for patients with focal seizures with or without secondary generalization. Anecdotal reports of its efficacy in other seizure types, particularly myoclonic seizures, need to be formally tested. Recommended doses are between 200 and 500 mg/day, although some patients may derive benefit from doses outside this range. The recommended starting dose for most patients is 100 mg once daily, titrating upwards every two weeks in 100 mg/day increments until seizure control is achieved or side effects develop. Its long elimination half-life allows once-daily dosing. Zonisamide does not affect levels of carbamazepine, barbiturates or valproate, but may increase the plasma concentration of phenytoin by about 10-15%. Zonisamide metabolism is, however, induced by carbamazepine, barbiturates and phenytoin and higher zonisamide doses may be necessary during co-administration with these AEDs. Side effects of zonisamide include dizziness, drowsiness, headaches, hyporexia, nausea and vomiting, weight loss, skin rashes, irritability, impaired concentration and fatigue. These are mostly transient and seem to be related to the dose and rate of titration. Nephrolithiasis has also been reported, particularly in Caucasians. It is not recommended for women of child-bearing age as there are issues about its teratogenic potential.[26]

Antiepileptic drugs currently in development

At present there are several potential antiepileptic compounds undergoing clinical evaluation. These include: perampanel, brivitiracetam and ganaxalone, which are in the final stages of development.

Side effects of new antiepileptic drugs

Eslicarbazepne acetate	Levitiracetam	Oxacarbazepine	Lacosamide
Fatigue	Headache	Fatigue	Nausea
Drowsiness	Asthenia	Drowsiness	Dizziness
Diplopia	Irritability	Diplopia	Headache
Dizziness	Ataxia	Dizziness	Lethargy
Hyponatraemia	Drowsiness	Hyponatraemia	Diplopia
Ataxia		Ataxia	
Nausea		Nausea	
Nystagmus		Nystagmus	
Tremor		Tremor	
		Rash	

Pregabalin	Retigabalin	Zonisamide
Dizziness	Drowsiness	Drowsiness
Drowsiness	Dizziness	Dizziness
Ataxia	Slurred	speech
Weight gain	Ataxia	Memory impairment
Diplopia	Tremor	Ataxia
Tremor	Diplopia	Confusion
Abnormal thinking		Word-finding difficulties
		Concentration impairment
		Depression
		Dysrasias
		Skin rash

CONCLUSION

Epilepsy is a chronic disorder of the brain that affects people in every country of the world. 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. Seizures can vary from the briefest lapses of attention or muscle jerks, to severe and prolonged convulsions (i.e. violent and involuntary contractions, or a series of contractions, of the muscles).

Seizures can also vary in frequency, from less than one per year to several per day. Epilepsy is one of the world's oldest recognized conditions. Fear, misunderstanding, discrimination and social stigma have surrounded epilepsy for centuries. Some of the stigma continues today in many countries and can impact the quality of life for people with the disorder and their families. In recent years, important advances have been made in the diagnosis & treatment of seizure disorders. However our understanding of the cellular and molecular mechanisms by which epilepsy develops, or epileptogenesis, is still incomplete. So there is need to treat this disease.

In this overview, we highlight some of the prevailing ideas about epilepsy by presenting epilepsy syndroms, theories of their origin mechanisms, & various antiepileptic drugs use in the treatment of epilepsy with their side effects which may helpful for researchers.

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