A review on antiepileptic drug and their uses, mechanism of actions, adverse effects and drug interaction

Mohammad Asif

Department of Pharmacy, GRD(PG) Institute of Management & Technology, Dehradun, 248009, (Uttarakhand), India
*Corresponding author’s E-mail: aasif321@gmail.com

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The main objective of antiepileptic drug (AED) therapy is to permit patients to maintain a normal lifestyle by totally control of seizures with minimal adverse effects. Phenobarbital (PBT), the first extensively used AED, consequently surge in AEDs such as valproic acid (VLPA), bezodiazepines (BZDs) and phenytoin (PHT) was a direct importance of the progress of animal seizure models. Thus many AEDs are developed and associated with dose limiting adverse effects, adverse reactions and toxicity by drug-drug interactions. The awareness that these early compounds could be further optimized for acceptability and properties has rational drug design efforts for progress of subsequent AEDs. Normally AEDs modulate voltage-gated ion channels, facilitate inhibitory neurotransmissions, reduce excitatory neurotransmissions and/or adjust synaptic release. This information, coupled with genetic links with epilepsy, has assisted a more recent target-based approach to novel AEDs.

Capsule Summary: Study on clinically used antiepileptic drugs and its effects on epileptic patients including their different adverse effects are discussed. The new generation AEDs with novel mechanism of actions will enhance the probability for success in treating a varied patient population together with those patients suffering from drug resistant forms of epilepsy.

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INTRODUCTION

Epilepsy or convulsions affects approximately 20-40 million people globally. It is more commonly affected children than adults, with frequency of nearly eight per 1000 children below the age of seven years. Epilepsy is the second most general neurological disorder, after stroke. It is a disorder of the CNS and illustrated by extreme electrical discharge. A typical seizure may comprise brief and periodic episodes of change in the usual state of consciousness, loss of muscle tone, sensory and behavioral changes. Seizures might be non epileptic if evoked in the normal brain by treatments, like electric shock or chemical convulsions, or epileptic when happening without evident provocation. Seizures are originated by “occasional, sudden, extreme, rapid, and local discharge of gray matter” and generalized convulsion outcomes when normal brain tissue is attacked by the seizure activity started in the abnormal focus. In few cases of epilepsy, a seizure may be linked with occurrence of an infection, stroke, tumor, or birth injury. Though, in other cases, it may be related with a biochemical and (or) physiological defects in the brain most probably due to an imbalance of excitatory and inhibitory neurotransmitters (NTMs). This imbalance of NTMs may be a result of genetic factors or structural pathology stress (Wagh et al., 2011; Porter, and Meldrum, 2001; Macdonald and Greenfield, 1997; Gerlach and Krajewski, 2010). A typical therapeutic approach is to optimize the use of a single antiepileptic drug (AED), given that about 60% of patients have become seizure free by this approach. As a second line approach, concomitant therapy with more than one ADE is used. Unluckily, only 5% of patients who fail to react effectively to monotherapy incident long term liberty from seizures using poly therapy. The remaining patients are therapy-resistant in that seizures are not
effectively controlled (Coulter, 1998; French, et al., 2004; Fisher, et al., 2005; Birbeck et al., 2007).

Seizure Classification

More than 40 distinctive epileptic signs have been recognized and generally classified into partial and generalized seizures. The partial seizures report for about 60 percent of all epilepsies and usually are due to a lesion in some part of the cortex, tumors, trauma, developmental malformations, stroke, and infections. Partial seizures are related with electrical discharge that begins locally and often remains localized. Partial seizure may generate relatively simple signs without loss of consciousness, such as involuntary muscle contractions, autonomic discharge or abnormal sensory experiences or, they may cause more complex effects on consciousness, mood and behavior, often termed psychomotor epilepsy. In psychomotor epilepsy, which is often related with a focus in the temporal lobe, the attack may consist of stereotyped movements such as rubbing or tapping movements, or much more complex behavior like walking, dressing, or hair-combing. The seizure generally lasts for a few minutes, after which the patient get wells with no memory of the event. The manners during the seizure can be bizarre and convoyed by a strong emotional response. The generalized epilepsy report for approximately 40 percent of all epilepsies and etiology is normally genetic. Generalized seizures involve the entire brain, as well as the reticular system, thus generating abnormal electrical activity throughout both hemispheres. Instant loss of consciousness is feature of generalized seizures.

The major categories are tonic-clonic seizures (grand mal) and absence seizures (petit mal). A tonic-clonic seizure consists of an initial powerful contraction of the entire musculature, generating a rigid extensor spasm. Respiration prevents and micturition, defecation, and salivation are often occurs. The tonic phase lasts for about one minute and is followed by a series of violent synchronous jerks that slowly finishes in about 2-4 minutes. The patient continues unconscious for a few more minutes and then slowly recovers, feeling ill and confused. Injury may happen during the convulsive episodes. Absence seizures occur in children; they are much less dramatic but may occur more regularly than tonic-clonic seizures. The patient suddenly ceases whatever he/she was doing, occasionally stopping speaking in mid-sentence, and stares blankly for a few seconds, with slight or no motor disturbance. With optimal drug treatment, epilepsy is prevented completely in about 75 percent of patients, and about 10 percent continue to have seizures at gaps of one month or less, which severely interrupt their life and work. Therefore need to improve the efficacy of therapy. The certain generalized seizures are well correlated with experimental seizures produced in animals by pentylenetetrazol (scPTZ), and partial seizures correlated with seizures generated by maximal electroshock (MES) method (Dunn et al., 1990; Mattson, et al., 1992; Rho, et al., 1994; Bazil, and Pedley. 1998; Kwan, and Brodie. 2000; Kwan, and Sander. 2004; Bialer et al., 2004; Bialer. 2006).

Common mechanism of action of antiepileptic drugs

Three major mechanisms of action are recognised: modulation of voltage-gated ion channels; enhancement of γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; and attenuation of glutamate-mediated excitatory neurotransmission (Lowenstein, and All dredge. 1998; Lusczzki. 2009; Macdonald, and Kelly. 1993; McAllister 1992; Rand, et al., 1995; Rogawski, and Loscher. 2004; Scheffer, and Bercovic. 2003).

1. Voltage-gated ion channels:

Ion channels regulate the flow of positively and negatively charged ions across neuronal cell membranes and ultimately control the intrinsic excitability of the CNS. Voltage-gated Na⁺ channels are responsible for depolarization of the nerve cell membrane and conduction of action potentials across the surface of neuronal cells. At nerve terminals, voltage-gated Ca²⁺ channels are recruited by Na⁺ channel dependent depolarization, leading to Ca²⁺ entry, NTM release and chemical signaling across the synapse. Ca²⁺ channels are distributed, on a cellular and anatomical basis. The AEDs (e.g., PHT, CBZ, valproate (VPA), lamotrigine (LTG) involves the prolongation and and closing of inactivation gate of Na⁺ ion channels, therefore reducing the capability of neurons to fire at elevated frequencies. This mechanism supplies protections against MES in animals and focal seizures in humans. A low threshold Ca²⁺ ion current (T-type) manages oscillatory comebacks in thalamic neurons. The reduction of current by the use of AEDs such as [(ethosuximide (ESM)], dimethadione, VPA).

2. Inhibitory neurotransmission:

The GABA is the predominant inhibitory NTM in the mammalian CNS and is released at up to 40% of all synapses in the brain. GABA is synthesized from glutamate by the action of the enzyme glutamic acid decarboxylase. Following release from GABA-ergic nerve terminals, it acts on the post-synaptic GABA-A receptor, a ligand-gated ion channel comprising five independent protein subunits arranged around a central chloride ion (Cl⁻) pore. Nineteen GABA-A receptor subunits have been identified to date (α1-6, β1-3, γ1-3, δ, ε, θ, π, ρ1-2), any five of which could in theory form a functional channel, with subunit composition conferring physiology and pharmacology. The GABA-A receptor responds to GABA binding by increasing Cl⁻ conductance resulting in fast neuronal hyper-polarization or inhibition. The drug may work directly on the GABA-receptor-Cl⁻ ion channel complex (e.g., barbiturates, BZDs), and inhibit the metabolism of GABA (e.g., VPA, vigabatrin) or enhance the release of GABA (e.g., gabapentin). This system affords protection against generalized and focal seizures.

3. Excitatory neurotransmission:

Glutamate is the principal excitatory NTM in the mammalian brain. Release from glutamatergic nerve terminals, it exerts its effects on three specific subtypes of ionotropic receptor in the postsynaptic membrane, designated according to their agonist specificities-AMPA, kainate and NMDA. These receptors respond to glutamate binding by increasing cation conductance resulting in neuronal depolarisation or excitation. The AMPA and kainate receptor subtypes are permeable to Na⁺ and involved in fast excitatory synaptic transmission. In contrast, the NMDA receptor is permeable to both Na⁺ and Ca²⁺, owing to a voltage-dependent blockade by Mg²⁺ at resting membrane potential, is only activated during periods of prolonged depolarization, as might be expected during epileptiform discharges. Metabotropic glutamate receptors perform a similar function to GABA-B
receptors; they are G-protein coupled and act predominantly as auto receptors on glutamatergic terminals, limiting glutamate release. Glutamate is removed from the synapse into nerve terminals and glial cells by a family of specific Na+-dependent transport proteins and is inactivated by the enzymes glutamine synthetase (glial cells only) and glutamate dehydrogenase. Some AEDs (e.g., PBT, topiramate) block the AMPA receptor and some (Felbamate, remacemide) block NMDA receptors. This vital mechanism has effects in the progress of new AEDs.

**Antiepileptic drugs**

Available AEDs manage seizures in about two thirds of the epileptic patients. The potassium bromide (KBr) in year 1857 was used as an antiepileptic agent. The PBT was launched in year 1912, and later, in year 1938, PHT was used as AED. For a prolonged time period it was considered that a single AED would be able to treat all types of epilepsy. The AEDs used in the management of two major types of seizures namely partial and generalized seizure, are relatively different in their profiles. The phenobarbitone (PBT) was the first synthetic drug accepted as AED. Its effectiveness was limited to generalized tonic-clonic seizures, and to a lesser extent, simple and complex partial seizures and had no effect on absence seizures. The PHT reduced seizures without causing sedative effects. The MES test is important, because drugs that are valuable against tonic hind limb extension usually have proven to be useful against partial and tonic-clonic seizures in humans. Another experiment, seizures encouraged by the chemo-convulsant agent scPTZ, is mainly valuable in recognizing drug molecules that are effective against myoclonic or absence seizures in humans. The structures of most of the AEDs introduced before 1965 were closely related to PBT included hydantoins and succinimides. Between 1965 and 1990, chemically distinct structures of BZDs, iminostilbene (CBZ), and branched-chain carboxylic acid (VLPA) were introduced, followed in the 1990s by a phenyltriazine (LTG). Cyclic analog of GABA (gabapentin), sulfamate-substituted monosaccharide (topiramate), nipeptic acid derivative (tiagabine), and pyrrolidine derivative (levetiracetam) (Miller, et al., 1999; Mohanraj, and Brodie. 2003; Morrell. 1998; Motte, et al., 1997).

**General classification of Antiepileptic drugs**

The Various AEDs are classified in various classes (Dwivedi. 2001; Anderson. 1998; Chisholm. 2005), some AEDs were used in earliest time and some drugs are currently used.

1. **Aldehydes:** Paraldehyde is one of the earliest anticonvulsants. It is still used to treat status epilepticus, particularly where there are no resuscitation facilities.
2. **Aromatic allylic alcohols:** Stiripentol, indicated for the treatment of severe myoclonic epilepsy in infancy (SMEI).
3. **Barbiturates:** Barbiturates are drugs that act as CNS depressants and produce a wide spectrum of effects, from mild sedation to anesthesia. The following are classified as anticonvulsants: PBT, MethylPBT, Metharbital, Barbexaclone.
4. **Benzodiazipines:** Clobazam, clonazepam (CZP), Clorazepate, Diazepam (DZP), Midazolam, Lorazepam, Nitzazepam, and especially nitemazepam are powerful AEDs.
5. **Bromides:** Potassium bromide (in 1857), earliest effective treatment for epilepsy.

6. **Carbamates:** Felbamate.
7. **Carboxamides:** Carbamazepine (CBZ).
8. **Fatty acids:** The following are fatty-acids: The VPAs
9. **GABA analogs:** Some AEDs are GABA analogue, example Gabapentin, Pregabalin.
10. **Hydantoins:** AEDs with htdantion nucleus are Ethotoin, PHT, MePHT
11. **Oxazolidinediones:** Paramethadione, Trimethadione, Ethadione, Propionate.
12. **Pyrimidinediones:** Primidone.
13. **Pyrrolidines:** Brivaracetam, Levetiracetam, Seletracetam.
14. **Succinimides:** ESM, Phensuximide (PSM), Mesuximide.
15. **Sulfonamides:** Acetazolamide, Sultiame, Methazolamide, Zonisamide.
16. **Triaazines:** LTG.
17. **Ureas:** Pheneturide, Phencamamide.
18. **Valproylamides (amide derivatives of VPA):** Valpromide, Valnoctamide.

**Drug development for epilepsy**

For a long time it was assumed that a single drug could be developed for the treatment of all forms of epilepsy, but the causes of epilepsy are extremely diverse, encompassing genetic and developmental defects, infective, traumatic, neoplastic, and degenerative disease processes. Drug therapy to date shows little evidence of etiologic specificity. However some specificity is according to seizure types. Drugs acting selectively on absence seizures can be identified by animal screens, using either threshold PTZ clonic seizures in mice or rats showing absence-like episodes. In contrast, the MES test, with suppression of the tonic extensor phase, identifies drugs such as PHT, CBZ, and LTG that are active against generalized tonic-clonic seizures or complex partial seizures. Use of the MES test as the major primary screen for new drugs has probably led to the identification of drugs with a common mechanism of action involving prolonged inactivation of the voltage-sensitive Na+$^+$ channel. Limbic seizures induced in rats by the process of electrical kindling (involving repeated episodes of focal electrical stimulation) probably provides a better screen for predicting efficacy in complex partial seizures (Dunn and Fielding. 1987; Dunn and Corbett. 1992; Dwivedi, and Smar. 1994).

**Basic pharmacology of antiepileptic drugs**

The AEDs can be classified into five very similar chemical groups: barbiturates, hydantoins, oxazolidinediones, succinimides, and acetylureas. These groups have in common a similar heterocyclic ring structure with a variety of substituents. For drugs with basic structure, the substituents on the heterocyclic ring determine the pharmacologic class, either anti-MES or anti-PTZ. Very small changes in structure can alter the mechanism of action and biological properties of the compound. The remaining drugs-CBZ, VLPAs, and the BZDs-are structurally dissimilar, ie, felbamate, gabapentin, LTG, oxcarbazepine (OXC), tiagabine, topiramate, vigabatrin, and levetiracetam. Existing AEDs provide adequate seizure control in about two thirds of patients. A fraction of the epileptic population is resistant to all available drugs. New AEDs are being sought not only by the screening tests but also by more rational approaches. Compounds are sought that act by one of three mechanisms: (1)
enhancement of GABAergic (inhibitory) transmission, (2) diminution of excitatory (usually glutamate ergic) transmission, or (3) modification of ionic conductance (Farwell, et al., 1990; Frank, et al., 1999; French, et al., 1999; He, et al., 2004; Honmou, et al., 1995; Huguenard. 1999).

Drugs used in partial and generalized tonic-clonic seizures

The major drugs for partial and generalized tonic-clonic seizures are PHT (or congeners), CBZ, VPA, and barbiturates. However, availability of newer drugs - LTG, gabapentin, OXC, topiramate, vigabatrin, and levetiracetam is altering clinical practice.

1. Phenytoin

Phenytoin is the oldest non sedative AED, introduced in 1938 that altered electrically induced seizures in lab animals. It has much lower sedative properties than compounds with alkyl substituents at the 5 position. A more soluble prodrug of PHT, fosPHT, is parenteral use. This phosphate ester compound is rapidly changed to PHT in the plasma. PHT has major effects on several physiologic systems. It alters Na⁺, K⁺, and Ca²⁺ conductance, membrane potentials, and concentrations of amino acids, NTMs norepinephrine, acetycholine, and GABA. PHT blocks sustained high-frequency repetitive firing of action potentials. This effect is seen at therapeutically relevant concentrations. It is a use-dependent effect on Na⁺ conductance, arising from preferential binding to and prolongation of the inactivated state of the Na⁺ channel. This effect is also seen with therapeutically relevant concentrations of CBZ and VPA and probably contributes to their antiseizure action in the MES model and in partial seizures. PHT, CBZ, and sodium VPA all markedly reduced the number of action potentials elicited by the current pulses. At high concentrations, PHT also inhibits the release of serotonin and norepinephrine, promotes the uptake of dopamine, and inhibits monoamine oxidase (MAO) activity. In addition, PHT paradoxically causes excitation in some cerebral neurons. A reduction of Ca²⁺ permeability, with inhibition of Ca²⁺ influx across the cell membrane, may explain the ability of PHT to inhibit a variety of Ca²⁺ induced secretory processes, including release of hormones and NTMs. The mechanism of PHT’s action probably involves a combination of actions at several levels. At therapeutic concentrations, the major action of PHT is to block Na⁺ channels and inhibit the generation of repetitive action potentials. PHT is one of the most effective drugs against partial seizures and generalized tonic-clonic seizures. Other drugs, notably PBT and CBZ, cause decreases in PHT steady-state concentrations through induction of hepatic microsomal enzymes. The INH inhibits the metabolism of PHT, resulting in increased steady-state concentrations when the two drugs are given together.

2. Mephenytoin, ethosotoin, and phenacemide

Many congeners of PHT have been synthesized, but only three have been marketed in the USA, and one of these (phenacemide) has been withdrawn from the market. The first two congeners, mPHT and ethosotoin, like PHT, appear to be most effective against generalized tonic-clonic seizures and partial seizures. The occurrence of severe responses like agranulocytosis, dermatitis, or hepatitis is higher for mephenytoin than for PHT. Ethotoin may be proposed for patients hypersensitive to PHT, but larger doses are essential. The unfavorable effects and toxicities are usually less severe than those related with PHT, but the drug appears to be less efficient. Both ethotoin and mephenytoin (MPHT) share with PHT the property of saturable metabolism within the therapeutic dosage variety. Mephenytoin is metabolized to 5,5-ethylphenylhydantoin by demethylation. This metabolite, nirvanol, gives most of the antiepileptic activity of mephenytoin. Both mephenytoin and nirvanol are hydroxylated and undergo successive conjugation and excretion. The third congener of PHT, phenacemide, is a analog of PHT.

3. Carbamazepine

Carbamazepine (CBZ) is closely related to imipramine and other tricyclic antidepressants, it is a tricyclic compound useful in management of bipolar depression. It was initially used for the therapy of trigeminal neuralgia but has established as useful antiepileptic agent as well. The ureide moiety (-N-CO-NH₂) present in the heterocyclic ring of the majority AEDs is also exist in CBZ. The mechanism of action of CBZ showed to be like as of PHT. Like PHT, CBZ exhibited activity against MES seizures. The CBZ blocks Na⁺ channels at therapeutic concentration and inhibits high-frequency recurring firing in neurons. It also operates presynaptically to reduce synaptic transmissions. These effects possibly account for the anti-epileptic action of CBZ. It interacts with adenosine receptors and also inhibits uptake and release of norepinephrine from brain synaptosomes but does not control GABA uptake in brain. The indication suggested that the postsynaptic action of GABA can be potentiated by CBZ. It is the drug of choice for partial seizures, and may be use for treatment of generalized tonic-clonic seizures. It is also valuable in some patients with mania (bipolar disorder).

4. Oxycarbazepine

Oxycarbazepine is directly related to CBZ and helpful in the same seizure types, but it may have a superior toxicity profile. Its activity, consequently, resides nearly entirely in the 10-hydroxy metabolite, to which it is rapidly converted and which has a half-life similar to that of CBZ (8–12 hrs). The drug is mostly excreted as the glucuronide of the 10-hydroxy metabolite. It is less potent than CBZ, doses of OXC may need to be 50% higher than those of CBZ to obtain equivalent seizure control. Fewer hypersensitivity reactions to OXC were reported. It induce hepatic enzymes to a lesser extent than CBZ. Adverse effects such as hyponatremia that do occur with OXC are similar in character with CBZ.

5. Phenobarbital

Aside from the bromides, PBT is the oldest currently available AEDs. Although it has long been considered one of the safest of the AED, the use of other medications with lesser sedative effects has been urged. The barbiturates are considers as the drugs of choice for treatment of seizures only in infants. The four barbituric acid derivatives are clinically useful as AEDs are phenobarbitone (PBT), mepobarbital, metharbital, and primidone. The first three are subsequently similar and considered collectively. The metharbital is methylated barbital and mepobarbital is methylated PBT; both are demethylated. The PBT may selectively repress abnormal neurons, inhibiting the extending and suppressing firing from the foci. Like PHT,
PBT suppresses high-frequency recurring firing in neurons in culture by an action on Na+ ion conductance, but only at elevated concentrations. Also at elevated concentrations, barbiturates block some Ca2+ ion currents (L-type and N-type). The PBT binds to an allosteric regulatory site on the GABA-BZD receptor, and it improved the GABA receptor-mediated current by extending the openings of the Cl-channels. The PBT also blocks excitatory responses stimulated by glutamate, mainly those mediated by activation of the AMPA receptor. Both the enrichment of GABA-mediated inhibition and the decline of glutamate mediated excitation are seen with therapeutically applicable concentrations of PBT. The PBT is valuable in the therapy of partial seizures and generalized tonic-clonic seizures, even though the drug is often tried for all seizure type, particularly when attacks are complicated to manage.

6. Primidone

Primidone (2-desoxyPBT) was metabolized in to PBT and phenylethylmalonamide (PEMA). All these three compounds are active against convulsions. Although primidone is changed to PBT, the mechanism of action of primidone itself may be further like that of PHT. Primidone, similar to its metabolites, is useful against partial seizures and generalized tonic-clonic seizures and may be more effective than PBT. It was considered to be drug of choice for partial seizures, but the partial seizures in adults strongly suggest that CBZ and PHT are superior to primidone. Finally, MES seizures in animals suggest that primidone has an antiepileptic action independent of its conversion to PBT and PEMA (relatively weak).

7. Vigabatrin

Drugs to enhance the effects of GABA include efforts to find GABA agonists and prodrugs, GABA transminase inhibitors, and GABA uptake inhibitors. Vigabatrin (-vinyl-GABA) is an irreversible inhibitor of GABA aminotransferase (GABA-T), enzyme responsible for degradation of GABA. It apparently acts by increasing the amount of GABA released at synaptic sites, thereby enhancing inhibitory effects. Vigabatrin may also potentiate GABA by inhibiting the GABA transporter. It is effective in a wide range of seizure models. The S(+) enantiomer is active and R(-) enantiomer appears to be inactive. It is used in the management of partial seizures and West's syndrome. Typical toxicities consist of dizziness, drowsiness and weight gain. Less frequent but more worrying adverse effects are confusion, agitation and psychosis.

8. Lamotrigine

Lamotrigine was developed when some scientist considered that the antifolate action of certain AEDs (eg, PHT) may contribute to their efficiency. Some phenyl-triazine compounds were developed for their antifolate properties and were active against seizure. The LGT, like PHT, reduces continued rapid firing of neurons and produces a voltage and use-dependent inactivation of Na+ channels. This effect most likely explained the LTG is effectiveness in focal epilepsy. It shows likely that LTG has a different mechanism of action to report for its efficacy in generalized seizures, together with absence attacks; this mechanism may occupy actions on voltage-activated Ca2+ channels. The LTG is effective as monotherapy for partial seizures. It is also effective against absence and myoclonic seizures in children. Adverse effects comprise nausea, dizziness, headache, diplopia, somnolence, and skin rash.

9. Felbamate

Felbamate has been is successful in some patients with partial seizures, the drug causes aplastic anemia and hepatitis at surprisingly high rates. The mechanism of action is not identified. The strong indication suggested that it is a NMDA receptor blockade via the glycine binding site. Felbamate has a half-life of 20 hrs and is metabolized by hydroxylolation and conjugation; considerable amount of the drug is excreted unaffected in urine. When added to therapy with other AEDs, felbamate enhanced plasma PHT and VLPA levels but reduces levels of CBZ. It is used in partial seizures and also active against the seizures that happen in Lennox-Gastaut syndrome.

10. Gabapentin

Gabapentin is a derivative of GABA and effective against partial seizures. It is found to be more effective as an AED and appears not to act on GABA receptors. It may change GABA metabolism, its non synaptic release, or its reuptake by GABA transporters. An enhancement in brain GABA concentration is seen. Gabapentin is carrying into the brain by the L-amino acid transporter. It anticonvulsant action is against MES-induced seizure model. The drug also connected to the subunit of voltage-sensitive Ca2+ channels. Gabapentin is active as an adjunct against partial and generalized tonic-clonic seizures. It is also effective in neuropathic pain and for post therapeutic neuralgia in adults. The most frequent adverse effects are somnolence, ataxia, dizziness, headache, and tremor.

11. Topiramate

Topiramate is a substituted monosaccharide and structurally different from other AEDs. Topiramate blocks recurring firing of cultured spinal cord neurons, like PHT and CBZ. Its mechanism of action is blocking of voltage dependent Na+ channels and also appears to potentiate the inhibitory effect of GABA, acting at a site unlike from the BZD or barbiturate sites. Topiramate also reduced the excitatory action of kainate on AMPA receptors. It is possible that all three actions given to topiramate as antiepileptic agent. It is effective against both partial and generalized tonic clonic seizures. It has a broader range, with effective against Lennox-Gestaut syndrome, West's syndrome and absence seizures. Although no idiosyncratic reactions have been well-known, side effects are somnolence, fatigue, cognitive slowing, dizziness, paresthesias, nervousness and confusion. Acute myopia and glaucoma may require quick drug withdrawal. The drug is teratogenic in animal models but no human fetal deformities.

12. Tiagabine

Tiagabine is a nipecotic acid derivative and act as an inhibitor of GABA uptake in both neurons and glia. It preferentially inhibited the transporter isof orm-1 (GAT-1) rather than GAT-2 or GAT-3 and raises extracellular GABA levels in the forebrain and hippocampus parts of brain. It extended the inhibitory activity of synaptically released GABA. In rodents it is effective against kindled seizures but weak against the MES model. Tiagabine is
point out for the adjunctive therapy of partial seizures. Adverse effects are nervousness, dizziness, tremor, difficulty in concentrating, and depression. Confusion, somnolence, or and ataxia may need discontinuation. Psychosis and rash is an rare adverse effects.

13. Zonisamide

Zonisamide is a sulfonamide analogue and it mainly site of action appears to be on the Na+ channel; it may also operates on voltage-dependent Ca 2+ channels. The drug is efficient against partial and generalized tonic-clonic seizures and may also be helpful against infantile spasms and certain myoclonias. Adverse effects contain drowsiness, cognitive impairment, and potentially severe skin rashes and it does not interact with other AEDs.

14. Levetiracetam

Levetiracetam is a piracetam derivative that is unsuccessful against seizures induced by MES or PTZ but has well-known activity in the kindling model. Its mechanism of action is indefinite. It has a brain-specific binding site and affects allosteric modulations of GABA receptors, high-voltage activated Ca2+ channels and several K + channels. The drug is used for therapy of partial seizures. Levetiracetam is not metabolized by cytochrome P450. Adverse effects consist of somnolence, asthenia, and dizziness. Idiosyncratic reactions are uncommon.

Drugs used in generalized seizures

1. Ethosuccimide

Ethosuccimide (ESM) is a succinimide and has little effect against MES but considerable efficacy against PTZ-induced seizures and was originated as a "pure petit mal" drug. Its responsibility as the first choice anti-absence drug as idiosyncratic hepatotoxicity of the optional drug VLPA. The ESM is the last AED which having cyclic ureide structure. The three anti-seizure succinimide drugs are ESM, PSM, and methsuximide. The ESM has an essential effect on Ca2+ currents, reducing the low-threshold (T-type) current. The T-type Ca2+ currents are thought to provide a pacemaker current in thalamic neurons responsible for generating the rhythmic cortical discharge of an absence attack. Inhibition of this current could account for the specific therapeutic action of ESM. It also inhibits Na+/K+ATPase, depresses cerebral metabolic rate, and inhibits GABA aminotransferase. PSM and methsuximide are phenylsuccinimides that were developed before ESM and used mainly as anti-absence drugs. Methsuximide has been used for partial seizures, it is more toxic, PSM less effective than ESM. Unlike ESM, these two compounds have some activity against MES seizures. The desmethyl metabolite of methsuximide has exerts the major anti-seizure effect.

2. Vaproic acid and sodium valproate

Sodium valproate (VPA) is also used as the free acid, VLPA has antiseizure activity. It was marketed in France in 1969. VLPA is fully ionized at body pH for that reason the active form of the drug may be assumed to be the VPA ion. VLPA is a series of fatty carboxylic acids that have antiseizure effect; this activity appears to be greatest for carbon chain lengths of five to eight atoms. Branching and unsaturation do not significantly alter the activity but may increase its lipophilicity, thereby increasing its duration of action. The amides and esters of VLPA are also active AEDs. VPA is active against both PTZ and MES seizures like PHT and CBZ. VPA blocks sustained high-frequency repetitive firing of neurons at therapeutic concentrations. Its action against partial seizures may be a consequence of this effect on Na+ currents. Blockade of NMDA receptor-mediated excitation may also be important. The increased levels of GABA in the brain after administration of VPA, although the mechanism remains unclear. An effect of VPA to facilitate glutamic acid decarboxylase (GAD), enzyme responsible for GABA synthesis has been described. An inhibitory effect on the GABA transporter GAT-1 may contribute. At very high concentrations, VPA inhibits GABA-T in the brain, thus blocking degradation of GABA. However, at the relatively low doses of VPA needed to abolish PTZ seizures, brain GABA levels may remain unchanged. VPA produces a reduction in the aspartate content of rodent brain. At high concentrations, VPA has been shown to increase membrane K+ conductance. The low concentrations of VPA tend to hyperpolarize membrane potentials and may exert an action through a direct effect on the K+ channels of the membrane. VPA probably owes its broad spectrum of action to more than one molecular mechanism. It is very effective against absence seizures. Although ESM is the drug of choice when absence seizures occur alone, VPA is preferred if the patient has concomitant generalized tonic-clonic attacks. The reason for preferring ESM for uncomplicated absence seizures is VPA's idiosyncratic hepatotoxicity. VPA has unique ability to control certain types of myoclonic seizures. Other uses of VPA include management of bipolar disorder and migraine prophylaxis. It inhibits the metabolism of several drugs, including PBT, PHT, and CBZ. The side effects and toxicity of PHT are enhanced. The inhibition of PBT metabolism may cause levels of the barbiturate to rise precipitously, causing stupor or coma.

3. Oxazolidinediones

Trimethadione, the first oxazolidinedione, was introduced 1945 and drug of choice for absence seizures until the introduction of succinimides in 1950s. The use of the oxazolidine -diones (trimethadione, paramethadione, and dimethadione) is now very limited. They contain an oxazolidine ring and have similar in structure to other AEDs introduced before 1960. These drugs are active against PTZ-induced seizures. Trimethadione raises the threshold for seizure discharges following repetitive thalamic stimulation. Its active metabolite dimethadione has the same effect on thalamic Ca2+ currents as ESM (reducing the T-type Ca2+ current). Thus, suppression of absence seizures is likely to depend on inhibiting the pacemaker action of thalamic neurons. The most common adverse effect is sedation and unusual adverse effect is hemeralopia, a glare effect in which visual adaptation is impaired. Accumulation of dimethadione causes a very mild metabolic acidosis and should not be used during pregnancy.

Other drugs used in management of epilepsy

Some drugs not classifiable by application to seizure type are discussed in this section.

1. Benzodiazepines
Fig. 1: Structures of various antiepileptic drugs
Six BZDs play prominent roles in the therapy of epilepsy. Many BZDs are quite similar chemically, slight structural alterations result in differences in activity. They have two different mechanisms of anti-seizure action, which are shown to different degrees by the six compounds. The DZP is relatively more potent against MES and CZP against PTZ (latter effect correlate with an action at the GABA-BZD allosteric receptor site). DZP is highly effective against continuous seizure activity, especially generalized tonic-clonic status epilepticus. Lorazepam is to be more effective and longer-acting than DZP in the treatment of status epilepticus. CZP is a long-acting drug with efficacy against absence seizures. It is one of the most potent AED. It is also effective in some cases of myoclonic seizures and infantile spasms. Nitrazepam used especially for infantile spasms and myoclonic seizures but less potent than CZP. Clorazepate dipotassium is used for treatment of complex partial seizures. Drowsiness and lethargy are common adverse effects. Clobazam is widely used in variety of seizures. It is a 1,5-BZD (all other BZD drugs are 1,4-BZDs) has less sedative. It does interact with some other AEDs and causes adverse effects. Two prominent aspects of BZDs limit their usefulness. The first is their pronounced sedative effect. Children may manifest a paradoxical hyperactivity. The second problem is tolerance, in which seizures may respond initially but recur within few months.

2. Acetazolamide

Acetazolamide is a diuretic its main action is the inhibition of carbonic anhydrase. Mild acidosis in the brain may be the mechanism by which the drug exerts its antiseizure activity. The
depolarizing action of bicarbonate ions moving out of neurons via GABA receptor ion channels will be diminished by carbonic anhydrase inhibition. It has been used for all types of seizures but it rapid development of tolerance, with return of seizures usually within a few weeks.

3. Ziprasidone

Ziprasidone led the exploration of oxindole. It is a novel effective atypical antipsychotic agent having an oxindole scaffold and approved for the treatment of schizophrenia. Ziprasidone was, however, known to be a potent serotonin and dopamine antagonist.

**Therapeutic strategy**

For most AEDs, relationships between blood levels and therapeutic effects have been characterized to a high degree. The therapeutic index for most AEDs is low. Thus, effective treatment of seizures requires an awareness of the therapeutic levels and pharmacokinetic properties as well as the characteristic toxicities of each agent. Measurements of AED plasma levels are extremely useful (VanLandingham, et al., 1998; Wallace, et al., 1998; Xie, et al., 1995; Lambert et al., 1994; Sachdeo, et al., 1999; Sachdeo, et al., 1997; Sivenius, et al., 1991).

**Management of epilepsy**

1. Partial Seizures & Generalized Tonic-Clonic Seizures

The choice of drugs was usually limited to PHT, CBZ, or barbiturates. There has been a strong tendency in the past few years to limit the use of sedative AEDs such as barbiturates and BZDs to patients who cannot tolerate other medications. In the 1980s, the trend was to increase the use of CBZ. Although the choice now appears to be divided between CBZ and PHT, all of the newer drugs have shown effectiveness against these seizures.

2. Generalized Seizures

The drugs used for generalized tonic-clonic seizures are the same as for partial seizures. In addition, VPA is clearly useful. Three drugs are effective against absence seizures. Two are non-sedating and therefore preferred, ESM and VPA. CZP is also highly effective but has disadvantages of dose related adverse effects and development of tolerance. The drug of choice is ESM, although VPA is effective in some ESM-resistant patients. LTG and topiramate may also be useful. Specific myoclonic syndromes are usually treated with VPA. Other patients respond to CZP, nitrazepam, or other BZDs, although high doses may be necessary, with accompanying sedation and drowsiness. Zonisamide and levetiracetam may be useful. Another specific myoclonic syndrome, juvenile myoclonic epilepsy, can be aggravated by PHT or CBZ; VPA is the drug of choice followed by LTG and topiramate. Atonic seizures are often refractory to all available medications, although some reports suggest that VPA may be beneficial, as may LTG. BZDs have been improve seizure control in some patients but may worsen the attacks in others. Felbamate has been effective in some patients, although the drug's idiosyncratic toxicity limits its use. If the loss of tone appears to be part of another seizure types (absence or complex partial).

3. Drugs Used in infantile spasms

The treatment of infantile spasms is unfortunately limited to improvement of control of the seizures rather than other features of the disorder, such as retardation. Most patients receive corticotropin, therapy must often be discontinued because of adverse effects. If seizures recur, repeat courses of corticotropin or corticosteroids can be given, or other drugs may be tried. Other drugs used are BZDs such as CZP or nitrazepam, their efficacy in this heterogeneous syndrome may be nearly as good as that of corticosteroids. Vigabatrin may also be effective.

4. Status Epilepticus

There are many forms of status epilepticus. The most common, generalized tonic-clonic status epilepticus is a life-threatening emergency, requiring immediate cardiovascular, respiratory, metabolic management as well as pharmacologic therapy. The latter virtually always requires i.v. administration of AEDs. DZP is the most effective drug in most patients and is given by i.v. to a maximum total dose of 20–30 mg in adults. DZP may depress respiration. The effect of DZP is not lasting, but the 30- to 40-minute seizure-free interval allows more definitive therapy to be initiated. For patients who are not actually in the throes of a seizure, DZP therapy can be omitted and the patient treated at once with a long-acting drug such as PHT. Some physicians prefer lorazepam, which is equivalent to DZP in effect and perhaps somewhat longer-acting. Until the introduction of fosphenytoin, the mainstay of continuing therapy for status epilepticus was i.v. PHT, which is effective and non sedating. It should be given as a loading dose of 13-18 mg/kg in adults; the usual error is to give too little. Administration should be at a maximum rate of 50 mg/min. It is safest to give the drug directly by i.v. push, but it can also be diluted in saline; it precipitates rapidly in the presence of glucose. Careful monitoring of cardiac rhythm and B.P is necessary, especially in elderly people. At least part of the cardiotoxicity is from the propylene glycol in which the PHT is dissolved. FosPHT, which is freely soluble in i.v. solutions without the need for propylene glycol or other solubilizing agents, is a better parenteral agent. This prodrug is two thirds to three quarters as potent as PHT on mg basis. In previously treated epileptic patients, the administration of a large loading dose of PHT may cause some dose-related toxicity such as ataxia. For patients who do not respond to PHT, PB can be given in large doses: 100–200 mg i.v. to a total of 400–800 mg. Respiratory depression is a common complication, especially if BZDs have already been given, and there should be no hesitation in instituting intubation and ventilation. Although other drugs such as lidocaine have been recommended for the treatment of generalized tonic-clonic status epilepticus, general anesthesia is necessary in highly resistant cases. For patients in absence status, BZDs are still drugs of first choice. Rarely, i.v. VPA may be required. The generalized tonic-clonic status epilepticus is a life threatening emergency requiring immediate cardiovascular, respiratory, metabolic management along with AEDs. The i.v. injection of 20-30 mg of DZP or lorazepam is followed by a long acting drug such as PHT (15-20 mg/kg), i.v. PHT (15-20 mg/kg) alone successfully treats 41-90 percent of patients, i.v. PB (20 mg/kg in adults) is also effective in treatment of status epilepticus.

5. Neuropathic pain and anxiety
All AEDs must applied for their actions by adjusting the activity of the basic mediators of neuronal excitability: voltage and NTM-gated ion channels. The Ca²⁺ channel subunit is accountable for chronic pain states and anxiety. Gabapentin is exclusive among Ca²⁺ channel ligands. Since the subunit appears to be ordinary to all voltage-dependent Ca²⁺ channel, it is believable that gabapentin modulates the activity of more than one type of neuronal Ca²⁺ channel. It is likely that gabapentin exerts functional effects only with particular combinations of subunits. The modulations of voltage-dependent neuronal Ca²⁺ channels are essential in the antiepileptic action of ligands. Pregabalin was used for the therapy of both neuropathic pain and anxiety.

Special aspects of the toxicology of antiepileptic drugs

1. Teratogenicity

The teratogenicity of AEDs shows that a distinctive pattern of physical abnormalities in infants of mothers with epilepsy is associated with the use of AEDs during pregnancy, rather than with epilepsy itself. AEDs taken by pregnant women to prevent seizures are among the most common causes of potential harm to the fetus. AEDs are used frequently to prevent seizures, PBT, PHT, and CBZ were found to cause major malformations, microcephaly, growth retardation, and distinctive minor abnormalities of the face and fingers in infants exposed to them during pregnancy. Moreover, epilepsy is very often associated with CNS psychiatric disorders. The potential teratogenicity of AEDs is controversial and important. It is important because teratogenicity resulting from long-term drug treatment and may have a profound effect even if the effect occurs in only a small percentage of cases. Furthermore, patients with severe epilepsy, in whom genetic factors rather than drug factors may be of greater importance in the occurrence of fetal malformations, are often receiving multiple AEDs in high doses. The children born to mothers taking AEDs have an increased risk, perhaps two fold congenital malformations. PHT has been implicated in a specific syndrome called fetal hydantoin syndrome (skeletal, CNS, limb, and orofacial defects) and a similar syndrome has been attributed both to PBT and to CBZ. VPA has also been implicated in a specific malformation, spina bifida. It is estimated that a pregnant woman taking VPA has a 1–2% risk of having a child with spina bifida. In problem of a pregnant woman with epilepsy, most epileptologists agree that while it is important to minimize exposure to AEDs, both in numbers and dosages, it is also important not to allow maternal seizures to go unchecked. Topiramate has shown teratogenic effects in animals. The risk of the pregnant mother having a full blown seizure and having brain injury (hypoaxia) are much higher than having a fetus with congenital defects. Thus, the risk to benefit ratio should be seriously considered.

2. Withdrawal conditions

Abrupt withdrawal of AEDs may increase seizure frequency and severity in patients with epilepsy. Some drugs are more easily withdrawn than others. Withdrawal of AEDs whether by accident or by design can cause increased seizure frequency and severity. There are two factors to consider: the effects of the withdrawal itself and the need for continued drug suppression of seizures in the individual patient. In many patients, both factors must be considered. The abrupt discontinuance of AEDs ordinarily does not causes seizures in non epileptic patients provided the drug
levels are not above the usual therapeutic range when the drug is stopped. Barbiturates and BZDs are the most difficult to discontinue; weeks or months may be required, with very gradual dosage decrements, to accomplish their complete removal, especially if the patient is not hospitalized. Because of the heterogeneity of epilepsy, complete discontinuance of AEDs is an especially difficult problem. If a patient is seizure-free for 3 or 4 years, gradual discontinuance is usually warranted.

3. Overdose

The AEDs are CNS depressants but are rarely lethal. Very high blood levels are usually necessary before overdoses can be considered life-threatening. The most dangerous effect of AEDs after large overdoses is respiratory depression, which may be potentiated by other agents, such as alcohol. Treatment of AED overdose is supportive; stimulants should not be used. Efforts to hasten removal of AEDs, such as alkalinization of the urine (PHT is a weak acid), are usually ineffective.

4. General side effects of antiepileptic drugs

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Features</th>
<th>Antiepileptic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Partial Seizures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple partial</td>
<td>Diverse manifestations determined by the region of cortex activated by seizure (e.g., if motor cortex representing left thumb, clonic jerking of left thumb results; if somatosensory cortex representing left thumb, paresthesias of left thumb results), lasting approximately 20-60 seconds. Key feature is preservation of consciousness. May progress from hand- arm-shoulder-girdle-trunk to entire body.</td>
<td>CBZ, PHT, PBT, primidone, VPA</td>
</tr>
<tr>
<td>Complex partial</td>
<td>Impaired consciousness lasting 30 seconds to two minutes, often associated with purposeless movements such as lip smacking or hand wringing. Confusion, amnesia, full coordination (e.g. dressing, undressing) and aura.</td>
<td>CBZ, PBT, Gabapentin, LTG</td>
</tr>
<tr>
<td>Partial with secondarily generalized tonic-clonic seizure</td>
<td>Simple or complex partial seizure evolves into a tonic-clonic seizure with loss of consciousness and sustained contractions (tonic) of muscles throughout the body followed by periods of muscle contraction alternating with periods of relaxation (clonic), typically lasting 1 to 2 minutes. Increased heart rate, increased blood pressure, loss of bladder and bowel control.</td>
<td>CBZ, PBT, Gabapentin, LTG</td>
</tr>
</tbody>
</table>

| **Generalized Seizures** | | |
| Absence seizure (Petit mal) | Abrupt onset of impaired consciousness with staring and cessation of ongoing activities typically lasting less than 30 seconds. Common in children, disappears after adolescence. | CZP, ESM, VPA |
| Myoclonic seizure | A brief (perhaps a second), shock like contraction of muscles which may be restricted to part of one extremity or be generalized. | VPA |
| Tonic-clonic seizure (Grand mal) | As described above for partial with secondarily generalized tonic-clonic seizures except that it is not preceded by a partial seizure. | CBZ, PBT, primidone, VPA |
Diarrhea, vomiting, upper respiratory tract infection, constipation, dyspepsia, ataxia, nervousness, allergic skin reaction, nausea, headache, dizziness, aplastic anemia, hepatic failure is the common site effects of currently used AEDs. The cognitive side effects of CBZ, PHT and VPA Sod are comparable and associated with modest psychomotor slowing accompanied by decreased attention and memory. Neuropsychological side effects emerge according to a dose dependent relationship; however, both quality of life and memory may be affected, even when serum blood concentrations are within standard therapeutic ranges. In children, drug effects are seen in decreased performance or memory. Some children are at heightened risk for developing disproportionate cognitive side effects with CBZ.

**Interactions of drugs associated with antiepileptic agents**

Epilepsy is a chronic disease that may require long-term AED therapy. The efficacy of single AED therapy for the management of epilepsy is well recognized. For epileptic patients who do not respond to mono-drug therapy, treatment with multiple AEDs is essential. About 28% of epileptic patients were prescribed multiple drug therapy. The multiple drug therapy or polytherapy is commonly needed for the treatment of co-morbidities in epileptic patients. The AEDs are known to interact with cardiovascular agents including anticoagulants, β-blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers, Ca^2+ channel blockers, and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Moreover, AEDs are prescribed to treat a variety of non epileptic conditions including migraine headache, chronic neuropathic pain, mood disorders, and schizophrenia.

**Metabolic acidosis in a pediatric patient receiving topiramate**

Topiramate is used for the management of several seizure types in children >2 years of age. With the exception of cognitive dysfunction, nephrolithiasis, weight loss, and paresthesia, adverse effects in children are similar to other those noted with other AEDs. Three year old child with complex partial seizures and secondary generalization received topiramate 45 mg (6.2 mg/kg/d) orally twice daily for approximately 4 weeks. He developed asymptomatic metabolic acidosis that was evidenced by a decrease in HCO₃⁻, which was unresponsive to treatment with NAHCO₃. The child was weaned off topiramate and the metabolic acidosis resolved 48 hours after its discontinuation (Steiner, et al., 1999; Kelly, et al., 1990; Lynch, et al., 2004; Mattson, et al., 1985; Suzdak, and Jansen. 1995).

**Discovery of lesser neurotoxic and effective anticonvulsant agents**

The compounds were screened for antiepileptic properties in the MES, scPTZ, strychnine (scSTY) and picrotoxin (scPIC) seizure threshold tests in mice. Neurotoxicity was determined using the rotord test in mice. The compounds were also studied for behavioral despair and depression using actophotometer and porsolt’s swim pool test respectively.

**Anticonvulsant drugs and their structural features**

The chemical variety and different mechanisms of action of AEDs create it difficult to discover a general way of discover new drug molecule. Novel AEDs are revealed through usual screening and/or structure alteration of available drug. Rational drug design procedure of new AEDs could be attained in several ways. The first approach is the recognition of new targets through improved accepting of molecular mechanisms of epilepsy. Another way is to alter already accessible drugs and regimens. The new AEDs showing different structures include amino acids, amides, sulfonamides (hydroxyamides, carboxamides, benzylamides, dimethylamides, alkanoamides,); heterocyclic compounds (derivatives of imidazoles, indazoles, indoles, piperazine and arylpiperazines, pyrrolidin-2,5-diones, lactams, pyridazinone, semi-thiosemicarbazones, quinazolines, thiazoles, thiadiazoles, isatin, xanthones), enamiones, imidooxy derivatives and VLPA derivatives. These innovative structural classes of drug molecules can confirm usefulness for
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effective level</th>
<th>Clinical uses</th>
<th>Mechanism</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>4-12 μg/ml</td>
<td>Partial and tonic-clonic.</td>
<td>Prolongs closing of inactivating gate of sodium channels of excitatory NT receptors in the CNS</td>
<td>Sedation. Ataxia. Blurred vision. Serious hematological toxicity (aplastic anemia, agranulocytosis) Potent inducer of drug metabolizing enzyme.</td>
</tr>
<tr>
<td>ESM</td>
<td>50-100 μg/ml</td>
<td>Absence seizures.</td>
<td>Inhibits low-threshold T-type calcium currents in thalamic neurons.</td>
<td>Nausea, anorexia, mood changes, headaches.</td>
</tr>
<tr>
<td>CZP</td>
<td>0-1 μg/ml</td>
<td>Absence and myoclonic.</td>
<td>Facilitates the inhibitory actions of GABA.</td>
<td>Sedation. Lethargy (50 percent). Dependence and withdrawal symptoms.</td>
</tr>
</tbody>
</table>
Table 4: Continuous…..

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Concentration</th>
<th>Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>DZP</td>
<td>Absence</td>
<td>600 µg/ml</td>
<td>Increases frequency of opening of chloride channel of GABA-A receptor</td>
<td>Behavioral disturbances in children. Interaction with alcohol. Interaction with VLP.</td>
</tr>
<tr>
<td>Lorazapam</td>
<td>Partial myoclonic, absence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorazepate</td>
<td>absence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethadione</td>
<td>Absence</td>
<td>20 µg/ml</td>
<td>Inhibits low-threshold T-type calcium currents in thalamic neurons</td>
<td>Sedation. Hemeralopia. Hepatitis and nephrosis. Mild neutropenia (20 percent). Aplastic anemia. Side effects are serious and limiting.</td>
</tr>
<tr>
<td>Bromide</td>
<td>Epilepsy in porphyrias.</td>
<td>10-20 µg/ml</td>
<td>Not known.</td>
<td>Sedation. Skin rash. Behavioral changes</td>
</tr>
</tbody>
</table>

Structural feature and structural activity relationship of antiepileptic drugs

For the compounds to act as AEDs, the molecules should have at least one aryl or lipophilic units (A), one or two hydrogen acceptor-donor atoms (HAD) and an electron donor atom (D) in a unique spatial arrangement to be recommended for antiepileptic activity. Some identified and structurally diverse molecule with antiepileptic activity, for examples, mephobarbitone, ethosotin, PHT, CBZ, gabapentin, LTG, progabide, ralitoloine and zonisamide etc are characterized their structural elements. The distance between these structural elements should be most favorable in the ranges represented (Fig 1.20). The distances are calculated using different computational tools for three dimensional structures of the drugs.

Over the years, the field of epilepsy has received a great deal of attention from research investigators in the hope of discovering new drugs that are more effective and have minimal adverse effects. Though several new AEDs have been introduced, some types of epilepsies are still not adequately controlled with the current therapy. Adverse reactions and lack of efficacy for certain types of epilepsies are some of the limitations of existing medications. The AEDs exert their action by different mechanisms. They include an enhancement of the GABA-ergic neurotransmission, effects on neuronal voltage-gated Na+ and/or Ca2+ channels. Epilepsy is most common neurological disorder, second to stroke. The number of drugs useful for the treatment of epilepsy is remarkably small. New AEDs have been developed that may constitute novel and effective therapies for epilepsies. Their use has been proposed in the treatment of seizure disorders such as epilepsy, in the therapy of stroke and other neurological disorders such as Parkinson's disease. They act as excitatory amino acid antagonists and inhibitors of L-glutamate neurotransmission. These compounds afford protection in the MES-model in both mice and rats, by either i.p or oral route. The study represents them as glutamate antagonists. Neurotoxicity of the compounds was also noticed at the same dose levels. Vitamin B6 is the precursor in the formation of co-enzyme pyridoxal-5-phosphate which is responsible for the decarboxylation of glutamic acid to form GABA and since hydrazine derivatives can inactivate the co-enzyme. Pyridoxal-5-phosphate via hydrazone formation, these facts conform the fundamental role of GABA in the arrest of convulsion (Privitera, et al., 2003; Ptacek. 1997; Sachdeo, et al., 1992; Twyman, et al., 1989; Biton, et al., 1999).

MePHT and Ethotonin are like PHT but require larger doses. Oxacarbazepine, a drug like CBZ, is metabolized to 10-hydroxy derivative which has lesser induction of drug metabolizing enzyme than CBZ. Primidone is metabolized to phenylethylmalinomide and PBT and has similar profile to PBT.

At last, upcoming efforts to finding novel AEDs are expected to focus on mechanism motivated discovery of novel drug molecules, followed by knowledgeable animal testing in appropriate drug-resistant animal models. Several latest achievements (pregabalin, brivaracetam) have shown that information of the mechanism of action gives the developer a significant benefit in improving effectiveness through improved target effectiveness and selectivity, thus reducing the potential for dose associated adverse effects. However, till date even current progresses have not appreciably reduced the size of DRE population. It is the anticipate that new generation AEDs with novel mechanisms will enhance the likelihood for success in treating a heterogeneous patient population together with those patients suffering from drug resistant types of epilepsy. New
AEDs have expanded the therapeutic alternatives in treating patients with refractory epilepsy and those who cannot bear conventional therapy. Although these drugs are capable, further clinical practice will be essential to validate the usefulness of these agents. This will supportive for researcher to find out newer AEDs with lesser adverse effects. A further study to

| Table 5: New antiepileptic drugs and their side effects |
|--------------|-----------------|-----------------|-----------------|
| Drug         | Clinical uses   | Mechanism       | Side effects    |
| LTG          | Adjunct for partial seizures with or without secondary generalization | Not known | Minimal drowsiness. Anxiety. Amnesia |
| Levetiracetan| Adjunct for partial seizures with or without secondary generalization | Not known | Minimal drowsiness. Anxiety. Amnesia |
| OXC          | Partial seizures with or without Generalization | Blockade of voltage sensitive sodium channels | CNS side effects, hematological abnormalities and effects on drug metabolizing enzymes are less than CBZ. |

| Table 6: Efficacy of antiepileptic drugs in other conditions |
|--------------|-----------------|-----------------|
| Drug         | Established efficacy | Possible efficacy |
| CBZ          | Mania, mood, stabilization, trigeminal neuralgia. | Behavioral disturbances of dementia, neuropathic pain. |
| Gabapentin   | Neuropathic pain (e.g., diabetic neuropathy). | Mania, movement disorders (e.g., Parkinson’s disease). |
| LTG          | None. | Mania, migraine, neuropathic pain. |
| PHT          | None. | Neuropathic pain, trigeminal neuralgia. |
| VPA          | Mania, migraine. | Behavioral disturbances of dementia, movement |
Acquire more information about biological activity is in improvement.

**Anticonvulsant drugs and their structural features**

Epilepsy is a common neurological disorder, affecting 0.5 to 1% of the population globally. Novel AEDs are exposed through predictable screening and/or structure alteration. Rational drug design procedure of a new anticonvulsant could be attained in a number of ways. The first approach is the recognition of new targets through improved understanding of molecular mechanisms of epilepsy. An additional way is to modify already presented drugs and formulations. The new AEDs representing a variety of structures include amino acids, sulfonamides, amides (hydroxyamides, alkanoamides, benzylamides, dimethylanilides, carboxyamides); heterocyclic compounds (analouges of imidazoles, indazoles, indoles, arylpiperazine and piperazines, pyrrolidin-2,5-diones, pyridazinone, lactams, semithiosemicarbazones, quinazolinones, thiadiazoles, isatin,
xanthones), imidooxy, enaminones compounds and valproic acid analogues (Birbeck et al., 2007; Bialer. 2006; Chisholm. 2005; Luszczki. 2009).

**Structural necessities for the AEDs and their SAR**

For the compounds to perform as AEDs, the molecules should hold at least one aryl or lipophilic group or units (A), one or two hydrogen acceptor-donor atoms (HAD) and an electron donor atom (D) in a unique spatial arrangement to be suggested for antiepileptic action. Some well known and structurally dissimilar compounds with antiepileptic activity, for examples of such drugs are ethphenytoin, mephobarbitalone, PHT, CVZ, gabapentin, lamotrigine, progabide, ralitoloine and zonisamide etc are represent their structural elements.

**DISCUSSION AND CONCLUSIONS**

The field of epilepsy has received a great deal of attention from research investigators in the hope of discovering new drugs that are more effective and have minimal adverse effects. Though several new AEDs have been introduced, some types of epilepsies are still not adequately controlled with the current therapy. Adverse reactions and lack of efficacy for certain types of epilepsies are some of the limitations of existing medications. Antiepileptic drugs exert their action by different mechanisms. They include an enhancement of the GABA-ergic neurotransmission, effects on neuronal voltage-gated sodium and/or calcium channels (Najafi et al., 2011). Epilepsy is most common neurological disorder, second to stroke. The number of patients suffering from drug resistance seizures patients (Kwan, and Brodie. 2000; Mohanraj and Brodie. 2003). In this regard, the natural resources might also be helpful (Ali et al., 2015; Ashraf et al., 2015; Asif, 2015a, b, c, d, e, f, g, h, i, 2016; Hussain et al., 2016; John et al., 2015; Mensah and Golomeke, 2015) and the new generation AEDs with novel mechanism of actions will enhance the probability for success in treating a varied patient population together with those patients suffering from drug resistant forms of epilepsy.

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