Review

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An overview on antiepileptic drugs

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ABSTRACT: Epilepsy is the most common chronic neurological disorder of the brain. For several decades different kinds of medications have been used to treat epilepsy. Even though many surgical advances has been made and implemented, medications remain the basis of treatment. The search for noble antiepileptic drugs (AEDs) with more selective activity and lower toxicity continues to be an area of intensive investigation in medicinal chemistry. Additionally, drug resistance is an important clinical problem in epilepsy and is associated with an increased risk of morbidity and mortality. This review intends to present a comprehensive overview on AED in particular along with discussion on some aspects of associated drug resistance and combination therapy.

Keywords: Epilepsy, anticonvulsants, resistance, combination therapy

1. Introduction

Epilepsy is a chronic neurological disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally that may remain localized (focal epilepsy) or become widespread (generalized epilepsy). The term epilepsy is derived from the Greek word epilepsia, which means "falling sickness" and can be called "seizure", "ictus", or "convulsion" (*1*). Both the electrical and the behavioral aspect of seizures can be quite variable and complex, even in a single patient. Seizures can be caused by a variety of pathologic conditions, including acquired injuries and genetic abnormalities. In addition, many physiologic disturbances of brain function can produce seizures and the prevalence of epilepsy varies from adults to children (*2*). Three to five percent of the population has a seizure sometime in their life and half to one per cent of the population have 'active epilepsy'. The heterogenicity of epilepsy makes it difficult to establish precise epidemiological statistics (*3*).

Etiology of epilepsy. Approximately 60% of all epilepsies are idiopathic. Almost any type of brain pathology can cause seizures/epilepsy. The underlying etiology is numerous and the abnormalities may range from symptomatic seizures due to tumor, infection, and trauma to cryptogenic forms. Cerebrovascular disease is the most commonly identified cause among adults, while prenatal insults seem to be most common among children (*4*). An imbalance between glutamate and γ-aminobutyric acid (GABA) neurotransmitter systems can lead to hyperexcitability. Catecholaminergic neurotransmitter systems and opioid peptides are also shown to play a role in epileptogenesis (*5*). Enhancement of excitatory transmission and simultaneous failure of inhibitory mechanisms together with changes in intrinsic neuronal properties results in repetitive neuronal discharges (*6*). Additionally, innate immunity/inflammation, adaptive immune responses, and inflammation markers including autoantibodies also play a role in the pathophysiology of several types of epilepsy (*7*).

Classification. Classification of epilepsy is the foundation for treatment. Several neuropsychiatrists with a special interest in epilepsy put forward the idea that the existing systems of classification of psychiatric disorders and personality disorders are inadequate as far as epilepsy is concerned. Classification of seizure type is dependent on the accuracy of history, availability and sophistication of diagnostic tests used, and age at which the patient's seizure type was classified. International Classification of Epileptic Seizures System (ICES) was introduced in 1970 and revised in 1981. Generally seizures can be classified as partial, generalized, and unclassified ones. The Commission on classification and terminology of the International League Against Epilepsy (ILAE) recently recommended new terminology and concepts on focal and generalized epilepsy. According to etiologic classification, *viz.*, the idiopathic, symptomatic, and cryptogenic forms of epilepsy have been conceptualized as genetic, structural/metabolic, and unknown forms of epilepsy (*8*). A general classification of epilepsy is shown in Figure 1.

Global burden. The WHO global burden of disease (GBD) 2004 update estimates that about 40 million individuals globally have epilepsy. Inclusion of epilepsy

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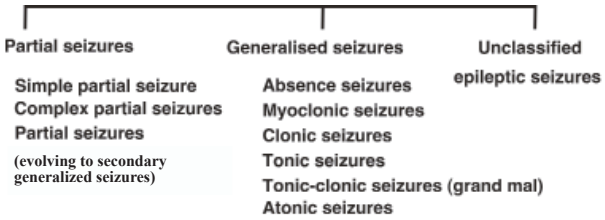

Figure 1. The classification of epilepsy.

caused by other disease or injury may increase the total number of persons affected in the world to about 50 million (*9*). The incidence of epilepsy in developed countries is between 40-70/100,000/year and the ratio is much higher (120/100,000/year) in resource poor countries (*10*).

Medication. An appropriate diagnosis together with proper selection and utilization of currently available antiepileptic drugs (AEDs) is necessary for therapeutic success in the management of epilepsy. With the range of drugs currently available, there are immense opportunities for patient-tailored drug therapy. However the management of epilepsy is primarily based on optimum use of AEDs with the choice of drugs varying considerably among physicians and across countries. The choice is primarily based on evidence of efficacy and effectiveness for the individual's seizure type, but other patient-specific factors, including age, sex, childbearing potential, adverse-effect profile, comorbidities, and concomitant medications are also needed to be considered (*11*). Further, better understanding of pharmacoresistance would help to replace the current empiricism with a more patient-centric approach towards the management of epilepsy.

2. Antiepileptic drugs (structures see Figure 2)

Bromides were the first medication introduced by Sir Charles Locock in 1857 to provide control for seizures. Bromides were rendered obsolete due to their side effects and are being replaced by newer therapeutics. However, it has now been re-established as an add-on therapy in some selected cases of intractable generalized tonic clonic seizure (*12*). Phenobarbital (PB) (1912) (**1**), a member of the barbiturate class serendipitously discovered by Alfred Hauptmann was as effective as bromides with a less toxic profile, is easier to administer and subsequently replaced the bromides. Primidone (**2**) is another member of the same family whose mechanism of antiepileptic action is not known. Primidone *per se* has anticonvulsant activity as do its two metabolites *viz.*, PB and phenylethylmalonamide (PEMA) (**3**). In the 1930s, the introduction of sulfanilamide was a major medical advance, but in 1937 a sulfanilamide preparation containing diethylene glycol was one of the most consequential mass poisonings of the 20th century known as the elixir sulfanilamide disaster. This led to new regulations for the preparation, safety, testing, labeling, distribution, and marketing of drugs. Hydantoin (glycolylurea) was first isolated in 1861. The precise mechanisms by which hydantoins work are unknown, but they are thought to exert their therapeutic effect by depressing abnormal neuronal discharges in the central nervous system (CNS). The hydantoins include phenytoin (Dilantin®) (**4**) and mephenytoin (Mesantoin®). Phenytoin (5,5-diphenylhydantoin, dilantin; 1938) known as the 'miracle' drug of its day was discovered by H. Houston Merritt and Tracy Putnam. This drug was used as a first choice, or when phenobarbital failed. It was one of the most widely used drugs, effective in tonic-clonic and partial seizures. An unknown substance positive to ninhydrin was found in 1949 by Roberts and Frankel in chromatographed fresh human brain tissue, which was later identified as GABA, the inhibitory neurotransmitter (*13*). The discovery of valproate's effectiveness as an AED created a new therapeutic paradigm. This drug was thought to be effective in enhancing GABA in the nervous system, and became one of the first drugs in which a mode of action was proposed. This drug has been licensed in the UK for clinical use since 1973 and in the USA since 1978. Its own metabolism may be enhanced by other anti-epileptic agents. In the 1970s and 1980s, the AEDs most frequently used to prevent seizures were phenobarbital, phenytoin, and carbamazepine. Later on they 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. Gabapentin (**5**) (Neurontin®), marketed in the U.S. in 1993, was the first approved AED not metabolized in the liver, making drug interactions a lesser problem. The mode of action of gabapentin is largely unknown (*14*). Parker *et al.* (2004) (*15*) demonstrated that gabapentin selectively activates presynaptic $GABA_B$ heteroreceptors. Recent studies suggest that it interacts with an auxiliary α2β subunit of voltage-sensitive calcium channels and inhibits the calcium currents leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability (*16*). Carbamazepine (Tegretol®) (**6**) is considered as a drug of choice for tonic clonic seizures, partial seizures, and trigeminal neuralgia. It works by decreasing nerve impulses that cause seizures and pain. Succinimides such as ethosuximide (Zarontin®) (**7**) and methsuccimide (Celontin®) are also widely used for absence (petitmal epilepsy) seizures. Another class of compounds that are widely used in the management of epilepsy is benzodiazepines (BDZs). Clinical advantages of these drugs include rapid onset of action, high efficacy rates and minimal toxicity. Among the approximately 35 BZDs available, clorazepate (Tranxene®) (**8**) has a distinctive and favorable profile that includes a long half-life of its active metabolite and slow onset of tolerance (*17*). Standard AEDs usually

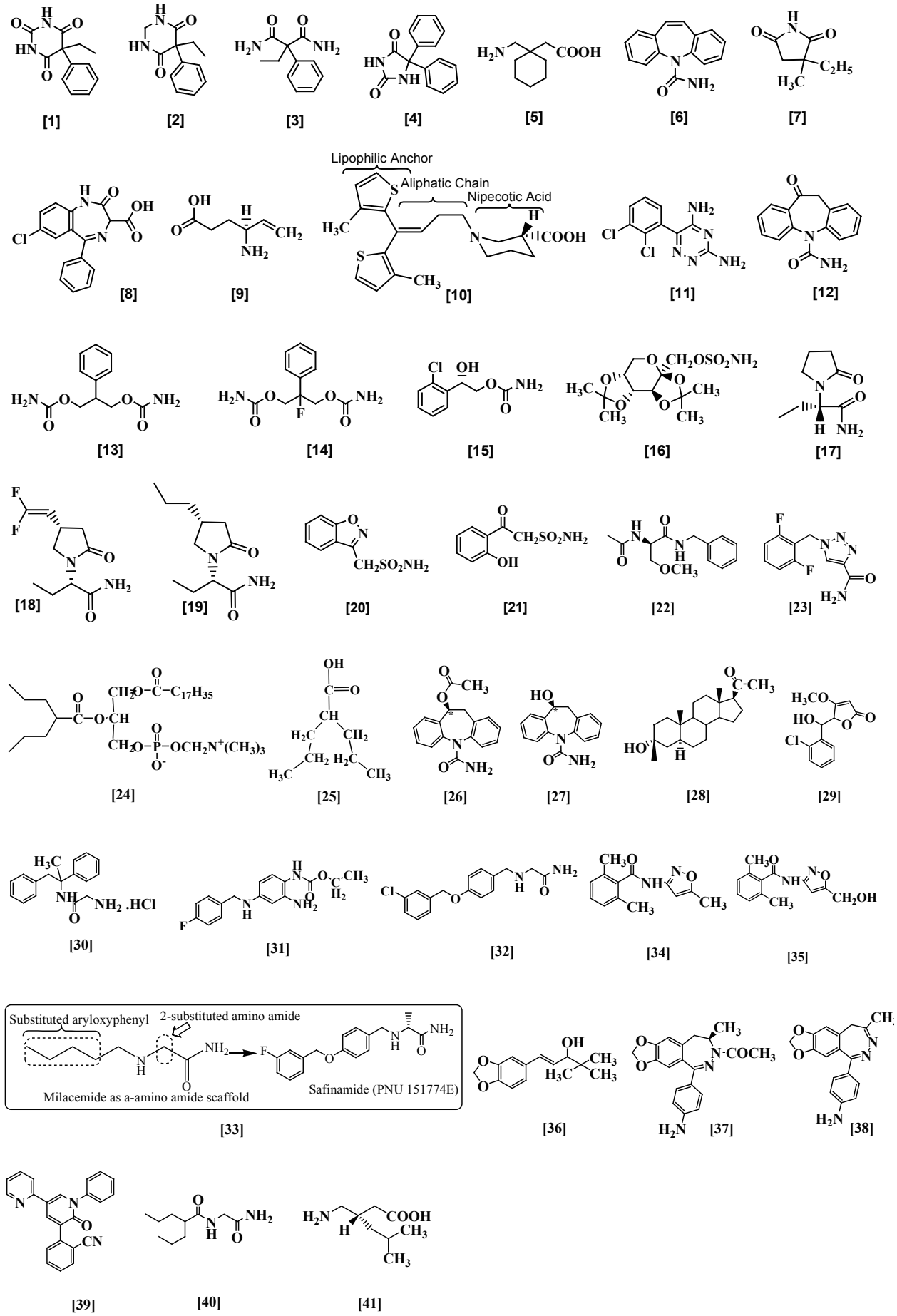

Figure 2. Chemical structures of antiepileptic drugs.

produce side effects in 50% or more of patients treated. Rare but serious idiosyncratic reactions were reported which include agranulocytosis, Stevens-Johnson syndrome, aplastic anaemia, hepatic failure, allergic dermatitis, serum sickness, and pancreatitis (*18*). Once the seizure type and epilepsy syndrome have been determined, an AED can be appropriately selected. During the past decade, a number of new AEDs have been developed with diverse mechanism of action (Table 1). Most of the AEDs are efficacious for partial-onset seizures and were originally approved based on their efficacy as add-on therapy in patients with refractory partial-onset seizures. For patients with generalized-onset seizures the choice of therapy is narrower and includes valproate as well as the newer agents such as lamotrigine and topiramate. From the last 30 years many newer drugs were introduced with better safety profiles. The aim of epilepsy therapy is to keep the patient free of seizures without interfering with normal brain function. The currently available armamentarium of AEDs is discussed below.

*Vigabatrin (γ-vinyl GABA, Sabril®) (**9**).* Vigabatrin (VGB), a structural analogue of GABA possesses a vinyl appendage. It irreversibly inhibits GABA-transaminase (GABA-T), the enzyme responsible for the catabolism of GABA, thereby increasing the whole-brain levels of GABA making it more available to its receptor site (*19*). Thus VGB acts as an indirect GABA agonist. It has emerged as a first choice AED in the treatment of refractory epilepsies such as infantile spasms (also called WEST syndrome), particularly those accompanied by tuberous sclerosis (*20*). Long term vigabatrin treatment is associated with persistent visual field problems that have led to a reduction in the use of the drug (*21*). In order to minimize the chance of visual field defects, the treatment of infantile spasm may be started for brief periods at very early onset with low doses of VGB (*22*).

*Tiagabine (**10**).* Tiagabine (TGB) [(*R*)-(−)-l-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]3-piperidine carboxylic acid hydrochloride] is a nipecotic acid analogue, into which a lipophilic anchor has been incorporated to facilitate crossing of the blood-brain barrier after oral administration. It is a highly selective and potent inhibitor of GABA transporter 1 (GAT-1) in presynaptic neurons and glial cells. TGB selectively increases the amount of the inhibitory neurotransmitter GABA at the GABAergic synapse and is the first of its kind to be introduced into clinical practice (*23*). Isobolographic analysis of the interactions of TGB with three conventional AEDs: valproate (VPA), carbamazepine (CBZ), and phenobarbital (PB) in amygdala-kindled rats showed synergistic interaction (fixed-ratio combinations of 1:3, 1:1, and 3:1, respectively). The study suggested that TGB appears to be a valuable drug for an add-on therapy of refractory complex partial seizures in humans (*24*). However, a recent study revealed that the efficacy of tiagabine in newly diagnosed epilepsy is relatively low when prescribed along with other AEDs. A critical side effect such as induction of non-convulsive status epilepticus limits its use (*25*).

*Lamotrigine (Lamictal®) (**11**).* Lamotrigine (LTG), a triazine derivative that inhibits the release of glutamate (an excitatory amino acid) has been approved for use as an adjunct drug in treatment of refractory partial seizure

Table 1. Antiepileptic drugs and their mechanism of action

Drugs	Mechanism of action
Vigabatrin	Irreversibly inhibits GABA-T
Tiagabine	Inhibitor of GAT-1
^Lamotrigine	Inhibits the release of excitatory neurotransmitter glutamate. It also inhibits the voltage-sensitive Na^+ channels (VDSC); Blockade of α4β2-nAChR
Carbamazepine, oxcarbazepine, eslicarbazepine	Stabilize the inactivated state of VDSC
^Felbamate, fluorofelbamate	Inhibits NMDA receptor. Also potentiates GABA-mediated inhibition and blocks VDSC
Carisbamate, rufinamide, losigamone, soretolide, valrocemide	Yet to be ascertained
^Topiramate	Selectively blocks excitatory synaptic transmission mediated by GluR5 kainate receptors; also acts at VDSC
Levetiracetam, seletracetam, brivaracetam	Interacts with the synaptic vesicle protein 2A
^Zonisamide	Block sodium channels and reduce voltage dependent T-type Ca^{2+} currents; also modulates dopaminergic, GABA ergic, and serotonergic systems
^Lacosamide	Enhances slow inactivation of VDSC and modulates CRMP-2
Ganaxolone	Positive allosteric modulation of the $GABA_A$ receptor
Remacemide	Potent Na^+ channel blocker and non-competitive NMDA channel antagonist.
Retigabine	It is a KCNQ K^+ channel opener that involves opening of neuronal Kv7.2 (KCNQ2) voltage activated K^+ channels
^Safinamide	Antagonize the Ca^{2+} and Na^+ channels; also reversibly inhibit MAO-B
Stiripentol	It is positive allosteric modulator of $GABA_A$ receptor
Talampanel, perampanel	Non-competitively blocks AMPA receptor
Pregabalin	It binds potently to the α2-γ subunit, an auxiliary protein associated with voltage-gated Ca^{2+} channels

^ Indicates multiple mechanisms.

with or without generalized tonic/clonic seizures. It also inhibits the voltage-sensitive sodium channels thereby stabilizing the neuronal membrane (*26*). Recent studies further suggested that the neuronal α4β2-nAChR (neuronal nicotinic acetylcholine receptor) is likely an important target. The blockade of α4β2-nAChR might represent the mechanism through which LTG effectively controls some types of epilepsy such as autosomal dominant nocturnal frontal lobe epilepsy or juvenile myoclonic epilepsy (*27*). Among the adverse effects, idiosyncratic drug reactions, especially skin rashes are considered fatal and may require discontinuation of the drug. The parent drug rather than a reactive metabolite causes LTG-induced skin rashes. Rash is relatively more common in children than in adults and it is safe when used in general practice to treat epilepsy inadequately controlled by other medications. Serious adverse events were rarely reported and included Stevens-Johnson syndrome (*28*). Long term treatment with LTG may cause hepatic inflammation and it has been found that dextran conjugate prodrug has the potential to reduce the hepatotoxicity (*29*). LTG monotherapy was found to be an effective treatment for children with newly diagnosed childhood absence seizures and an extended-release formulation (LTG-XR) may be given once daily for increasing compliance (*30*). Further a randomized, double-blind, placebo-controlled study reported that adjunctive therapy with LTG-XR administered once daily to a target of 200 to 500 mg/day significantly reduced weekly frequency of primary generalized tonic-clonic (PGTC) seizures and increased the percentage of patients with a ≥ 50% reduction in PGTC seizure frequency (*31*). A retrospective population-based study by Knoester *et al*. (2005) suggests that LTG was effective in 40% of the patients with refractory epilepsy measured by reduction in seizure frequency and retention time as observed in 165 patients. The drug is known to have a more favorable side-effect profile than conventional AEDs (*32*). An unblinded randomized controlled trial carried out by the Standard and New Antiepileptic Drugs (SANAD) study group found lamotrigine to be clinically better than CBZ, the standard drug treatment, for time to treatment failure outcomes and is considered as a cost-effective alternative for patients diagnosed with partial onset seizures (*33*).

*Oxcarbazepine (TRILEPTAL®) (**12**).* Oxcarbazepine (OBZ), 10,11-dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide is a prodrug which is activated to eslicarbazepine in the liver. OBZ is primarily used in the treatment of epilepsy. It is also used to treat anxiety and mood disorders and benign motor ticks. OBZ is a structural derivative of CBZ, with a ketone in place of the carbon-carbon double bond on the dibenzazepine ring. This difference helps reduce the impact on the liver of metabolizing the drug, and also prevents the serious forms of anemia or agranulocytosis occasionally associated with CBZ (*34*).

*Felbamate (Felbatol®) (**13**).* Felbamate (FBM) is structurally related to meprobamate. Its activity in epilepsy probably involves effects on the NMDA receptor. It also potentiates GABA-mediated inhibition and blocks voltage-dependent sodium channels. FBM is an effective and safe AED for either monotherapy or add-on treatment in adults with refractory partial seizures. It is also effective and safe for the treatment of refractory Lennox-Gastaut syndrome in both children and adults (*35*).

*Fluorofelbamate (**14**).* Fluorofelbamate (FFBM, 2-phenyl-2-fluoro-1,3-propanediol dicarbamate) is new chemical entity different from FBM in that fluorine is substituted for hydrogen in the two position of the propane. Mazarati *et al*. (2002) (*36*) studied the effectiveness of FFBM using a rat model of self-sustaining status epilepticus (SSSE). They found that FFBM exhibited a much better activity profile including no recurrent seizure activity in aborting SSSE when injected at both its early and advanced stages where diazepam and phenytoin failed to abort SSSE when administered after 40 or 70 min after the onset of stimulation. The drug candidate is designed to retain the activity of felbamate but with a different metabolic pathway that restricts the formation atropaldehyde/acid-glutathione adduct (ATPAL-GSH and ATPA-GSH) the reactive aldehyde and acid metabolite of FBM. Thus fluorofelbamate is devoid of serious idiosyncratic toxicity associated with FBM (*37*). The presence of the fluoro atom protects the amide groups by its inductive effect and does not undergo the formation of ATPAL-GSH and ATPA-GSH (*38*).

*Carisbamate (**15**).* Carisbamate (CBM), or RWJ-333369 ((*S*)-2-*O*-carbamoyl-1-*o*-chlorophenyl-ethanol), is a novel neuromodulator under investigation for the adjunctive treatment of epilepsy. This AED is structurally similar to felbamate. CBM was found to possess a broad spectrum of activity in rodent seizure and epilepsy models. Molecular action that contributes to its broad-spectrum antiepileptic activity is yet to be ascertained (*39*). A study was initiated to investigate mechanisms underlying the antiepileptic effects of carisbamate using the hippocampal neuronal culture models of status epilepticus and spontaneous epileptiform discharges (*40*). CBM has demonstrated antiepileptic activity in a variety of *in vivo* seizure models including hippocampal, corneal kindling, and the Genetic Absence Epilepsy Rats of Strasbourg (GAERS) model of absence epilepsy (*41*). It was also found to be effective in protecting against spontaneous recurrent seizures in kainate-treated animals (*42*) and in genetic models of epilepsy. It delays or prevents the Li-pilocarpine model of status epilepticus (*43*). It is rapidly and almost completely absorbed from the gut with a bioavailability of approximately 95% and with a peak plasma concentration achieved within 1-3 h (*44*).

*Topiramate (Topamax®) (**16**)*. Topiramate (TPM) (2,3:4,5-bis-*O*-(l-methylidene)-*β*-D-fructopyranose sulphamate) is a sulphamate substituted monosaccharide. The specific mechanism of action of TPM is not well understood. Preliminary reports suggested that it has a multiple mode of action. It acts at voltage-dependent sodium channels blocking the spread of seizures, it enhances $GABA_A$ evoked chloride currents at a non-benzodiazepine receptor site and it also antagonizes the 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid (AMPA) subtype of glutamate receptors (*45*). Gryder and Rogawski (2003) (*46*) established that it selectively blocks excitatory synaptic transmission mediated by GluR5 kainate receptors. It is rapidly absorbed with linear pharmacokinetics and in the absence of enzyme inducers *viz.*, phenytoin or carbamazepine has a plasma elimination half-life of 20-30 h. It has relatively low potential for interaction with other AEDs. However during TPM adjunctive therapy with phenytoin, CBZ, and VPA, the minimum plasma concentration level of TPM was reduced to 50%, 40%, and 14%, respectively. In addition, administration of TPM in patients already taking phenytoin twice a day, a 25% rise in the concentrations of phenytoin were found and may require a downward adjustment of phenytoin dosage (*47*). Besides in patients with pharmacoresistant epilepsy, Luna-Tortos *et al*. (2009) (*48*) provided evidence that brain levels of topiramate may be affected by overexpression of P-glycoprotein. Enhanced elimination of TPM was also observed during pregnancy. In particular the plasma concentration of TPM was found to decline approximately by 40% in the 2nd and 3rd trimester (*49*). To evaluate the efficacy of TPM in infants, Grosso *et al*. (2005) (*50*) found that TPM is effective across a broad range of seizure types in infants aged less than 2 years. The study also provides evidence regarding the usefulness of TPM in cryptogenic infantile spasms but it showed poor efficacy in symptomatic infantile spasms and in Dravet's syndrome. A randomized double-blind clinical trial demonstrated that TPM may be an alternative for phenytoin in patients for whom urgent treatment is required. TPM was found to be well tolerated as observed from the lower rate of incidence of adverse effects in the TPM treatment group (*51*).

*Levetiracetam (Keppra®) (**17**)*. Levetiracetam (LEV), a water soluble pyrrolidone derivative, is the S-enantiomer of α-ethyl-2-oxo-pyrrolidine acetamide. Although LEV shares some targets (such as delayed rectifier channels and N- and P/Q-type calcium channels) with other AEDs, it is a novel AED with a unique mechanism of action related to an interaction with synaptic vesicle protein 2A (SV2A) (*52*). This anticonvulsant drug is structurally related to the nootropic drug piracetam. In contrast to the activity of the (*S*)-isomer, the (*R*)-form of LEV was at least 150-fold less potent in the audiogenic seizure susceptible mouse and largely inactive in other models (*53*). It has been approved by the USFDA for adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy (*54*).

LEV analog. Seleteracetam and brivaracetam exemplifiethe analog of prototype anticonvulsant LEV that exerts site selectivity and illustrates the possibility of widening the target specificity respectively.

*Seletracetam (**18**)*. Seletracetam (STM) (UCB 44212; (2*S*)-2-[(4*S*)-4-(2,2-difluorovinyl)-2-oxopyrrolidin-1-yl] butanamide, is a structural analog of the AED levetiracetam which binds selectively and stereospecifically to SV2A (a novel binding site, synaptic vesicle protein 2A) with a 10-fold greater affinity than LEV. SV2A is thought to be involved with synaptic vesicle exocytosis and neurotransmitter release (*55*). SV2A represents a novel molecular target that seems to have an important role in the pharmacological activity of STM. The SV2A protein is thought to assist with the coordination of synaptic vesicle exocytosis and neurotransmitter release (*56*). Proteins involved in exocytosis, and SV2 in particular, could be considered as promising novel targets for the development of new CNS drug therapies. Discovering the mechanism of drug action through this receptor triggered a drug discovery program which led to the identification of brivaracetam (currently in phase III clinical trials for epilepsy), and seletracetam. Studies show that STM binds selectively to SV2A, without direct modulation of Na^+ channels (*57,58*). A study was performed by Klitguard and coworkers on an *in vitro* high K^+ low Ca^{2+} concentration fluid (HKLCF) model of epilepsy (mice and rat) and they have concluded that STM induces a more potent and complete suppression of neuronal synchronization than LEV. Furthermore, STM showed no psychomimetic effects and a very high tolerability index in both kindled and GAERS rats, which is markedly superior to that of LEV and other AEDs (*59*). Apart from various similarities seletracetam differs from levetiracetam by a very potent and selective effect against Zn^{2+} inhibition of glycine-gated currents as well as a more potent inhibition of high-voltage-operated Ca^{2+} currents and epileptiform elevation of intracellular Ca^{2+} concentrations involving multiple high-voltage-operated Ca^{2+} channels. In pharmacokinetic studies seletracetam was found to reach C_{max} within 1 h. The linear, time-independent pharmacokinetics of the drug combined with a rapid and almost complete absorption indicates that STM has a major uncomplicated pharmacokinetic profile (*60*).

*Brivaracetam (UCB 34714) (**19**)*. has had a drug discovery program carried out by Kenda *et al*. (2004) (*61*) for ligands with significant affinity to LBS (levetiracetam binding site) as a novel molecular target. Brivaracetam (BVT) ((2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidinyl] butanamide), the 4-*n*-propyl structural analog of LEV, emerged as the single most

potent drug candidate among a series of compounds having a 4-substituted lactam ring by small-sized hydrophobic groups. It is approximately 10 times more potent than LEV as an antiseizure agent in audiogenic seizure-prone mice. Further Tai and Truong (2007) (*62*) demonstrated that BVT possesses more potent anti-seizure and anti-myoclonic activity than LEV in an established rat model of cardiac arrest induced post-hypoxic myoclonus. It possesses a binding affinity for the synaptic vesicle protein 2A (SV2A) and also shows an ability to inhibit Na^+ channels. BVT has a half-life of 8 h and its metabolites are not pharmacologically active. In various experimental models of epilepsy, brivaracetam exhibited properties superior to LEV as an AED and has an excellent tolerability profile in humans (*63*). A phase II clinical trial established that it produced a dose-dependent reduction in the frequency of seizures in adults with refractory partial seizures. The drug is currently under phase III clinical trials (*64*).

*Zonisamide (Zonegran®) (**20**).* Zonisamide (ZNS) is a benzisoxazole with a sulfonamide side chain (1, 2-benzisoxazole-3-methanesulfonamide). The main actions of ZNS are blockade of sodium channels and reduction of voltage dependent T-type Ca^{2+} currents (*65*). It also enhances neuronal inhibition *via* modulation of neurotransmitter systems, including dopaminergic, GABAergic and serotonergic systems. It may enhance GABA function through interaction at allosteric or other binding sites and/or by influencing GABA transport. ZNS is also reported to be a weak inhibitor of carbonic anhydrase (*66*). It has a favorable pharmacokinetic profile as it is rapidly and completely absorbed and has a long half-life (63-69 h in healthy volunteers) which allows twice-daily, or even once-daily dosing. ZNS undergoes acetylation to form *N*-acetyl ZNS, and reduction to form the open ring metabolite, 2-sulfamoylacetyl phenol (**21**) that undergoes urinary excretion *via* glucuronide conjugation (*67*). It has been shown to be effective in patients whose seizures are resistant to other AEDs. Patients most often received ZNS as monotherapy. When ZNS was added to therapy with other AEDs, the dosage of the other AEDs was reduced. ZNZ or CBZ are favored over phenytoin, clobazam, valproate, or phenobarbital for simple partial and complex partial seizures (*68*). The drug has been approved in the US and Europe as an adjunctive therapy for refractory partial seizures in adults. It has several CNS dose-dependent side effects and by slow titration of dose the incidence could be minimized (*69*). A recent observational study was carried out by Kelemen *et al*. for accessing the efficacy and tolerability of ZNS in different resistant generalized epileptic syndromes. At a mean dose of 367 mg/day (100-600 mg/day), it was observed that ZNS showed excellent efficacy against progressive myoclonic epilepsy type 1. They suggested that the free radical scavenging and possible neuroprotective effects of zonisamide may be beneficial in acquired symptomatic epilepsies (*70*).

*Lacosamide (Vimpat®) (**22**).* Lacosamide (LCM) (formally known as harkoseride) is a new AED discovered by high throughput animal screening. Systematic evaluation of more than 100 *N*-benzyl-2-acetamidopropionamide derivatives of this compound in animal models led to the identification of LCM (*71*). It is the first drug to come from a class of compounds known as functionalized amino acids and it is an optical antipode of the naturally occurring amino acid L-serine (*72*). It has dual mode of action as LCM enhances slow inactivation of voltage-gated sodium channels and modulates the collapsin response mediator protein-2 (CRMP-2), a protein, which is part of neuronal signal transduction pathways and which is attributed to neuroprotection (*73*). In contrast to AEDs such as phenytoin, CBZ, and LTG that block sodium channels when activated, LCM facilitates slow inactivation of sodium channels both in terms of kinetics and voltage dependency (*74*). Clinically, LCM is at present in a late stage of development as an adjunctive treatment for patients with uncontrolled partial-onset seizures. It provides high oral bioavailability unaffected by food, good tolerability with twice daily dosing, and minimal drug-drug interactions (*75*).

*Rufinamide (Banzel®; Inovelon®) (**23**).* Rufinamide (RFM) (1-[(2,6-difluorophenyl) methyl]-1*H*-1,2, 3-triazole-4-carboxamide) is a triazole derivative structurally unrelated to any currently marketed AEDs. Comparative studies of rufinamide with established AEDs (phenytoin, phenobarbital, ethosuximide, valproate) in several rodent seizure models showed the superiority of rufinamide to other AEDs tested in terms of protective indices in the electrically and chemically induced seizure tests, and the MES safety ratio (*76*). The drug is effective orally and is relatively well absorbed in the lower dose range. The main route of metabolism involves hydrolysis of the carboxamide group by carboxylesterases to an inactive derivative that is eliminated mainly by renal excretion *via* glucuronide conjugation (*77*). The precise mechanisms of action of RFM are unknown, however *in vitro* studies suggest that modulation of sodium channels activity, particularly prolongation of the inactive state may be the main mechanism of its antiepileptic activity. It possesses several favourable properties which might pave its way as the orphan drug for the treatment of partial seizures and drop attacks associated with Lennox-Gastaut syndrome (*78*). Coppola *et al.* (2011) (*79*) showed that it is also effective and well tolerated as an adjunctive drug for the treatment of refractory childhood-onset epileptic encephalopathies. Vendrame *et al*. (2010) (*80*) in single-centric studies observed that it is also has potential for treatment of a wide range of other seizure types including both partial and generalized epilepsy syndromes in the pediatric population. Further it showed no effect on cognitive function in patients with refractory partial seizures (*81*).

*DP-valproic acid (DP-VPA) (**24**).* DP-VPA (SPD 421, DP 16, TVA, RAP-valproate), a novel prodrug of VPA (**25**) in which the VPA moiety is covalently bound to the phospholipid lecithin based on a new drug delivery technology known as Regulated Activation of Prodrug (D-RAPTM). The ED_{50} value is 50-fold lower than VPA with a longer half-life. It showed a high absorption rate and bioavailability with negligible hepatic metabolism. Side effects are restricted to dose-dependent gastrointestinal problems (*82*). It is currently under development for the treatment of partial and generalized seizures (*83*). The absorption pattern of DP-VPA follows a unique pattern whereby the complex permeates through the gut wall and enters intact to the enterocyte. Then it associates itself with chylomicrons and reaches the systemic blood circulation *via* the lymphatic route (*84*).

*Eslicarbazepine acetate (BIA 2-093) (**26**).* Eslicarbazepine acetate (ESL) [(*S*)-(−)-10-acetoxy-10,11-dihydro-5*H*-dibenz[b,f]azepine-5-carboxamide], formerly known as BIA 2-093 is a novel central nervous system (CNS)-active agent. It belongs to the members of first-line AEDs represented by carbamazepine (first-generation) and oxcarbazepine (second-generation) having the dibenz/b,f/azepine nucleus bearing the 5-carboxamide substitute but is structurally different at the 10,11-position (*85*). This molecular variation results in differences in metabolism, preventing the formation of toxic epoxide metabolites such as carbamazepine-10,11 epoxide. It is the prodrug of ESL (*S*-licarbazepine (**27**)), the entity responsible for pharmacological activity. It is currently under clinical development for the treatment of epilepsy and bipolar disorder and acts by inhibiting voltage-gated sodium channels. Among the other dibenz[b,f] azepine-5-carboxamide derivatives ESL has the highest protective index (*86*). A recent phase III study of ESL demonstrated that ESL in a once-daily dosage of 800 and 1,200 mg was effective in reducing standardized seizure frequency. It was well tolerated as adjunctive therapy for partial-onset seizures in patients who were refractory to treatment with standard AED therapy. Mild to moderate dizziness, headache, diplopia, somnolence, and vertigo were the most commonly reported dose related adverse effects (*87*).

*Ganaxolone (**28**).* Ganaxolone (GNX) (3α-hydroxy-3β-methyl-5α-pregnan-20-one), a neuroactive steroid currently in clinical trials represents a potential AED. It is a beta methylated synthetic analogue of allopregnanolone (3α-hydroxy-21xi, 22-oxido-21-homo-5α-pregnan-20-one) and thought to act through positive allosteric modulation of the $GABA_A$ receptor (*88*). In healthy human volunteers, GNX, administered in doses ranging from 50 to 1,500 mg, either as drug alone or formulated with pharmaceutical grade excipients, is rapidly absorbed from the gastrointestinal tract after oral administration. The 3β-methyl substituent minimizes metabolism at the 3β-hydroxyl group so GNX is orally active, is not converted to the hormonally active 3-keto form, and hence lacks hormonal side effects (*89*). GNX has been shown to be well tolerated in adults and children and the commonly observed adverse events in children were agitation and somnolence. It is currently undergoing further development against newly diagnosed infantile spasms (*90*), in adults with refractory partial-onset seizures (*91*) and in women with catamenial epilepsy (*92*).

*Losigamone (**29**).* Losigamone (LSG), a racemic mixture of 5-α-5 (2-chlorphenylhydroxmethyl)-4-methoxy-2(5*H*)-furanone is related to β-methoxy-butenolides and is very similar to fadyenolides and piperolides isolated from *Piper fadyenii* and *Piper sanctum*, respectively. It is the first drug that has been identified using medicinal plant-based drug discovery (*93*). The mechanism of action for LSG is not clearly known, although several have been proposed (*94*). Initially it was thought that the anticonvulsant effect of losigamone may be due to NMDA (*N*-methyl-D-aspartic acid) antagonism and inhibition of excitatory amino acid release (*95*). *In vitro* and *in vivo* experiments carried out on genetically epilepsy prone DBA/2 mice by Jones and Davies suggested that the clinically effective anticonvulsant activity of LSG is attributed to its *S* (+)-enantiomer rather than *R* (−)-enantiomer or its racemic mixture (*96*). Present data suggests that the drug decreases neuronal excitability *via* a decrease in the persistent Na^+ current in rat hippocampal neurons (*97*). In a multi-center, double-blind, randomized clinical trial LSG was found to be an effective and safe add-on drug for refractory partial epilepsy in adults. The median reduction in seizure frequency as well as responder rate was significantly greater for a dose of 1,500 mg/day than for 1,200 mg/day, indicating a dose-response relationship (*98*).

*Remacemide hydrochloride (**30**).* Remacemide hydrochloride (RMD) [(±)-2-amino-*N*-(1-methyl-1,2-diphenylethyl)-acetamide monohydrate] is a racemic mixture and the (–) isomer is more potent than the (+) isomer in a maximal electroshock seizure (MES) test in mice. The major route of metabolism of remacemide involves desglycination and the principal metabolite is desglycinyl-remacemide (DGR). The drug may be considered as a prodrug because the anticonvulsant effects of the drug may be primarily mediated by DGR (*99*). It is a two-fold more potent Na^+ channel blocker and a 100-fold more potent non-competitive NMDA channel antagonist. Further, it also exhibits a greater efficacy than RMD itself in a variety of animal seizure models (*100*). Regardless of the activity of DGR, RMD exhibits inconsistent clinical efficacy as add-on therapy because DGR appears to be more susceptible to hepatic enzyme induction than the parent compound (*101*). Studies also showed that remacemide was significantly less effective than carbamazepine in preventing seizure

recurrence. Although significant pharmacodynamic interactions were observed between remacemide and other AEDs (valproate, CBZ, phenytoin, and phenobarbital) (*102*), unfavorable pharmacokinetic interactions make RMD an unsuitable candidate for adjunctive treatment of epilepsy (*103*).

*Retigabine (**31**).* Retigabine (RTG), *N*-(2-amino-4-(4-fluorobenzylamino) phenyl) carbamic acid ethyl ester effective against partial-onset seizures is the first novel KCNQ opener in the late stages of clinical development with an excellent safety profile (*104*). Rundfeldt (1997) (*105*) demonstrated that RTG initiates a membrane conductance which is selective for K^+ ions and it contributes to the anticonvulsant activity. Further studies established that it acts as a KCNQ potassium channel opener that involves opening of neuronal Kv7.2 (KCNQ2) voltage activated K^+ channels (*106*). Besides opening of peripheral KCNQ channels it hyperpolarizes the axotomized terminals that may constitute a novel and selective mechanism for attenuation of neuropathic pain symptoms (*107*). RTG as an adjunctive drug displayed promising improvement in patients with partial drug-resistant epilepsy. The most prominent adverse effects due to retigabine add-on therapy were dizziness, somnolence, and fatigue. It is metabolized primarily by glucuronidation to *N*-glucuronide metabolites and by acetylation (*108*).

*Safinamide (**32**).* By retaining the acetamide portion and replacement of the pentylamino moiety of milacemide (with residues present in the structures of substrates and inhibitors of the MAO (Mono Amine Oxidase), Pevarello *et al*. (1998) (*109*) derived the lead 2-[[4-(3-chlorobenzoxy)benzyl]amino]acetamide. As an outcome of this study, safinamide (SAF), ((*S*)-2-[[4-(3-fluorobenzoxy)benzyl]amino]propanamide methanesulfonate) (**33**), a 2-substituted amino amide emerged as a potent, orally active AED with a good safety margin. It has been shown to antagonize the calcium and sodium channels; as well as inhibit monoamine oxidase type-B (MAO-B) and the inhibition is reversible. Selectivity of SAF for the B isoform of the enzyme versus A is 5,000 and 1,000 times higher in rat and human brains, respectively (*110*).

*Soretolide (D-2916) (**34**).* Soretolide (SRT), (2,6-dimethylbenzamide *N*-(5-methyl-3-isoxazolyl)) is a new potent anticonvulsant exhibiting similar pharmacological properties to those of carbamazepine. Maurizis *et al*. hypothesized that SRT follows two metabolic degradation pathways. The active metabolite D3187 (**35**) has a better ability to cross the blood-brain barrier than the unchanged drug in female rats which may be attributed to the longer anticonvulsant activity of SRT (*111*). It is effective in the MES test in rodents but STR and its active metabolite are ineffective in protecting against PTZ-induced clonic seizures and in blocking generalized seizures in the hippocampal kindling rat model (*112*).

*Stiripentol (**36**).* Stiripentol (STP) is an efficient drug for add-on therapy in severe myoclonic epilepsy in infancy. When combined with CBZ and clobazam, it prevents the formation of the inactive metabolite of CBZ, epoxy-carbamazepine, and hydroxylation of the active metabolite of clobazam into hydroxy-norclobazam respectively (*113*). *In vitro* and *in vivo* studies suggest that STP can be considered as a "booster" of clobazam as the inhibitory effect of STP on CYP2C19 (Ki = 0.14 μM) was found to potentiate the antiepileptic effect of clobazam (*114*). It is positive allosteric modulator acting directly upon the $GABA_A$ receptor. Although it does not solely depend on the subunit composition of the receptor, STP elicits higher activity at the α3- or δ-subunit containing receptors. This drug with target selectivity is of particular importance if the said receptor subunits are responsible for any kind of neuronal dysfunction associated with neuronal hyperexcitability (*115*).

*AMPA receptor antagonist talampanel (**37**).* 2-Amino -3-(3-hydroxy-5-methyl-4-isoxazolyl) propionic acid receptors (AMPARs) play important roles in neurotransmission in the CNS and in the synaptic plasticity that underlies learning processes and memory (*116*). However, under certain pathological conditions the AMPARs over-activation determines neuronal cell death related to various neurological diseases such as stroke, Huntington's chorea, epilepsy, *etc*. Therefore, AMPAR antagonists have been considered useful as therapeutic agents for these disorders, particularly in epileptic seizures and are emerging as a promising new target for epilepsy therapy (*117*). The majority of the researches on AMPAR receptor antagonists are on the non-competitive (allosteric) AMPAR antagonists interacting with an allosteric AMPA binding site (Figure 3). The non-competitive antagonists have the advantage of remaining effective independently of the level of glutamate or the polarization state of the synaptic membrane during a neurological disease (*118*).

Moreover, they do not influence the normal glutamatergic activity after prolonged use. Thus, in recent years some important classes of these ligands have been developed. The first lead to be identified as a selective, non-competitive AMPA receptor antagonist is 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine (GYKI 52466) (**38**) (*119*). Based on this template, various 2,3-benzodiazepine compounds were synthesized and evaluated. Among all the compounds, the dioxolo-benzodiazepine talampanel also named LY300164 emerged as a highly active molecule. Its phase II clinical trials in the U.S. in patients with severe epilepsy not responsive to other drugs have yielded positive results. Phase III trials in epilepsy are underway to confirm and expand these results (*120*). Talampanel (TLP) (GYKI-53773, LY300164), a non-competitive AMPA receptor blocker has undergone initial assessment in patients with

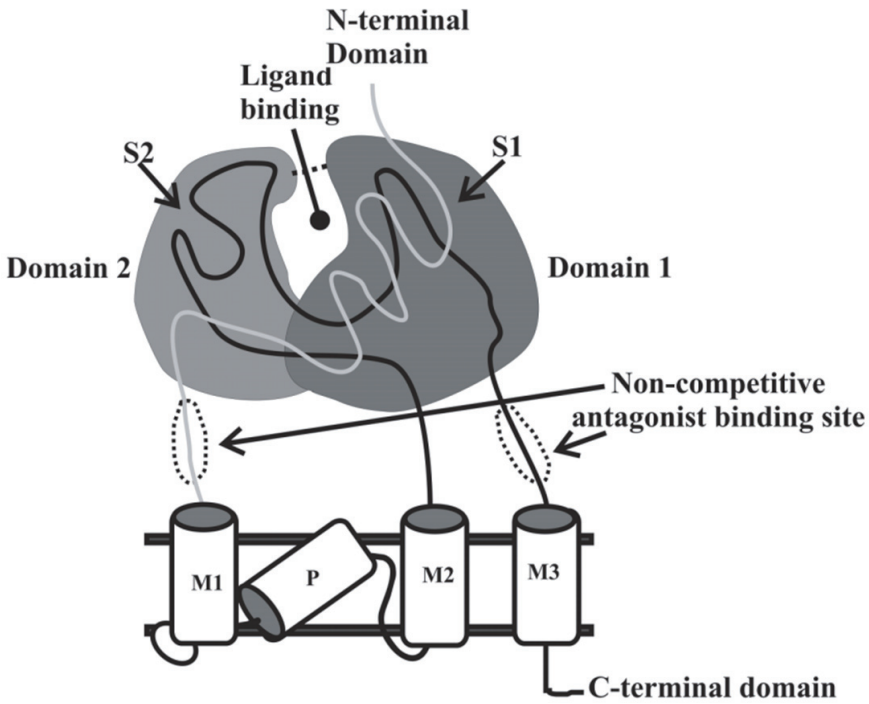

Figure 3. Schematic model of an AMPA receptor subunit. The model illustrates the agonist binding core (such as glutamate and AMPA) and competitive antagonist binding site. The putative sites of action of allosteric non-competitive antagonist talampanel are also shown. The agonist binding core consists of two domains (S1 and S2) attached by linkers to the cation channel domain consisting of three membrane-spanning segments (M1-M3) and a pore loop (P). The C-terminal domain is intracellular and the *N*-terminal domain is extracellular. (Figure reproduced with permission, Bialer *et al*., 2007)

epilepsy. In an early adjunctive-therapy crossover trial in 49 patients with refractory partial seizures, median seizure frequency was 21% lower on talampanel than on the placebo, a statistically significant effect (*121*). A recent review that deals with talampanel extensively summarizes that the antiepileptic is generally well tolerated in adults with refractory complex partial seizures. The most commonly reported adverse event is dizziness and at higher doses sedation and ataxia may occur (*122*). A new potent noncompetitive AMPA receptor antagonist perampanel (**39**) that has demonstrated efficacy and good tolerability in the treatment of refractory partial onset seizures is in late stage clinical development (*123*). Whether the drug will prove adequately effective to reduce the morbidity and mortality of epilepsy is yet to be ensured.

*Valrocemide/ TV1901 (**40**).* Valrocemide (VGD) is a combination of VPA and glycinamide (*N*-valproyl glycinamide), a chemical derived from glycine, an amino acid that can have an antiepileptic effect if its concentration in the brain is increased (*124*). Isoherranen *et al*. (2001) (*125*) investigated the anticonvulsant activity of VGD in various animal (rodent) models of human epilepsy to determine its anticonvulsant profile and safety margin. The results obtained in this study suggest that VGD has a broad spectrum of anticonvulsant activity and promising potential as a new AED. VGD is currently under development by Teva and Acorda therapeutics as a potential therapeutic for the treatment of epilepsy. In the year 2003, a phase II trial using valrocemide as an adjunct therapy in refractory epilepsy patients had been completed and phase III trials were being planned. VGD was also being investigated for potential utility in the treatment of bipolar disorder and neuropathic pain (*126*).

*Pregabalin (Lyrica®) (**41**).* Pregabalin (PGB) is the alkylated analogue of the neurotransmitter GABA. Its binds potently to the α2γ subunit, an auxiliary protein associated with voltage-gated calcium channels (VGCC) in the CNS and reduces calcium influx at nerve terminals thereby (*127*) modulating the release of excitatory neurotransmitters in "hyper-excited" neurons, restoring them to normal physiological state (*128*). It is indicated as an adjunctive therapy in adults with partial seizures with or without secondary generalization, peripheral neuropathic pain and in patients with generalized anxiety disorder or social anxiety disorder (*129*). A recent study by Briggs *et al*. suggested that PGB at a higher dose is effective in reducing the absolute frequency of secondarily generalized tonic-clonic seizures in patients with clinically refractory partial epilepsy, but not secondary generalization (*130*).

The majority of the newer AEDs used clinically are derived from structural modification of the existing drugs. These include vigabatrin, oxcarbazepine, fluorofelbamate, brivaracetam, DP-valproic acid, eslicarbazepine, valrocemide, and pregabalin. The drugs are developed with an objective to augment the efficacy and safety margin and few of them are

effective in combination. Although it may provide a solution to contained epilepsy an absolute seizure-free state is still not attainable and often "evergreening" may be one of the criteria for such structural modifications. This phenomenon of existing drug modification also does not encourage sustained research for exploring new targets. Nevertheless, few drugs acting on newer molecular targets *viz.*, SV2A protein, AMPA receptor *etc*. with promising clinical trial results might shape a better therapeutic outcome. Few currently available investigational agents act at diverse targets that are involved in the pathogenesis of this complex neurological disorder and therefore, it is impossible to anticipate all the agents that provide an equivalent level of potency and efficacy. Additionally, the complexity increases when taking into consideration the nature of epileptogenesis in an individual patient. Application of plant-based drug discovery is still in its infancy as far as epilepsy is concerned and demands more screening of this novel source for generation of leads or prototype drugs as exemplified by losigamone.

3. Pharmacoresistance

Pharmacoresistance to medication is an important clinical problem in epilepsy. The phenomenon is observed in approximately one third of patients, and is associated with an increased risk of death and other ill consequences. Pharmacoresistance in epilepsy may be defined as seizures that continue to occur despite treatment trials with at least three appropriate AEDs at maximum tolerated doses (*131*). When a patient fails to respond to two or three appropriate AEDs then the chance of significant benefit from other drugs is 10% or less (*132*).

There are a number of factors associated with drug resistance and varies from one patient to another including early age of seizure onset combined with high seizure frequency, type of epileptic syndrome and seizure, structural brain lesions (*e.g.* cortical dysplasia) or electroencephalographic abnormalities and history of status epilepticus (*133*). At present two hypotheses have been asserted to explain the development of pharmacoresistance to AEDs *viz.*, the target hypothesis and the transporter hypothesis. The target hypothesis denotes that epilepsy related changes in the molecular properties of the drug targets contribute to pharmacoresistance. For example, Remy *et al.* (2003) (*134*) studied cellular mechanisms underlying drug resistance in resected hippocampal tissues from patients. They suggested that a loss of Na^+ channel drug sensitivity may constitute the development of resistance. The transporter hypothesis accentuates that resistance develops due to overexpression or increase in functioning of multidrug transporters in the brain, leading to poor penetration of AEDs into brain targets and thereby contributing to multidrug resistance (MDR) in epilepsy. To substantiate the hypothesis, Volk and Loscher using a rat model of temporal lobe epilepsy demonstrated that there is an increase in expression of multidrug transporter proteins such as the ATP-binding cassette sub-family B member 1 (ABCB1, also known as MDR1 and P-glycoprotein 170) in the brain of the rat with drug-resistant spontaneous seizures (*135*). Siddiqui *et al*. (2003) (*136*) recognized a genetic factor associated with resistance to AEDs. They hypothesized that polymorphisms in the drug transporter gene (CC genotype at the *ABCB1* C3435T) is associated with increased expression of the ABCB1 protein which inturn influences the response to AED treatment. Although no genetic stratification is underpinned, a recent study found a significant association between *ABCB1* polymorphisms and drug resistance when patients were stratified by the same type of epilepsy and/or in those treated with the same AEDs (*137*). Researchers' efforts might target development of AEDs that are not recognized by MDR proteins or that can evade ABCB1. Alternatively, agents that inhibit these proteins (*138*) can be concomitantly administered with the currently available AEDs thereby decreasing the incidence of pharmacoresistance.

4. Combination therapy

Monotherapy is generally recommended for patients with newly diagnosed epilepsy. Combination therapy (CT) should only be initiated upon unresponsiveness to monotherapy. As the mechanism of action does not generally provide much guidance while combining AEDs, it is important to know the efficacy of each drug in different seizure types. CT has been found to be successful in about 30% of patients. A non-randomized trial suggested the efficacy of combination therapy in achieving seizure-freedom in epilepsies refractory to single drug treatment (*139*). Drug interaction is a common phenomenon observed during CT. This may be avoided by choosing non-interacting drugs. If such alternatives are not available, interacting drugs may be administered together by monitoring the plasma drug concentration followed by adjustment of dosage (*140*). For attaining a viable therapeutic outcome, CT requires rational combination to be tailored on an individual basis. In general, if the efficacy of two AEDs combined is shown to be additive or supra-additive and the burden of side effects is less than additive, the combination is considered to be advantageous. On the contrary if there is no observed efficacy or it is less than additive while the side effect burden is equal to additive, the combination is regarded as unfavorable (*141*). With reservation to evidence-based findings, Karceski *et al*. (2009) (*142*) summarized the choice of specific medications as possible add-on agents that were identified as showing efficacy based on Class I and Class II evidence in the 2004 American Academy

Table 2. Combination/add-on therapy

Existing agent	Appropriate add-ons	
	Symptomatic localization related epilepsy	Idiopathic generalized epilepsy
Felbamate	–	***Valproate***, lamotrigine
Lamotrigine	***Levetiracetam***, topiramate, oxcarbazepine	Valproate, topiramate, levetiracetam, zonisamide
Levetiracetam	***Lamotrigine***, ***carbamazepine***, oxcarbazepine	***Valproate***, lamotrigine, topiramate
Topiramate	***Lamotrigine***, ***levetiracetam***, carbamazepine	***Lamotrigine***, ***valproate***, levetiracetam
Valproate	***Levetiracetam***, oxcarbazepine, lamotrigine	***Lamotrigine***, topiramate, levetiracetam, zonisamide
Vagus nerve stimulation	–	***Valproate***, lamotrigine, topiramate
Zonisamide	Levetiracetam, lamotrigine	***Lamotrigine***, ***valproate***, levetiracetam
Tiagabine	***Lamotrigine***, levetiracetam, topiramate	–
Phenytoin	***Levetiracetam***, ***lamotrigine***	–
Phenobarbital	***Lamotrigine***, ***levetiracetam***, oxcarbazepine	–
Oxcarbazepine	***Levetiracetam***, lamotrigine, topiramate	–
Gabapentin	***Lamotrigine***, ***levetiracetam***, oxcarbazepine	–
Carbamazepine	***Levetiracetam***, lamotrigine	–

Bold italic indicates treatment of choice.

of Neurology (AAN)/American Epilepsy Society (AES) guidelines (Table 2). Among the various possible combinations, the information from the table implied that LEV may be considered as the universal add-on drug. Furthermore, recent evidence revealed that a combination of LEV with other AEDs, particularly those enhancing GABAergic inhibition, lead to additive/synergistic effects on seizure protection with minimal side effects and pharmacokinetic interactions (*143*).

5. Conclusion

Despite the discovery of a number of AEDs, the management of epilepsy still remains an intricate task. Due to the prevalence of resistance to monotherapy, combination therapy proves workable. The utilization of available drugs to combat resistance requires rational adaptation of data arising out of clinical trials. Most of the currently available AEDs possess multiple mechanisms of action. With a few exceptions, the precise primary mode of action of some newer AEDs remains to be discovered. A multidiciplinary approach to identify potential receptor site, mechanism of action, and reason for resistance would pave the way for better therapeutic interventions towards the management of epilepsy.

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