

Antiepileptic drugs: newer targets and new drugs**Vihang S. Chawan, Abhishek M. Phatak*, Kalpesh V. Gawand, Sagar V. Badwane, Sagar S. Panchal**

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ABSTRACT

Epilepsy is a common neurological disorder affecting 0.5-1% of the population in India. Majority of patients respond to currently available antiepileptic drugs (AEDs), but a small percentage of patients have shown poor and inadequate response to AEDs in addition to various side effects and drug interactions while on therapy. Thus there is a need to develop more effective AEDs in drug resistant epilepsy which have a better safety profile with minimal adverse effects. The United States food and drug administration (USFDA) has approved eslicarbazepine acetate, ezogabine, perampanel and brivaracetam which have shown a promising future as better AEDs and drugs like ganaxolone, intranasal diazepam, ICA- 105665, valnoctamide, VX-765, naluzotan are in the pipeline.

Keywords: Epilepsy, Newer antiepileptic drugs, Eslicarbazepine Acetate, Ezogabine (Retigabine), Perampanel, Brivaracetam, Naluzotan

INTRODUCTION

Epilepsy is a common neurological disorder characterized by recurrent and unprovoked seizures. This occurs due to abnormal excessive or synchronous neuronal activity in the brain and symptoms vary depending upon the part of brain affected in the epileptic discharge. Epilepsy affects 0.5-1% of the population in India. There are about 5-10 million epileptic patients in India accounting for almost one-fifth (1/5) of global figures.^{1,2} Epilepsy is largely seen in patients less than 20 years of age with increased frequency of seizures in old age with other diseases affecting the brain function. The majority of patients with epilepsy are treated with various antiepileptic drugs (AED). It requires lifelong therapy. The small percentage of patients who have shown poor and inadequate response

to AEDs or those patient who have suffered from recurrent seizures, may require surgery. Thus there is a need to develop more effective AEDs to reduce seizure frequency in drug resistant epilepsy and have a better safety profile with minimal adverse effects. All currently available AEDs cause severe adverse effects such as gum hypertrophy (phenytoin), water intoxication (carbamazepine) and weight gain (valproate) with a continuous therapeutic drug monitoring with phenytoin therapy. All these AEDs are also involved in clinically important drug-drug interactions.¹ Thus the management of side effects of these currently available AEDs add to the burden of epilepsy.

Hence, there is a need for newer AEDs with no drug-drug interactions and less adverse effects. For those with

refractory epilepsy, newer AEDs are administered as an add-on therapy along with older AEDs. There are various newer AEDs introduced in the last few years and some of them are currently in various phases of drug development. Eslicarbazepine acetate, ezogabine (retigabine), perampanel and brivaracetam have been recently approved by the United State food and drug administration (USFDA) (Table 1). The article reviews the mechanism of action, preclinical efficacy, pharmacokinetic profiles, drug interactions and adverse effects of these recently approved newer antiepileptic drugs. Newer antiepileptic drugs have been classified according to their mechanism of action (Table 2).³⁻⁶

Table 1: Year of drug approval.

Drugs	Year of approval
Ezogabine/retigabine	June 2011
Perampanel	October 2012
Eslicarbazepine acetate	November 2013
Brivaracetam	February 2016

Table 2: Mechanism of action of new antiepileptic drugs.

Mechanism of action	Drugs
Drugs acting on sodium channels	Eslicarbazepine acetate
Drugs acting through GABA channels	Clobazam,
	Stiripentol,
	Losigamone,
	Ganaxolone
Drugs acting on potassium channel	Intranasal diazepam
	Ezogabine,
Drugs with novel mechanism	ICA105665
	Perampanel,
	Brivaracetam,
	Valnoctamide,
	VX-765,
	Naluzotan

Drugs acting on sodium (Na⁺) channels

Eslicarbazepine acetate

Eslicarbazepine acetate (ESL) is a third-generation member of the dibenzazepine family, which also includes carbamazepine (CBZ) and oxcarbazepine (OXC). It was approved by the european medicines agency (EMA) in 2009 and the USFDA in November 2013 as an adjunctive therapy in adults with partial-onset seizures with or without secondary generalization.⁷ Although the precise mechanism of action of ESL is not known, *in-vitro* studies suggest that like carbamazepine (CBZ), ESL also inhibits the slow activation of the voltage gated Na⁺ channels. Absorption of ESL from gastrointestinal tract is high following oral administration. Food does not affect its absorption. ESL is rapidly and extensively metabolized to

eslicarbazepine by hydrolytic first-pass metabolism within 1-4 hours. Unlike carbamazepine, it is not susceptible to metabolic autoinduction.^{8,9} ESL is a prodrug of eslicarbazepine, which is responsible for pharmacological activity. Plasma protein binding is about 40%. Plasma half-life of ESL is about 13-20 hours and the steady-state concentration reaches within 4-5 days of once daily dosing. The metabolites of ESL are primarily excreted through kidney in as unchanged form and as glucuronide conjugates. Dose adjustments may be necessary in patients with creatinine clearance below 60 mL/min.⁸ ESL has moderate inhibitory effect on CYP2C19 and mild induction of CYP2C9 resulting in decreased serum levels of (S)-warfarin when co-administered with warfarin. ESL does not interfere with clearance of carbamazepine, phenytoin, topiramate, clobazam, gabapentin, phenobarbital, levetiracetam and valproic acid. The adverse effects reported with ESL are dizziness, somnolence, nausea, diplopia, headache, vomiting, abnormal coordination, blurred vision, vertigo and fatigue.¹⁰

Drugs acting through GABA channels

Clobazam

Clobazam is used as an adjunctive therapy in treating seizures associated with Lennox-Gastaut syndrome. It was approved by USFDA in October 2011. Clobazam acts primarily through positive allosteric modulation of GABAA receptors. Clobazam is safe and effective for acute seizures. Its clinical utility for long-term therapy is often limited by side effects and the development of tolerance.¹¹ Clobazam is demethylated by cytochrome P450 CYP3A4 and CYP2C19 to its active metabolite N-desmethyloclobazam (norclobazam). It is also hydroxylated to an inactive form. Norclobazam undergoes hydroxylation by CYP2C19 to an inactive form. Since norclobazam itself is an anticonvulsant, an increase in its levels through inhibition of CYP2C19 greatly increases the duration of therapeutic effect.^{12,13} Adverse effects of clobazam are somnolence, behavioral abnormalities, irritability, ataxia and drooling.¹⁴

Stiripentol

Stiripentol currently has been classified as an orphan drug in 2007 in Europe for adjuvant therapy in Dravet Syndrome. Stiripentol is an AED used as an adjunctive therapy to clobazam and valproate in the treatment of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy i.e. Dravet syndrome (DS). More than 500 children have been safely treated and recent experiment in Japan confirmed stiripentol benefit in DS children with comedications other than valproate and clobazam.¹⁵ Stiripentol is the only compound that proved its efficacy in DS through two independent randomized placebo-controlled trials, when combined with valproate and clobazam as an adjunctive therapy in children with Dravet syndrome who do not

respond to valproate and clobazam and was shown to have better response rate (71%) as compared to placebo (5%).^{16,17} Their dose has to be decreased to minimize the side effects (mostly loss of appetite) resulting from pharmacokinetic interactions of stiripentol powerfully inhibiting cytochromes P450. It enhances central GABA-A transmission. Stiripentol is extensively metabolized and exhibits non-linear kinetics. It is a potent inhibitor of CYP3A4, CYP1A2 and CYP2C19 causing increases in the serum concentration of other AEDs such as phenytoin, carbamazepine, phenobarbital, valproic acid and clobazam.

Losigamone

Losigamone is a potential antiepileptic drug which is currently in phase-3 clinical trial. The exact mode of action of losigamone is unclear and does not involve specific binding of GABA, flunitrazepam or t-butyl-bicyclophosphorothionate (TBPS) to their receptors. It potentiates GABA-induced chloride influx in primary spinal cord neuron cultures. Another suggested possible mechanism of action for losigamone is K⁺ channel activation.¹⁸ According to results of randomized controlled, add-on trials comparing losigamone with placebo for partial epilepsy, for efficacy outcome it has been found that patients taking losigamone were significantly more likely to achieve a 50% or greater reduction in seizure frequency but associated with a significant increase of treatment withdrawal when compared with those taking placebo. For the safety outcomes, results indicated the proportion of patients who experienced adverse events in the losigamone group was higher than the placebo group, dizziness was the only adverse event significantly reported in relation to losigamone. However, trials included were of short-term duration and uncertain quality. Future well-designed randomized, double-blind, placebo-controlled trials with a longer-term duration are needed.¹⁹

Ganaxolone

Ganaxolone, the synthetic 3 β -methyl analog of allopregnanolone, has been evaluated in clinical trials for the treatment of epilepsy. It appears to be an efficacious, well-tolerated and safe treatment for partial seizures. Endogenous neurosteroids may play a role in catamenial epilepsy, stress-induced changes in seizure susceptibility, temporal lobe epilepsy, and alcohol withdrawal seizures. Moreover, neurosteroid replacement with natural or synthetic neurosteroids may be useful in these conditions and more generally in the treatment of partial seizures. Ganaxolone is currently undergoing phase 3 clinical trial. At low concentrations, such neurosteroids potentiate GABA-A receptor currents, whereas at higher concentrations they directly activate the receptor; large magnitude effects occur on nonsynaptic δ subunit-containing GABAA receptors that mediate tonic currents.²⁰

Intranasal diazepam

NRL-1 (intranasal diazepam) is a proprietary formulation of diazepam, delivered via an already marketed nasal sprayer, being developed for the management of pediatric and adult patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity. It is currently in phase 3 trial. In clinical trials, NRL-1 has demonstrated high bioavailability, low variability from dose to dose, and was well-tolerated.

There are over 2.7 million people with epilepsy in the United States with approximately 200,000 new patients diagnosed each year. It is estimated that between 30% and 40% of these patients are uncontrolled on oral therapy and are at-risk for acute breakthrough seizures. Studies have shown that prolonged or repetitive seizures can cause neurological damage and dramatically increase the risk of changes in neuropsychological function or even death.²¹

Drugs acting on potassium channels

Ezogabine

Ezogabine (EZG) is carbamic acid ethyl ester, also known as retigabine. It acts on potassium channels, GABA-A receptors, sodium and calcium channels. It is an useful agent in the treatment of benign familial neonatal convulsions (BFNC) which is caused by loss of function mutations involving KCNQ2/KCNQ3 genes. It was recently approved as an adjunctive treatment for partial-onset seizures by the EMA in March 2011 and USFDA in June 2011.^{22,23} Retigabine has a unique ability to activate potassium channels, specifically KCNQ2/KCNQ3 subunits, decreasing the excitability of neurons. The KCNQ2/KCNQ3 genes found in the hippocampus, neocortex and thalamus contribute to the M-current, which is inhibited by the activation of muscarinic acetylcholine receptors. The M-current activates slowly following depolarization and does not inactivate with sustained depolarization.

EZB also potentiates GABA-A receptor responses at higher concentrations. The activity against GABA receptors, however, was found to be ineffective against the administration of flumazenil, indicating that retigabine differs mechanistically from benzodiazepines.^{24,25} Retigabine is rapidly absorbed when given orally. Dose Ranges from 600-1200 mg/day with mean dose being 900 mg/day. Oral bioavailability is about 60%. Food does not interfere with its absorption peak plasma concentration is seen within 1.5 hours and the elimination half-life is about 8 hours.

Retigabine is widely distributed in the body and is 80% plasma protein bound. It is extensively metabolized in the liver by glucuronidation and acetylation. Mild hepatic impairment does not require dose reduction. Retigabine is mainly eliminated by kidneys. Patients with creatinine

clearance <50 ml/min require 50% reduction in the dosing of retigabine.²⁶ Retigabine does not induce or inhibit its own metabolism. It does not exhibit clinically significant drug interactions with other drugs like valproate, lamotrigine or imipramine. Phenytoin and carbamazepine (inducers of glucuronidation), increase the clearance of retigabine by 36% and 27% respectively. Adverse effects associated with use of EZB is development of retinal abnormalities, possible risk of visual loss and bladder symptoms such as urinary retention, hesitancy and dysuria which are dose related, discolouration of skin, nails, lips and psychiatric symptoms such as confusional state, disorientation, hallucinations and other symptoms of psychosis. It may cause dizziness, somnolence, memory impairment, abnormal coordination disturbance in attention are also seen.²⁷

ICA 105665

ICA-105665 is a highly selective opener of neuronal Kv7 (KCNQ) potassium channels; the molecular components of the slow voltage-gated M current. It is currently undergoing phase 2 trial. In healthy volunteers, ICA-105665 was well-tolerated following a single oral dose up to 400 mg and multiple doses up to 600 mg/day (300 mg b.i.d.). The compound is highly bound (>99%) and has a half-life of 5 to 9.5 h after oral administration. It neither induces nor inhibits liver enzymes.²⁸

Drugs with novel mechanism

Perampanel

Perampanel (PRP) has a broad spectrum anticonvulsant activity. It was approved by the European Commission in July 2012 and by the USFDA in October 2012, as an adjunctive treatment for partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy who are aged 12 years and older.²⁸ PRP is a selective and non-competitive 2-amino, 3-hydroxy, 5-methyl, 4-isoxale propionic acid (AMPA) antagonist. Perampanel inhibits AMPA-induced increase in intracellular Ca^{++} and selectively blocks AMPA receptor-mediated synaptic transmission, thus reducing the neuronal excitation.²⁹ PRP is well tolerated. Effective Dose ranges from 4-12 mg/day. It is rapidly and completely absorbed from gastrointestinal tract following oral administration. Maximum plasma concentration reaches between 25 min and 2 hours. It has a long half-life of about 70 hours which allows once a day dosing and the steady-state plasma concentration is achieved in 14 days. PRP is 95% protein bound and is extensively metabolized by oxidation by CYP3A4 and glucuronidation. It is mainly excreted in feces and remaining is eliminated by kidneys in the form of glucuronidated and hydroxylated metabolites.³⁰ PRP is not an enzyme inducer or enzyme inhibitor. Enzyme inducing agents such as carbamazepine, oxcarbazepine and phenytoin increases the clearance of PRP and decreases the plasma concentration by half. Adverse

effects seen with PRP are dizziness, somnolence, headache, fatigue, diarrhea, rhinitis, nasopharyngitis and convulsions. Most of these adverse effects are mild.³⁰

Brivaracetam

Brivaracetam (BRV) is a novel high affinity synaptic vesical protein 2A ligand and displays inhibitory activity at neuronal voltage gated sodium channels (VGSC). It is more potent and faster in achieving maximal SV2A occupancy. It has been recently approved by the USFDA in February 2016 for the treatment of uncontrolled partial seizure in adults. It showed superior and broad spectrum activity in various animal models of focal and generalized seizures than levetiracetam. It is well absorbed from gastrointestinal tract and has a half-life of about 8 hours. It interacts with carbamazepine metabolism and increases concentration of 10,11-epoxide metabolite of carbamazepine at doses of ≥ 50 mg/day. It is eliminated primarily by biotransformation through hydrolysis of acetamide group and CYP2C19 mediated hydroxylation. Adverse effects associated with brivaracetam use are headache, somnolence, dizziness, fatigue.^{28,31}

Valnoctamide

Sec-Butyl-propylacetamide (SPD) is a one-carbon homolog of valnoctamide (VCD), a chiral constitutional isomer of valproic acid's (VPA) corresponding amide valpromide. VCD has potential as a therapy in epilepsy including status epilepticus (SE) and neuropathic pain, and is currently being developed for the treatment of bipolar disorder. Both VCD and SPD possess two stereogenic carbons in their chemical structure. SPD possesses a unique and broad-spectrum antiseizure profile superior to that of valproic acid (VPA) and better than that of VCD. In addition SPD blocked behavioral and electrographic SE induced by pilocarpine and soman (organophosphate nerve gas) and afforded *in-vivo* neuroprotection that was associated with cognitive sparing. VCD has activity similar to that of SPD in pilocarpine-induced status epilepticus (SE), although at higher doses. The activity of SPD and VCD against SE is superior to that of diazepam in terms of rapid onset, potency, and ability to block SE when given 20-60 min after seizure onset. When administered 20 and 40 min after SE onset, SPD (100-174 mg/kg) produced longlasting efficacy (e.g., 4-8 h) against soman-induced convulsive and electrographic SE in both rats and guinea pigs. SPD activity in the pilocarpine and soman-induced SE models when administered 20-60 min after seizure onset, differentiates SPD from benzodiazepines and all other antiepileptic drugs. It is currently being undergoing in phase 2 clinical trial.^{28,32}

VX-765

It is indicated in patients with treatment-resistant partial onset epilepsy who did not benefit from the use of at least two currently available medicines. VX-765 is designed to

inhibit caspase-1, an enzyme involved in the production of interleukin-1 (IL-1) beta and linked to a wide range of immune and inflammatory responses. VX-765 has been shown to inhibit acute partial seizures in preclinical models and has shown activity in preclinical models of chronic partial epilepsy that do not respond to currently available medicines for epilepsy. It is currently undergoing in phase 2b clinical trial.²¹

Naluzotan (PRX-00023)

Naluzotan is a 5-HT_{1A} receptor agonist, has been shown to be safe and well-tolerated in over 400 patients. It will be entering into phase 2 clinical development for epilepsy. Epilepsy patients with localization-related epilepsy have reduced 5-HT_{1A} receptor binding as indicated by positron emission tomography (PET scan). It is thought that by increasing neurotransmitter activity at 5-HT_{1A} receptor sites, seizure incidence and severity may be decreased. This would represent a major breakthrough for treatment of epilepsy, a disease affecting approximately 50 million people worldwide.²¹

CONCLUSION

While all antiepileptic medications have some side effects, the choice of which drug to be used and the side effects which the patient can tolerate depends on the individual patient. So many newer AEDs have been introduced in the last few years with improved pharmacokinetics and potentially novel mechanism of actions. Results from clinical studies demonstrated that many of these newer AEDs are well tolerated and highly effective in reducing drug resistant seizures. Some of these are also used in treatment of recurrent seizures as adjunctive therapy. Availability of these new treatments for epilepsy will further increase the treatment options and thus provide a significant benefit to patients who remain refractory to existing therapy.

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