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Newer Anti Epileptic Drugs

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Abstract: ***Epilepsy is a disorder of the brain characterized by On 1 or 2 antiepileptic drugs, around 70-80% of people with newly diagnosed epilepsy will eventually achieve remission an enduring predisposition to generate seizures. Treatment of epilepsy with standard anticonvulsants such as phenytoin, carbamazepine, valproic acid and phenobarbital is often complicated by side effects. Thus, there is an unmet need for a highly efficacious AED with a good safety profile and very few side effects. A host of newer AEDs or modified versions of the previously available drugs, are available which if not more are at least equally efficacious to the older AEDs with a better safety profile and fewer drug interactions.***

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1. Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures. Patients with 2 or more 'recurrent' 'unprovoked seizures' are defined as having 'epilepsy'.[1] Epilepsy is one of the most common neurological disorders having a significant impact on the quality of life of an individual. Around 0.5 - 0.9% of the world population has epilepsy at any given time with a risk of 3% for an individual to develop epilepsy during their lifetime[2]. The prevalence rates vary in different parts of the world (overall – 5 per 1000 persons) roughly translating to around 70 million people in the world who are affected by this condition at a given point of time. In India, the prevalence of epilepsy is 6 – 10 per 1000 people. The British National General Practice Study of Epilepsy investigated remission rates in 1091 newly diagnosed patients with epilepsy who were put on anti-epileptic drug therapy[3]. On 1 or 2 antiepileptic drugs, around 70-80% of people with newly diagnosed epilepsy will eventually achieve remission. Most of those who remit while receiving AEDs can discontinue medication after 2-3 years and remain seizure free. Around 20 - 30% of patients with active epilepsy are resistant to AEDs and have what is known as drug resistant epilepsy. India, with a population of around one billion at any point of time has around 5 million people suffering from epilepsy of which the burden of medically refractory epilepsy is around 900,000. 4 Treatment of epilepsy with standard anticonvulsants such as phenytoin, carbamazepine, valproic acid and phenobarbital is often complicated by side effects (due to their narrow safety margin) and at times by therapeutic failure to adequately control seizures. The clinical goal of AED treatment, especially for those with intractable epilepsy, is to lead to a reduction in seizure frequency at doses which do not cause any significant side effects. However, adverse effects are experienced by about 60%5 of patients with epilepsy on treatment and about 4% of patients stop taking the drugs because of the side effects6. Thus, there is an unmet need for a highly efficacious AED with a good safety profile and very few side effects. A host of newer AEDs or modified versions of the previously available drugs, are available which if not more are at least equally efficacious to the older AEDs with a better safety profile and fewer drug interactions. Most new AEDs are less teratogenic, have far less effects on hormone secretion, and little or no effects bone and lipid metabolism, are milder. Some of these newer anti-epileptic drugs also have newer mechanism of actions, making them more advantageous as add-on therapy for drug resistant epilepsy.

2. The AED Story

The AED story began on 11th May 1857 when Charles Locock commented in the Lancet on his use of potassium bromide in 15 cases of ‘‘hysterical’’ epilepsy in young women[7]. The next development was the serendipitous discovery of the anticonvulsant properties of phenobarbital by Alfred Hauptmann in 1912. [8]This predated by more than 20 years the screening of potential therapeutic agents against ‘‘electrical seizures’’ in cats by Houston Merritt and Tracy Putnam.[9] The result was the launching of Phenytoin in 1938. Next came primidone, ethosuximide, carbamazepine and valproic acid, all of which can be regarded as first generation antiepileptic drugs. The modern era of AED development began in 1975 when the National Institute of Neurological Disorders and Stroke in the United States established the Anticonvulsant Drug Development Programme. Systematic screening of many thousands of compounds against rodent seizure models (maximal electroshock, subcutaneous pentylenetetrazole, 6 Hertz test)[10] took place and more than 28,000 new chemical entities from academic and pharmaceutical chemists have since been screened, resulting in the licensing of an increasing list of AEDs. Depending on their time of discovery, the side effect profile and mechanism of actions – Antiepileptics are divided in first, second and third generation as follows:

1st generation[11, 12]		2nd generation[13,14]		3rd generation[15]	
Bromide	1857	Vigabatrin	1989	Rufinamide	2007
Phenobarbitone	1912	Lamotrigine	1992	Stiripentol	2007
Phenytoin	1938	Gabapentin	1993	Brivaracetam	2006
Primidone	1954	Felbamate	1993	Eslicarbazepine	2008
Ethosuximide	1958	Topiramate	1996	Lacosamide	2008
Carbamazepine	1965	Tiagabine	1998	Retigabine	2008
Valproate	1967	Levetiracetam	1999	Perampanel	2012
Clonazepam	1968	Oxcarbazepine	2000		
Clobazam	1975	Fosphenytoin	2002		
		Pregabalin	2004		
		Zonisamide	2005		

Mechanism of Action of AED's[16]

They all have in common the ability to Decrease neuronal excitation or Increase neuronal inhibition. This can be achieved by either: Modulation of voltage-gated cation channels, Potentiation of GABA-ergic activity, Inhibition of glutamatergic processes or through novel mechanisms like action on SV2A protein or the CRMP2 protein.

Modulation of voltage-gated cation channels – Na+	Modulation of voltage-gated cation channels – Ca++	Potentiation of GABA-ergic activity	Inhibition of glutamatergic Processes
Carbamazepine	Ethosuximide	Barbiturates	NMDA rec Felbamate
Oxcarbazepine	Levetiracetam	Benzodiazepines	AMPA/Kainate rec Topiramate
Lamotrigine	Pregabalin	Gabapentin	
Phenytoin	Valproate	Levetiracetam	
Topiramate		Tiagabine	
Valproate		Topiramate	
Zonisamide		Valproate	
		Vigabatrin	

Need for Newer AED's

With the current AED's an individual is expected to obtain good seizure control in only 70% cases. Even in those patients when the drugs are effective, About 60% experience some form of adverse effects and of these nearly 33% have to change drugs because of intolerable side effects. In addition most drugs have teratogenic potential and women of child bearing age have to be extra cautious not to conceive when they are on these drugs. As a result, there is still a requirement of a drug which is more efficacious but has fewer adverse effects, drug interactions, lower teratogenicity and preferably an easy dosing schedule for good compliance.

Newer AED's

1) **Lacosamide[17]:** Lacosamide was approved as an adjunctive treatment for partial-onset seizures by the European Commission in August 2008 for patients above 16 years of age and by US Food and Drug in October 2008 for similar seizure semiology in those above 17 years of age.
2) **Mechanism of action:** It enhances slow inactivation of sodium channels thus preventing neuronal depolarisation and sustained repetitive firing of the neurons. It also binds to collapsing response mediator protein 2 (CRMP-2), which is involved in neuronal differentiation, regulation of gene expression, polarization, and axonal outgrowth. LCM may thus exert a modulatory effect on CRMP-2-induced axonal outgrowth of primary hippocampal cells following stimulation with neurotrophic factors. By interacting with the CRMP-2, it is postulated that LCM may have symptomatic and/or disease-modifying effects.
3) **Pharmacokinetics:** It has a very high oral bioavailability – nearly 100%. There is also 100% concordance with the oral and iv dose. There is no effect of concomitant food administration on absorption from GI tract. It also has a very fast rate of absorption with a peak plasma concentration within 30 mins – 4 hours of drug administration. There is only minimal plasma protein binding (<15 %) which is not affected by age, gender, ethnicity. 95 % of the drug is excreted renally while 40% of the LCM dose is excreted as unchanged compound.
4) **Preparations & Dosing:** Lacosamide is available in the following strengths in the Indian market as Coated tablets - 50, 100, 150, 200 mg, Liquid suspension- 15mg/ml, Injection- 10 mg/ ml. The average daily Dosage ranges from 200 – 400 mg per day. Usual starting dose is 50 mg BD, which can be increased weekly thereafter. Its elimination half-life is around 12-16 hours and hence it requires twice daily dosing. Dose modification in patients with mild or moderate renal impairment (creatinine clearance of >30 ml/min)- is unnecessary. However, for patients with severe renal impairment - a maximum dose of 250 mg/day (E.U.) or 300 mg/day (U.S.) is recommended.
5) **Use in Status Epilepticus:** Current evidence for lacosamide use in acute seizure treatment is restricted to retrospective studies. The most often used bolus dose was 200–400 mg over 3–5 min with overall success rate of 59%.
6) **Side effects:** Common adverse reactions include - Dizziness, headache, nausea, and diplopia which may be dose related and could be alleviated by reducing the dose. Serious Reactions may include asymptomatic, dose-related increase in the PR Interval, thus should be used

with caution in patients with known conduction problems or severe cardiac disease and in elderly patients.

7) **Teratogenicity:** Lacosamide is a Category C drug during pregnancy i.e. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Lacosamide produced developmental toxicity (increased embryo fetal and perinatal mortality, growth deficit) in rats following administration during pregnancy following administration during a period of postnatal development corresponding to the third trimester of human pregnancy. These effects were observed at doses associated with clinically relevant plasma exposures. Lacosamide has been shown in vitro to interfere with the activity of collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal differentiation and control of axonal outgrowth. Animal studies have shown excretion of lacosamide in breast milk, although it is unknown whether lacosamide is excreted in human breast milk. Lacosamide has no effect on the pharmacokinetics or pharmacodynamics of the oral contraceptive.
8) **Levetiracetam[18]:** Levetiracetam is very broad spectrum antiepileptic drug which is approved for partial onset seizures, Secondarily generalized seizures, Primary generalized seizures, Myoclonic epilepsies, both as an add on therapy and Monotherapy – in all older than 4 years of age.

9) **Mechanism of action:** The exact mechanism of action of levetiracetam is still not known. In vitro, it did not inhibit single seizures induced by maximal stimulation with electrical current or different chemoconvulsants and showed only minimal activity in submaximal stimulation and in threshold tests. Protection was observed, however, against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemoconvulsants that induce seizures that mimic some features of human complex partial seizures with secondary generalization. It also displayed inhibitory properties in the kindling model in rats, another model of human complex partial seizures, both during kindling development and in the fully kindled state. It has not demonstrated binding affinity for a variety of known receptors such as GABA , Glycine, NMDA, neuronal voltage-gated sodium or T-type calcium currents. It does however, show a strong affinity for binding to the SV2A protein. This protein is involved in vesicle fusion and exocytosis at the nerve terminal, thus potentially modifying neurotransmitter release.
10) **Pharmacokinetics:** Levetiracetam is rapidly and almost completely absorbed after oral administration. Both the tablets and oral solution are bioequivalent and the extent of bioavailability of levetiracetam is not affected by food. The pharmacokinetics are linear and levetiracetam is not significantly protein- bound. Levetiracetam and its major metabolite, at concentrations well above Cmax levels achieved within the therapeutic dose range. It is not an inhibitors of, nor a high affinity substrate for Human liver cytochrome P450 isoforms
11) **Side effects:** Somnolence, occasional headaches and mild vertigo can be seen. The most significant side effect of levetiracetam in clinical practice however is behavioural disturbances such as aggression, emotional lability, oppositional behavior, and psychosis along with increased risk of suicidal thoughts or behaviour. It is one of the safer antiepileptics in pregnancy (even though it is categorised as category C).
12) **Seletracetam[19]:** Phase II clinical trials of seletracetam were started but in July 2007 the company stated that the drug's development had been put on hold.[3] Although the conducted Phase II trials showed success, it was less than expected given the performance of seletracetam in animal models. Thus there were no known Phase IIb or Phase III trials.[3] As of 2010, development of seletracetam was halted in favor of the development of brivaracetam, a newer variation of the drug.[1]
13) **Brivaracetam[20]:** Brivarectam was approved for use by European Commission on 14 January 2016 & by the US Food and Drug Administration on 18 February 2016. (Approved under the trade name Briviact). Brivaracetam is used to treat partial-onset seizures with or without secondary generalisation, in combination with other antiepileptic drugs. No data are available for its effectiveness and safety in patients younger than 16 years.
14) **Mechanism of action:** Brivaracetam , a chemical analog of levetiracetam, is a racetam derivative. It is believed to act by binding to the ubiquitous synaptic vesicle glycoprotein 2A (SV2A), like levetiracetam but with 20-fold greater affinity. It also has additional Na channel blocking properties, potentially causing a higher therapeutic efficacy.

a) **Pharmacokinetics:** Brivaracetam exhibits linear pharmacokinetics over a wide dose range. It is rapidly and completely absorbed after oral administration and has an elimination half-life of 7 to 8 hours. It has a plasma protein binding of less than 20% and is extensively metabolized (>90%), primarily via hydrolysis of the acetamide group, and secondarily through hydroxylation mediated by the liver enzyme CYP2C19. The three major metabolites (hydroxy, acid, and hydroxyacid) are pharmacologically inactive. These are eered in the urine within 72 hours, including only 8.6% as unchanged brivaracetam.
b) **Dosing and preparations:** It is available in the following strengths in the Indian market - Tablets: 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg. Oral solution: 10 mg/mL, Injection: 50 mg/5 mL single-dose vial. The recommended starting dosage for monotherapy or adjunctive therapy is 50 mg twice daily. This may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day). Dose modification in hepatic impairment may be necessary - for all stages of hepatic impairment, the recommended starting dosage is 25 mg twice daily; maximum dosage is 75 mg twice daily.
c) **Side effects:** The most common adverse effects include sleepiness, dizziness, nausea and vomiting. More rarely, coordination problems and changes in behaviour can occur. However as compared to levetiracetam a study

comparing the drugs observed that 93.1% who switched to brivaracetam had clinically useful reduction in behavioural adverse events over 12 weeks.

d) **Interactions:** Coadministration of brivaracetam with carbamazepine may increase exposure to carbamazepine-epoxide, the active metabolite of carbamazepine, and could theoretically lead to reduced tolerability. Coadministration of brivaracetam with phenytoin may increase phenytoin levels. Coadministration of other antiseizure drugs are unlikely to affect brivaracetam exposure. Co-administration with Rifampin (CYP2C19 induction) will require an increase in the dosage in patients by up to 100% (i.e., double the dosage)

15) **Perampanel[21]:** Perampanel is approved for add on therapy for partial onset as well as primarily generalised tonic clonic seizures, in patients older than 12 years of age.

a) **Mechanism of Action:** Perampanel is a noncompetitive antagonist at the AMPA type of glutamate receptor. It has a broad spectrum of action with effect on Tonic–clonic generalized seizures (In audiogenic and maximal electric shock–induced seizure tests), Absence or myoclonic seizures (Pentylenetetrazole-induced seizure tests) and it also inhibits 6 Hz electroshock-induced seizures in vitro.

b) **Pharmacokinetics:** It is rapidly absorbed orally, however food delays absorbtion but there is no effect of food on extent of absorbtion. Bioavailability is 100% but the protien binding is high at around 95%. Pharmacokinetics of perampanel are linear and predictable. It is extensively metabolized (>90%) in the liver, primarily by cytochrome P450 (CYP) 3A4 to pharmacologically inactive metabolites. In healthy volunteers, the apparent terminal half-life is ~105 h whereas the calculated effective half-life is 48 h. With enzyme inducers like CBZ, oxcarbazepine and phenytoin the half-life reduced to around 25 hours. Since it may induce CYP enzymes itself so it may decrease the effectiveness of hormonal contraceptives containing levonorgestrel at high doses (~12mg/day).

c) **Dosing:** in the absence of enzyme-inducing AEDs, usual starting dose is 2 mg once daily orally at bedtime, increasing the dose based on clinical response and tolerability in increments of 2 mg once daily no more frequently than at weekly intervals. Recommended maintenance dose is around 8 mg per day for Partial-Onset Seizures and Primary Generalized Tonic-Clonic Seizures. In the presence of enzyme-inducing AEDs, starting dosage is 4 mg once daily with similar increments of 2 mg at weekly intervals. The highest dose studied in patients on concomitant enzyme-inducing AEDs was 12 mg once daily. Individual dosing should be adjusted based on clinical response and tolerability. When enzyme-inducing AEDs are introduced or withdrawn patient should be closely monitored for clinical response & tolerability. Dose adjustment in patients with Hepatic Impairment: Maximum recommended daily dose is 6mg for mild impairment, 4 mg for moderate impairment and in Severe Hepatic Impairment it is not recommended. Similarly in patients with Severe Renal Impairment or on Hemodialysis, permapanel is not recommended.

d) **Pregnancy and lactation:** It has been labelled as Category C. No adequate or well controlled studies are available in pregnant women. Abnormalities were seen in animals at clinically relevant doses. During Lactation - Excreted in rat milk, but excretion in human breast milk is unknown.

e) **Side effects:** The most common side effects include - dizziness, somnolence, fatigue, irritability, anxiety, vertigo, ataxia, headache, nausea, vomiting, weight gain and abdominal pain. Most side effects are dose related and seen within first 6 weeks of treatment. There are reports that perampanel treated patients experienced more hostility- and aggression-related adverse reactions that were serious, severe, and led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. Also noted have been other behavioural side effects such as Homicidal ideation and threats. These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression and hence careful observation of such symptoms is required.

16) **Eslicarbazepine Acetate[22]:** This was FDA approved in November 2013 as an adjunctive treatment for partial onset seizures. It inhibits voltage dependent sodium channels thereby reducing seizures in the brain. It is considered to be less toxic than oxcarbazepine and carbamazepine since it lacks the toxic epoxide. It also has minimal interaction with the liver cytochrome P450 enzyme system nd does not undergo autoinduction. It can be given at doses of 400-1200 mg/day and has a once daily dosing. Common side effects include headache, dizziness and nausea. Hyponatremia is less commonly seen as compared to its parent molecule.

To conclude, epilepsy is a highly prevalent chronic illness which often requires prolonged and sometimes life-long drug therapy. Compliance with medication is a major problem because of the need for long-term therapy together with unwanted effects of many drugs. The conventional anti-epileptic drugs, even though efficacious are known to have frequent and at times intolerable adverse effects. In recent years, a number of newer AEDs with more desirable safety profiles have been introduced on the market to offer better seizure control for patients with epilepsy, however due to the lack of head-to-head comparisons between these newer drugs, it is still uncertain whether the claimed efficacy and safety of these latest AEDs can exceed those have already been wildly prescribed. Also, even though the newer AEDs have a relatively good efficacy, safety profile, fewer drug interactions and are safer in pregnant women, they are much more expensive than their traditional counterparts, and in a country like India are still not easily available in the peripheries. The search for the perfect AED continues, but in the meantime these new additions to our armamentarium have been helpful to a large number of patients in defeating epilepsy.

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