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Newer antiepileptic drugs- Are they a boon

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Abstract

Epilepsy is a common but heterogenous disorder having many forms and many causes. It can be very complex and difficult to control, often requiring long and lifelong treatment. About 65% of patients with newly diagnosed epilepsy achieve sustained freedom from seizures with the initially prescribed antiepileptic drug (AED). An additional 15-20% becomes seizure free with subsequently prescribed AEDs, while the remainder cannot achieve seizure control with available medications. There is an unmet need for efficacious research in this field for an ideal AED.

Rational combinations of the new AEDs with older AED's have begun to emerge based upon side effects and tolerability (moving from monotherapy to polytherapy in selected patients). However, we need to establish the efficacy and safety of these combinations. We do not have adequate data on the possible teratogenic effects of new AED's.

Keywords: AED, Lacosamide, SV2A.

Introduction

After the introduction of sodium valproate in 1967, there was hiatus of two decades after which ten new AEDs were launched during the so called "decade of Brains". These expanded the armamentarium of therapeutics for intractable epilepsy. These newer AEDs are used as an adjunct to conventional AEDs in patients with intractable epilepsy.

However, caution must be exercised for possible drug interactions with conventional AEDs before using them as an adjunct. Moreover, many of these AEDs have been recently launched in Indian market and cost of some of them is largely prohibitive.

These medications should be prescribed by physicians with an in-depth knowledge of the pharmacokinetics of the drug, its indications, dosage, side effects and possible drug interactions. The present review intends to provide an insight to these aspects of use of antiepileptic drugs. We discuss the use of newer antiepileptic drugs, which are already in the market like lamotrigine, vigabatrin, Lacosamide, eslicarbazepine.

The Newer Anti-Epileptic Drugs

Vigabatrin

Vigabatrin is a structural analogue of gamma-aminobutyric acid (GABA), which irreversibly inhibits the enzyme GABA transaminase. It is used as a first line drug for treatment of infantile spasms in children with tuberous sclerosis. The major concern with the use of vigabatrin is the development of bilateral concentric peripheral casual field constriction, which has been in one third of adults and 20% of children treated with vigabatrin. Myoclonic seizures and absence seizures are known to be precipitated by vigabatrin.

Levetiracetam

Levetiracetam is a broad-spectrum AED which selectively inhibits high-voltage-activated calcium channels and reduces calcium release from intraneuronal stores. It also binds to a specific target in the brain, the synaptic vesicle protein 2A (SV2A), an integral membrane glycoprotein, which is involved in the control of vesicle fusion and exocytosis. Levetiracetam is effective as adjunctive therapy in patients with partial onset seizures and in primary generalized tonic-clonic seizures. Intravenous preparation has recently shown efficacy in neonatal seizures and status epilepticus. Levetiracetam has a favorable pharama cokinetic profile in terms of safety in patients with liver disease and minimal drug interaction with other AEDs. The "first dose effect" is classically seen with this. Levetiracetam is well tolerated with minor adverse events like headache, anorexia, and somnolence. However, there are concerns of behavioral side effects like aggression, emotional liability, oppositional behavior and psychosis.

Topiramate

Topiramate is a sulphamate substituted monosaccharide, a broad-spectrum AED acting on voltage dependent sodium channels, enhancement of GABA, decrease in glutamate and inhibition of carbonic anhydrase. Topiramate is a useful adjunct in refractory partial or generalized epilepsy and other epileptic syndromes. It has demonstrated efficacy as an adjective therapy in partial epilepsy, intractable epilepsy, Lennox Gastaut syndrome, infantile spasms, generalized epilepsy of infancy and myoclonic-astatic epilepsy. It is also useful in prophylaxis of bipolar disorders and migraine. Topiramate has good safety with no evidence of life-threatening adverse effects or organ toxicity. The most frequently reported side effects are dizziness, mental slowing, somnolence, ataxia, impaired concentration and confusion. Other reported side effects include metabolic acidosis, nephrolithiasis, decreases sweating and resultant hyperthermia.

Lamotrigine

Lamotrigine is another broad-spectrum AED which acts by blocking the voltage dependent sodium channels and thus blocks the release of glutamate through stabilization of presynaptic membrane. It is an effective adjunct to refractory partial and generalized epilepsy. It is particularly useful in typical and atypical absence seizure in Lennox Gastaut syndrome and in children with myoclonic-astatic epilepsy. It is also useful as a first line agent in children with idiopathic generalized epilepsy. It is indeed a preferred Antiepileptic as add on in pregnancy. Common dose related side effects include somnolence, sleep disturbances, dizziness, diplopia, ataxia, nausea and vomiting. Serious side effects of lamotrigine which often require drug with drawls include skin rash and rarely Steven Johnson syndrome and toxic epidermal necrolysis. The neurotoxicity and skin rash is more often seen when lamotrigine is administered with valproate or when the dose is titrated rapidly. The drug dosage is reduced to half when used in combination with

valproate as the latter prolongs the half-life of lamotrigine.

Oxcarbazepine

Oxcarbazepine is the 10-keto analogue of carbamazepine which blocks high frequency voltage dependent repetitive firing of sodium channels. Oxcarbazepine is used as first line drug for partial and secondarily generalized seizures. Amongst the newer AED, oxcarbazepine is established as evidence-based effective initial monotherapy for children with partial-onset seizures and focal epilepsy. Unlike carbamazepine, oxcarbazepine is not metabolized to epoxide derivative thus minimizing side effects like skin rash encountered with carbamazepine. Reported side effects of oxcarbazepine include hyponatremia, headache, dizziness, and ataxia. The advantage of oxcarbazepine over carbamazepine is that it does not cause hepatic induction nor does it undergo auto-induction.

Zonisamide

Zonisamide is a sulphonamide derivative, a broad-spectrum AED that acts through multiple actions: facilitation of dopaminergic and serotoninergic neurotransmission through the blockade of T-type calcium channels, prolongation of sodium channel inactivation and as a weak inhibitor of carbonic anhydrase. Zonisamide has also been found useful in progressive myoclonic epilepsy syndromes such as Unverricht- Lundborg disease and Lafora body disease. Somnolence, poor appetite, weight loss, headache, pruritus, and skin rash are commonly observed adverse effects. Other rare side effects include kidney stones, oligohydrosis and hyperthermia.

Lacosamide

Lacosamide is a functionalized amino acid that selectively enhances slow inactivation of voltage-gated sodium channels, increasing the proportion of sodium channels unavailable for depolarization. Lacosamide is used in patients with refractory epilepsy with 30-50% of children having more than 50% reduction in seizure frequency. Lacosamide is available in both oral and as an injection for intravenous preparation, which may have a role in status epilepticus. It is also useful in patients having comorbid medical illness involving hepatic and renal dysfunction Ing. Lacosamide is generally well tolerated with reports of irritability, oral tics, and prolonged crying as adverse effects in children.

Perampanel

Perampanel is a selective, non-competitive antagonist of alpha–amino-3-hydroxy 5-methy 1-4-isoxazolepropionic acid (AMPA) type glutamate receptors, currently in clinical development as adjunctive therapy for the treatment of refractory partial-onset seizures. Efficacy and tolerability of adjunctive perampanel in patients aged > 12 years with refractory partial-onset seizures has been demonstrated in three phase III, randomized, double-blind, placebo-controlled trials.

Current Status of the Newer AEDs

The dosages and adverse effects of the newer AED currently available in India are summarized in Table. Amongst the newer AED, oxcarbazepine is established as effective as initial monotherapy for children with partial-onset seizures. Vigabatrin is the drug of choice for infantile spasms associated with Tuberous selerosis. Lamotrigine may be considered as monotherapy in adolescent females with idiopathic generalized epilepsy. Levetiracetam is a good option as monotherapy for females with juvenile myoclonic epilepsy. It is also preferred agent in all Antiepileptic drug induced skin allergies. Topiramate and Zonisamide are good options in patients with infantile spasms who have failed hormonal therapy and vigabatrin. Lamotrigine, levetiracetam and Lacosamide are good add-on drugs for patients with

refractory partial seizures. Lamotrigine is also effective in tonic seizures seen in children with Lennox-Gas taut syndrome.

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Legend Tables

Table 1: Characteristics of the New Antiepileptic Drugs

Drug	Initial dose (mg/kg/day)	Maintenance (mg/kg/day)	MOA	Side Effects
Lamotrigine	0.2-0.5	2-10	Inhibition of voltage gated sodium channel	Allergic skin rash, somnolence, dizziness, nausea, diplopia
Vigabatrin	20-50	50-150	Inhibition of GABA transaminase	Hyperkinesia, weight gain, insomnia, visual field defects
Oxcarbazepine	5-8	10-30	Inhibition of voltage sensitive sodium channel	Dizziness, ataxia, somnolence, hyponatremia
Topiramate	1	6-9	Blockage of voltage dependent Na+ channel, inhibition of GABA	Wt. loss, lethargy, anorexia, hyper pyrezia, renal calculi
Zonisamide	1-2	8-12	Acts on sodium and voltage dependent Ca channel	Ataxia, renal calculi, hyperpyrexia, wt. loss
Levetiracetam	10	20-60	Inhibition of N-type calcium channel	Headache, anorexia, somnolence, behavioral problems
Lacosamide	1-2	6-9	Enhances slow inactivation of voltage gated sodium channel	Dizziness, headache, diplopia, nausea, prolonged PR interval