

Newer Anti-epileptic Drugs

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Need and Purpose of review: A number of newer anti-epileptic drugs have been developed in the last few years to improve the treatment outcomes in epilepsy. In this review, we discuss the use of newer anti-epileptic drugs in children.

Methods used for locating, selecting, extracting and synthesizing data: MEDLINE search (1966-2013) was performed using terms "newer anti-epileptic drugs", "Oxcarbazepine", vigabatrin, topiramate, "zonisamide", "levetiracetam", "lacosamide", "rufinamide", "stiripentol", "retigabine", "eslicarbazepine", "brivaracetam", "ganaxolone" and "perampanel" for reports on use in children. Review articles, practice parameters, guidelines, systematic reviews, meta-analyses, randomized controlled trials, cohort studies, and case series were included. The main data extracted included indications, efficacy and adverse effects in children.

Main conclusions: Oxcarbazepine is established as effective initial monotherapy for children with partial-onset seizures. Vigabatrin is the drug of choice for infantile spasms associated with tuberous sclerosis. Lamotrigine, levetiracetam and lacosamide are good add-on drugs for patients with partial seizures. 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. Topiramate is a good add-on drug in patients with epileptic encephalopathies such as Lennox-Gastaut syndrome and myoclonic astatic epilepsy.

Keywords: *Refractory epilepsy; Epileptic encephalopathies; Oxcarbazepine; Vigabatrin; Lamotrigine; Levetiracetam.*

About 65% of children with newly diagnosed epilepsy achieve sustained freedom from seizures with the initially prescribed antiepileptic drug (AED). An additional 15-20% become seizure free with subsequently prescribed AEDs, while the remainder cannot achieve seizure control with available medications. There is an unmet need for efficacious AED with good safety profile in this group, and there is a continued research in this field for an ideal AED. 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 children with intractable epilepsy. However, more studies are required to evaluate their use as first line AED for children with epilepsy. These newer drugs are more efficacious and have a better safety as compared to conventional AED. However, caution must be exercised for possible drug interactions with conventional AEDs before using them as an adjunct. Moreover, many of these newer AEDs have been recently launched in Indian market and cost of some them are largely prohibitive.

Intractable epilepsy refractory to appropriate conventional AED is an indication for the newer drugs. Among children presenting with refractory epilepsy, one must always look for causes of pseudointractability including possibility of non epileptic event, misdiagnosis of seizure type, and wrong choice of conventional AEDs. These causes must always be thought before using newer AEDs as an adjunct.

These medications should be prescribed by pediatricians 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 pediatric use of newer anti-epileptic drugs, both the ones which are already in the market (lamotrigine, topiramate, levetiracetam, oxcarbazepine, zonisamide, vigabatrin, lacosamide, eslicarbazepine), and the newer ones in development and which are likely to be available soon (rufinamide, stiripentol, retigabine, brivaracetam, ganaxolone, and perampanel). The use of gabapentin and pregabalin will not be discussed in this review as these are used predominantly for the management of neuropathic pain, and not epilepsy.

THE NEWER ANTI-EPILEPTIC DRUGS

Vigabatrin

Vigabatrin is a structural analogue of gamma-aminobutyric acid (GABA), which irreversibly inhibits the enzyme GABA transaminase.

Indications: It is used as a first line drug for treatment of infantile spasms in children with tuberous sclerosis [1]. As there is insufficient evidence for the use of other AEDs in infantile spasms [2], it may be considered as a first line treatment in other patients with infantile spasms in whom the use of hormonal treatment (corticosteroids, ACTH) is contraindicated.

Efficacy: Clinical trials have shown that spasm cessation is greatest in patients with tuberous sclerosis complex (74%) compared with other symptomatic etiologies (50%) [3]. In a large randomized controlled trial, it was shown that hormonal treatment (ACTH and prednisolone) was associated with better outcome at 2 weeks (73%) when compared to vigabatrin (54%) [4].

Advantages: It has good oral bioavailability and the drug is excreted unchanged by kidney. Drug interactions are minimal with conventional AEDs.

Side effects: The major concern with the use of vigabatrin is the development of bilateral concentric peripheral visual field constriction, which has been seen in one third of adults and 20% of children treated with vigabatrin [5]. Because of the difficulties and inconsistencies with formal visual field testing in young infants and children, visual fields in children have been tested using highly sensitive electroretinograms. The earliest finding of the first abnormal field examination in adults was after 9 months of treatment; in children, the earliest sustained onset of the vigabatrin induced retinal defect in infants was 3.1 months [6]. Most patients with abnormalities received treatment for at least 6 months, and even those treated for more than 2 years have been reported to have stable visual fields [7]. As infantile spasms comprise a severe epileptic encephalopathy with poor developmental outcome if uncontrolled, the risks and benefits should be weighed before starting vigabatrin treatment. Myoclonic seizures and absence seizures are known to be precipitated by vigabatrin.

Dosage: Pediatric doses range from 50 mg/kg/day to 150 mg/kg/day [8]. The dose may be increased by 30-40 mg/kg/day every 4-5 days till the maximum dose is reached. The time to response with vigabatrin is quite short, usually within 2 weeks. If the infant has not shown improvement in spasms within 2 weeks, vigabatrin should be discontinued [9]. In infants with good response

consider stopping the drug after 6 months.

Levetiracetam

Levetiracetam is a broad spectrum AED which selectively inhibits high-voltage-activated calcium channels and reduces calcium release from intraneuronal stores [10]. 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.

Indications: Levetiracetam is effective as adjunctive therapy in pediatric patients with partial onset seizures and in primary generalized tonic-clonic seizures [11]. Intravenous preparation has recently shown efficacy in neonatal seizures [12] and status epilepticus [13].

Efficacy: In a randomized, double-blind, placebo-controlled, multicenter trial in 101 children with refractory partial seizures, >50% seizure reductions was seen in 44.6% receiving levetiracetam and 19.6% in patients receiving placebo [14]. Levetiracetam has been evaluated in childhood epilepsy syndromes including rolandic epilepsy [15], electrical status epilepticus in slow sleep, myoclonic and tonic clonic seizures of Lennox Gastaut syndrome [16] and as an alternative to valproate in juvenile myoclonic epilepsy in adolescent girls [17]. Beneficial effects on language development have been reported [18].

Advantages: Levetiracetam has a favourable pharmacokinetic profile in terms of safety in patients with liver disease and minimal drug interaction with other AEDs.

Side effect: Levetiracetam is well tolerated in children with minor adverse events like headache, anorexia, and somnolence. However, there are concerns of behavioural side effects like aggression, emotional lability, oppositional behavior, and psychosis in children [19].

Dosage: Pediatric dose start from 10 mg/kg/day (divided twice daily) to be hiked by 10-20 mg/kg every two weeks to a maximum dose of 40-60 mg/kg/day.

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.

Indications: Topiramate is a useful adjunct in refractory partial or generalized epilepsy and other epileptic syndromes.

Efficacy: Topiramate has demonstrated efficacy as an

adjunctive therapy in partial epilepsy [20], intractable epilepsy [21], Lennox Gastaut syndrome [22], infantile spasms [23], generalized epilepsy of infancy and myoclonic-astatic epilepsy [24]. Pooled data from two randomized, double-blind studies found that topiramate adjunctive therapy may be efficacious for juvenile myoclonic seizures in adults and children [25].

Side effects: 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 [24]. Most of these are transient and observed during the initial weeks of therapy and can be reduced by slow titration of the dose. Anorexia and mild weight loss has been observed during the therapy. Other reported side effects include metabolic acidosis, nephrolithiasis, decreased sweating and resultant hyperthermia [26]. Children on combination of topiramate and valproate should be monitored for signs of encephalopathy resulting from hyperammonemia [27].

Dosage: Pediatric dosage is 1-3 mg/kg/day (divided twice daily) hiked bi-weekly to 3-8 mg/kg/day.

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. Enzyme inducing drugs like phenytoin and carbamazepine may shorten the half life of Lamotrigine.

Indications and efficacy: It is an effective adjunct to refractory partial and generalized epilepsy [28]. It is particularly useful in typical and atypical absence seizure in Lennox Gastaut syndrome and in children with myoclonic-astatic epilepsy [22, 29]. It is also useful as a first line agent in children with idiopathic generalized epilepsy.

Side effects: Common dose related side effects include somnolence, sleep disturbances, dizziness, diplopia, ataxia, nausea and vomiting. Serious side effects of lamotrigine which often require drug withdrawals include skin rash and rarely Steven Johnson syndrome and toxic epidermal necrolysis [30]. The neurotoxicity and skin rash is more often seen when lamotrigine is administered with valproate or when the dose is titrated rapidly. Lamotrigine may exacerbate myoclonic seizures in patients with Dravet syndrome [31].

Dosage: Lamotrigine is started at 1-2 mg/kg followed by slow hiking biweekly to 3-8 mg/kg/day. 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.

Indications and efficacy: Oxcarbazepine is used as first line drug for partial and secondarily generalized seizures [32]. Amongst the newer AED, oxcarbazepine is established as evidence-based effective initial monotherapy for children with partial-onset seizures and focal epilepsy.

Side effects: 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 [33]. The advantage of oxcarbazepine over carbamazepine is that it does not cause hepatic induction nor does it undergo auto-induction [33].

Dosage: Oxcarbazepine can be started with initial dose of 5 to 8 mg/kg/day in 2 divided doses increasing by 5 to 8 mg/kg after 5 to 7 days up to a maximum of 30 mg/kg. The usual effective dose ranges from 10 to 30 mg/kg/day.

Zonisamide

Zonisamide is a sulphonamide derivative, a broad spectrum AED that acts through multiple actions: facilitation of dopaminergic and serotonergic neurotransmission through the blockade of T-type calcium channels, prolongation of sodium channel inactivation and as a weak inhibitor of carbonic anhydrase.

Indications: Zonisamide has also been found useful in progressive myoclonic epilepsy syndromes such as Unverricht-Lundborg disease and Lafora body disease [36]. Useful as a second-line agent for infantile spasms, Lennox-Gastaut syndrome, and juvenile myoclonic epilepsy [35].

Side effects: Somnolence, poor appetite, weight loss, headache, pruritus, and skin rash are commonly observed adverse effects [37]. Other rare side effects include kidney stones, oligohydrosis and hyperthermia [38]. Higher doses (6-8 mg/kg) has been associated with problems of language development like vocabulary acquisition [39].

Dosage: The usual starting dose is 2-4 mg/kg/day, and the maintenance dose is 4-8 mg/kg/day;divided once or twice daily.

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.

Indication: Lacosamide is used in children with refractory epilepsy with 30-50% of children having more than 50% reduction in seizure frequency [40].

Efficacy: Lacosamide is available in both oral and as an injection for intravenous preparation, which may have a role in status epilepticus. Pediatric experience with lacosamide has been limited [40]. Most of the available literature are retrospective data on small number of patients with an efficacy rate of 30-50% [41-43].

Side effect: Lacosamide is generally well tolerated with reports of irritability, oral tics, and prolonged crying as adverse effects in children [40].

Rufinamide

Rufinamide is a triazole derivative that was approved by FDA in 2008 for adjunctive use in the treatment of seizures associated with Lennox-Gastaut syndrome in children aged above 4 years [44]. Its mechanism of action is not completely understood but it is believed to work by prolonging the inactive state of sodium channels and therefore limiting excessive firing of sodium-dependent action potentials.

Indication: The only approved indication in children (>4 yrs) is with refractory Lennox Gastaut syndrome].

Efficacy: In Lennox-Gastaut syndrome, rufinamide was studied in a randomized, double-blind, parallel-group, placebo-controlled, multicenter trial in patients aged 4 to 37 years with multiple seizure types [45]. At the end of 12 weeks of therapy, median total seizure frequency was decreased by 32.7% in the rufinamide group compared to 11.7% in the placebo group. Rufinamide has demonstrated efficacy in partial onset seizures in older adolescents and adults [46]. Rufinamide has also been evaluated in a prospective study for the treatment of refractory partial onset seizure and childhood onset refractory epileptic encephalopathy [47, 48].

Side effect: The most commonly observed adverse are headache, dizziness, fatigue, somnolence, and nausea.

Stiripentol

Stiripentol is an AED used as an adjunctive 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 [49]. It

enhances central gamma-aminobutyric acid transmission and inhibits the metabolism of concurrently administered anticonvulsants that are substrates for various cytochrome P450 isoenzymes, such as clobazam [50]. In a randomized, double-blind, placebo controlled trial conducted in France, stiripentol was used as an adjunctive therapy in children with Dravet syndrome who failed to respond to valproate and clobazam and was shown to have better response rate (71%) as compared to placebo (5%) [51].

Other Newer AEDs

Retigabine (ezogabine) is a novel investigational AED developed as an adjunctive treatment for partial epilepsy. Retigabine opens voltage-gated KCNQ2/3 and KCNQ3/5 potassium channels leading to cellular membrane hyperpolarization (52). In a pooled analysis of three randomized controlled trials, 1240 patients were included, with 813 patients randomized to retigabine and 427 to placebo (53). Responder rates (>50% reduction in seizure frequency) were 35% and 45% for retigabine dose at 600 and 900 mg/day, respectively. There is no pediatric experience so far, but retigabine may potentially be a useful agent in the treatment of benign familial neonatal convulsions which is caused by loss of function mutations involving the KCNQ2/3 genes [54].

Brivaracetam is an analogue of levetiracetam, which has been found useful in adults with photosensitive epilepsy, and as an adjunctive treatment in refractory partial-onset epilepsy. There is no pediatric experience till now.

Ganaxolone is a synthetic analogue of allopregnenolone, a neurosteroid, which is an allosteric modulator of the GABA-A receptor complex. In a 3-month pediatric add-on study, 20 subjects aged 6 months to 7 years with refractory infantile spasms, or with continuing seizures after a prior history of infantile spasms were titrated up to 12 mg/kg. Sixteen patients completed the study; 25% showed a > 50% reduction in seizures, and one patient was seizure free (55). Ganaxolone may also have efficacy for catamenial seizures.

Eslicarbazepine acetate is structurally related to carbamazepine and oxcarbazepine and has been used as adjunctive therapy for adults with partial seizures. There is no pediatric experience so far.

Perampanel is a selective, non-competitive antagonist of α -amino-3-hydroxy 5-methyl-4-isoxazolepropionic acid (AMPA) -type glutamate receptors, currently in clinical development as adjunctive therapy for the treatment of refractory partial-onset seizures [56]. 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 I**. 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 sclerosis. Lamotrigine may be considered as monotherapy in adolescent females with idiopathic generalized epilepsy. Certain newer AEDs such as lamotrigine and vigabatrin are known to worsen myoclonic seizures. There is paucity of data on the use of newer AEDs in children from India. Indian Guidelines for diagnosis and management of childhood epilepsy were recently published [57]. As per these guidelines, the only newer AED which are recommended for use as monotherapy in new-onset epilepsy are lamotrigine in partial and generalized seizures, and oxcarbazepine in partial seizures. The others are recommended as adjunctive treatment in children who have failed conventional AED.

Levetiracetam is a good option as monotherapy for females with juvenile myoclonic epilepsy. Topiramate and

zonisamide are good options in patients with infantile spasms who have failed hormonal therapy and vigabatrin. Topiramate is a good add-on drug in patients with epileptic encephalopathies such as Lennox-Gastaut syndrome and Myoclonic astatic epilepsy. 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-Gastaut syndrome.

Rare but serious side effects must always be borne in mind while prescribing newer AEDs: irreversible peripheral field defect with vigabatrin, allergic rash/Steven Johnson syndrome with lamotrigine, arrhythmias with rufinamide (short QT interval) and lacosamide (prolonged PR interval) and fatal hyperammonemic encephalopathy with topiramate. Role of monitoring serum levels of newer AEDs are limited as the recommended levels are not well defined.

CONCLUSION

Most of these newer AED have been tested as add-on therapy in drug resistant epilepsy and are not superior to the first generation AEDs in efficacy. The main advantage of some of the newer agents was their better tolerability and pharmacokinetic profiles compared to

TABLE I CHARACTERISTICS OF THE NEW ANTI-EPILEPTIC DRUGS

<i>Drug</i>	<i>Initial dose (mg/kg/day)</i>	<i>Maintenance (mg/kg/day)</i>	<i>Daily doses no</i>	<i>Side effects</i>	<i>Formulation</i>
Lamotrigine					
Monotherapy	0.5	2-10	2	Skin rash, somnolence, dizziness, nausea, diplopia	Tab 5 mg; 25 mg, 50 mg
With enzyme inducing AEDs	2	5-15	2		
With valproate	0.2	1-5	1-2		
Vigabatrin	20-50	50-150	2	Hyperkinesia, weight gain, insomnia, visual field defects	Tab 500 mg
Oxcarbazepine	5-8	10-30	2	Dizziness, ataxia, somnolence hyponatremia	Tab 150 mg, 300 mg, Syrup 300 mg/5 mL
Topiramate	1	6-9	2	Wt. loss, lethargy, anorexia, hyperpyrexia, renal calculi	Tab 25 mg, 50 mg, 100 mg
Zonisamide	1-2	8-12	2	Ataxia, renal calculi hyperpyrexia	Cap 25mg, 50 mg, 100 mg
Levetiracetam	10	20-60	2	Headache, anorexia, somnolence, behavioral problems	Tab 250 mg, 500 mg, Syrup 500 mg/5 mL
Lacosamide	1-2	6-9	2	Dizziness, headache, diplopia, nausea	Tab 50 mg, 100 mg

TABLE II PHARMACOKINETIC PROPERTIES OF NEWER ANTIEPILEPTIC DRUGS

<i>Drug</i>	<i>Oral bioavailability</i>	<i>Elimination t1/2</i>	<i>Protein binding</i>	<i>Metabolism</i>
Vigabatrin	80-100%	5-8 hrs	Nil	Renal
Levetiracetam	100%	6-8 hrs	<10%	2/3 rd renal 1/3 rd enzymatic hydrolysis
Topiramate	>80%	21 hours	15-40%	30% metabolised 70% excreted unchanged
Lamotrigine	<100%	29 hours	55%	Metabolized in liver
Oxcarbazepine	>95%	8-10 hours	38%	Metabolized in liver to active metabolite
Zonisamide	100%	60 hours	40-60%	Metabolized in liver
Lacosamide	100%	13 hours	<15%	Metabolized in liver
Rufinamide	Dose dependent	6-10 hours	34%	Metabolized in liver
Stiripentol	Quick absorption	4.5 hours	99%	Metabolized in liver

TABLE III MECHANISM OF ACTION, INDICATIONS AND MAIN ADVERSE EFFECTS OF NEWER ANTIEPILEPTIC DRUGS

<i>Drug</i>	<i>Principal mechanism of action</i>	<i>Indications in pediatric epilepsy</i>	<i>Main adverse effect</i>	<i>Remarks</i>
Vigabatrin	Inhibition of GABA transaminase	Monotherapy in infantile spasm (tuberous sclerosis); adjunctive therapy in resistant partial epilepsy	Visual field defects	It can aggravate absence and Myoclonic seizure
Levetiracetam	Inhibition of N- type calcium channel	Adjunctive therapy in partial onset seizure; Myoclonic seizure of JME; GTCS in IGE	Behavioural disturbances	No drug interaction; good safety profile; safe in liver disease
Topiramate	Blockage of voltage dependent Na ⁺ channel, inhibition of GABA	Adjunctive therapy (>2 yrs) in refractory partial, generalized and seizures associated with LGS	Behavioural and cognitive problem; weight loss; metabolic acidosis; nephrolithiasis	Slow titration mandatory; never withdraw drug abruptly
Lamotrigine	Inhibition of voltage gated sodium channel	Adjunctive treatment for focal or generalized seizures and seizures of LGS	Allergic rash/Steven Johnson syndrome	Slow titration; half dose when used with valproate; can precipitate Myoclonic seizures
Oxcarbazepine	Inhibition of voltage sensitive sodium channel	Monotherapy or adjunctive therapy (>4 yr) for focal seizure with or without secondary generalization	CNS side effects, hyponatremia	Can worsen absence and Myoclonic seizure,
Zonisamide	Acts on sodium and voltage dependent calcium channel	Adjunctive therapy in refractory focal seizures	CNS side effects, cognitive effect, weight loss	Drug interactions with other AEDs
Lacosamide	Enhances slow inactivation of voltage gated sodium channel	Adjunctive therapy in refractory focal and generalized epilepsy	Frequent CNS effects, prolongation of PR interval	Limited experience in children; more studies required
Rufinamide	Reduces recovery capacity of sodium channel inactivation	Adjunctive treatment in refractory seizures in LGS	Occasional CNS side effects	Avoid in patients with familial short QT syndrome
Stiripentol level	Increase in GABA refractory seizures in	Adjunctive therapy for dravet syndrome	Few minor CNS effects of drug interaction	Limited experience;

(GABA- Gamma amino butyric acid, CNS-Central nervous system, IGE- idiopathic generalized epilepsy, JME- juvenile myoclonic epilepsy, GTCS- generalized tonic clonic seizure, LGS- Lennox Gastaut syndrome).

the earlier AED. Other than Oxcarbazepine for partial epilepsy, there is no evidence for the use of the newer AED as monotherapy in new-onset epilepsy in children. Some of the newer AEDs have proven efficacy for some childhood epileptic syndrome *e.g.* vigabatrin for infantile spasms, levetiracetam for juvenile myoclonic epilepsy, rufinamide for Lennox-Gastaut syndrome and stiripentol for Dravet syndrome. The current choice of available AEDs also allows for options for children with concomitant systemic illnesses and co-morbidities based on the pharmacokinetic profiles of these drugs.

However, the cost of these drugs increases the cost of therapy and limits their use in low and middle income countries.

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