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Current and Emerging Therapies of Severe Epileptic Encephalopathies

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In this article, we review the treatment options for the pediatric epileptic encephalopathies and provide an update on the new and emerging therapies targeted at the underlying pathophysiology of many of these syndromes. We illustrate how the identification of the specific genetic and autoimmune causes has made possible the evaluation and development of novel, better targeted therapies, as and at times, avoidance of potentially offending agents.
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Introduction

Recent advances in genetics have markedly affected our understanding of multiple epilepsy syndromes and are expanding our therapeutic options. Epileptic encephalopathies (EEs) comprise a group of clinical entities each with a specific disease course and with electroencephalographic (EEG) abnormalities that cause progressive disturbances of cerebral functions.[1] Failure to appropriately recognize an EEs in question results in ongoing cognitive and behavioral impairments. EEs are often resistant to conventional antiepileptic drugs (AEDs), hence the interest in new and emerging therapies. Studies have shown that early initiation of therapy often correlates with better outcomes. For example, the United Kingdom Infantile Spasms Study demonstrated that delayed treatment of infantile spasms correlated with poor outcomes.[2] Also, in children with tuberous sclerosis, time of cessation of spasms correlates with the degree of subsequent intellectual disability.[3] Given the importance of therapy of EEs, we in the following sections review the current and emerging treatments of pediatric EE (Table 1).[4-6]

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Early Infantile EEs: EIEE or Ohtahara Syndrome, and Early Myoclonic Encephalopathy

Traditional treatment of early infantile EE (EIEE) usually consists of trials of AEDs, most commonly vigabatrin (VGB), which has some chance of success, as well as phenytoin, topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), phenobarbital, or combinations of these AEDs.[4] In some cases, the use of the steroids or the ketogenic diet has been helpful. There have been reports of the use of functional hemispherectomy or even focal resection surgeries in cases of unilateral hemispheric dysplasias presenting with EIEE with good seizure control and good neurodevelopmental outcomes in some.[7]

The emerging data that multiple channelopathies (such as *SCN2A* and $KCNQ_2$ mutations) may cause this and other forms of epileptic encephalopathy have raised interest in the search for specific targets of therapy.[8] This now is being translated into clinical applications (Fig.). In addition, it may prove to be helpful, in some conditions, to treat secondary biochemical changes. It has been reported that in *SCN2A*–mutation-associated EE, there can exist secondary neurotransmitter deficiency, and that treatment with 5-hydroxytryptophan, L-dopa-carbidopa, and dopa agonists to correct for such a deficiency may help with seizure control.[9] Therapy for early myoclonic encephalopathy focuses on treating the underlying metabolic etiology if one is identified and on the use of therapies similar to those used in ohtahara syndrome, although vigabatrin may not be as useful.

West Syndrome

West syndrome comprises the triad of infantile spasms, psychomotor regression, and the characteristic EEG pattern

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Table 1 AED Options Based on Epileptic Encephalopathy Type

Epileptic Encephalopathy (EE)	First-Line AEDs	Adjunctive AEDs/ Therapies	AEDs That May Worsen EE
Early infantile epileptic encephalopathy	Corticosteroids Levetiracetam	Ketogenic diet Zonisamide Vigabatrin Phenobarbital	
West syndrome	ACTH Vigabatrin (in case of Tuberous sclerosis)	Vigabatrin Prednisolone Topiramate Ketogenic diet	Carbamazepine Oxcarbazepine
Lennox Gastaut syndrome	Sodium valproate	Lamotrigine Clobazam Levetiracetam Corticosteroids Felbamate Rufinamide Topiramate Ketogenic diet Vagal nerve stimulation	Carbamazepine Gabapentin Oxcarbazepine Pregabalin Tiagabine Vigabatrin
Epilepsy with continuous spike wave during sleep/ Landau Kleffner syndrome	Corticosteroids Clobazam	Sodium valproate Ethosuximide Sulthiame Valproate Clobazam Sulthiame Multiple subpial transection Ketogenic diet	Carbamazepine Phenobarbital Phenytoin
Dravet syndrome	Sodium Valproate Topiramate	Clobazam Stiripentol Ketogenic diet	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenytoin Pregabalin Tiagabine Vigabatrin
Malignant migrating partial seizures of infancy	Levetiracetam Clonazepam	Stiripentol Ketogenic diet Corticosteroids Bromides	

Adapted with permission from Vigevano et al. Epilepsia, 54:45-50, 2013 (suppl 8) and NICE guidelines 2012 with modifications.

of hypsarrhythmia. The goals of treatment include complete cessation of the seizures and disappearance of the hypsarrhythmia. The first-line treatment in West syndrome is adrenocorticotropic hormone (ACTH).[10-12] The recommended dose of ACTH has ranged from low to high doses.[10] The Food and Drug Administration recommended regimen of ACTH is a daily dose of 150 units/m^2 divided into a twice daily dose for 2 weeks followed by 30 units/m^2 for 3 days, then 15 units/m^2 for 3 days, then 10 units/m^2 for 3 days, then 10 units/m^2 every other day for 6 days, and then the medication is stopped.

Alternative options include longer courses of ACTH, other ACTH regimen, or oral steroids such as a dose of prednisolone (15 mg/5 mL) orally 40 mg/day as 13.3 mg tid (4.44 mL tid) for 2 weeks, then 15 mg bid (5 mL bid) × 5 days, then 10 mg bid (3.33 mL bid) × 5 days, then 5 mg bid (1.67 mL bid) × 5 days, then 5 mg/d (1.67 mL in AM) × 5 days, then 5 mg (1.67 mL in AM) qod × 5 days, and then stop the medication. If no response after 1 week on 40 mg, then increase to 20 mg tid (6.67 mL tid) for 2 weeks, then reduce to 40 mg daily as 13.3 mg tid (4.44 mL tid) for 2 weeks, then 15 mg bid (5 mL bid) × 5 days then 10 mg bid (3.33 mL bid) × 5 days, then 5 mg bid (1.67 mL bid) × 5 days, then 5 mg/day (1.67 mL in AM) × 5 days, then 5 mg (1.67 mL in AM) qod × 5 days, and then the medication is stopped.[11,13]