New and emerging pharmacologic treatments for developmental and epileptic encephalopathies

Alejandra Vasquez, Ersida Buraniqi, and Elaine C. Wirrell

Purpose of review
Summarize evidence on Developmental and Epileptic Encephalopathies (DEEs) treatments focusing on new and emerging pharmacologic therapies (see Video, http://links.lww.com/CONR/A61, Supplementary Digital Content 1, which provides an overview of the review).

Recent findings
Advances in the fields of molecular genetics and neurobiology have led to the recognition of underlying pathophysiologic mechanisms involved in an increasing number of DEEs that could be targeted with precision therapies or repurposed drugs, some of which are currently being evaluated in clinical trials. Prompt, optimal therapy is critical, and promising therapies approved or in clinical trials for tuberous sclerosis complex, Dravet and Lennox–Gastaut Syndromes including mammalian target of rapamycin inhibitors, selective membrane channel and antisense oligonucleotide modulation, and repurposed drugs such as fenfluramine, stiripentol and cannabidiol, among others, may improve seizure burden and neurological outcomes. There is an urgent need for collaborative efforts to evaluate the efficacy and safety of emerging DEEs therapies.

Summary
Development of new therapies promise to address unmet needs for patients with DEEs, including improvement of neurocognitive function and quality of life.

Keywords
developmental delay, encephalopathy, genetics, pediatric, refractory epilepsy

INTRODUCTION

Developmental and epileptic encephalopathies (DEEs) are a group of heterogeneous disorders characterized by drug-resistant epilepsy and electrographic abnormalities that impede brain development and lead to severe cognitive, behavioral, and/or motor impairments. There is both *developmental encephalopathy*, caused directly by the underlying etiology, and *epileptic encephalopathy* where epileptic activity itself causes or further exacerbates the neurocognitive dysfunction or decline [1,2]. DEEs may be classified by syndrome (age of onset, seizure type, distinctive Electroencephalogram (EEG) patterns) or etiology (see Supplementary Tables 1, http://links.lww.com/CONR/A62 and 2, http://links.lww.com/CONR/A63, which provide an overview of DEEs).

Furthermore, DEEs are frequently associated with other medical (e.g., gastrointestinal disturbances, recurrent pneumonias) and comorbid neuropsychiatric conditions including autism spectrum disorder [3,4], and movement or behavioral disorders [5,6] that markedly impact the quality of life, morbidity and mortality.

The overall prognosis of DEEs is poor with increased mortality [7,8]; however, prompt recognition and treatment may lead to improved neurocognitive function [9]. Treatment of DEE-associated seizures generally entails a broad spectrum of medications, surgery, or dietary therapy. In recent years, research has focused on understanding the underlying pathophysiologic mechanisms to develop precision (targeted to pathogenesis) therapies with the goal to prevent or ameliorate neurocognitive

Division of Child and Adolescent Neurology, Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to Elaine C. Wirrell, Professor, Divisions of Child and Adolescent Neurology and Epilepsy, Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA. Tel: +507 266 0774; fax: +507 284 0727; e-mail: Wirrell.Elaine@mayo.edu

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KEY POINTS

- Early recognition and intervention in developmental and epileptic encephalopathies are crucial as it can impact neurological outcomes and may improve quality of life.
- In the era of precision therapies, identification of underlying etiology will likely be most impactful on choosing optimal treatment for DEEs patients.
- Multinational collaborative efforts are critical to evaluate the safety and efficacy of evolving precision and nontargeted therapies.

deficits. In this review, we summarize evidence on DEE treatments focusing on new and emerging pharmacologic therapies.

GOALS OF TREATMENT

The main goals of treatment are to improve seizure control and alleviate or prevent associated comorbidities to maximize quality of life. In many DEEs, complete seizure freedom is not feasible. Rather, reduction or alleviation of the most problematic seizure type(s) (while accepting some degree of less severe seizures) and avoidance of marked medication side effects are the priority.

With some DEEs, such as Lennox–Gastaut syndrome (LGS), there is a window between initial presentation and full expression, raising the possibility that early intervention may ameliorate the course in some cases [10]. However, improved seizure control does not necessarily lead to recovery of cognitive development. When considering addition of therapies, those that have had little impact on seizure control should be tapered. In appropriate candidates with DEE, epilepsy surgery is an important option as it may improve overall development and quality of life [11,12]. Finally, a multidisciplinary approach for comorbidity management and a network of support for families and caregivers is essential.

TREATMENTS

Precision therapies

Advances in the field of molecular genetics have been crucial in improving our understanding of the genetic basis of DEEs. In recent years, next-generation sequencing has led to the discovery of numerous genes implicated in the development of these disorders, providing essential information to guide treatment approaches and deliver accurate genetic counseling to patients and families. Although the genetic landscape in DEEs is extensive, identifying the genetic etiology has served as foundation for ongoing development of precision therapies as well as disease-specific treatments (Table 1, Supplementary Table 3, http://links.lww.com/CONR/A64) for certain DEEs [13–29,30▪,31–36▪,37–46,47▪,48–54].

Drugs targeting underlying pathogenic mechanism

Everolimus and *Sirolimus* are mammalian target of rapamycin (mTOR) inhibitors which have been evaluated for tuberous sclerosis complex (TSC) and other mTORopathies [14,55]. mTOR is comprised of two intracellular signaling complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2) [56], which are particularly important in the nervous system as they regulate neurogenesis, neural activity, and synaptic transmission. Upstream regulation of this pathway involves the complex hamartin-tuberin, encoded by *TSC1* and *TSC2* genes, respectively, which inhibits the GTP-binding protein Rheb and subsequently mTORC1, leading to decreased cell growth and metabolism [57].

Everolimus emerged as a promising therapeutic option in TSC. Although initially approved for management of subependymal giant cell astrocytoma and renal angiomyolipoma [55,58], in 2018 the US Food and Drug Administration (FDA) approved its use as adjunctive treatment in patients over 2 years of age with TSC-associated focal-onset seizures, based on the phase 3 EXIST-3 clinical trial. TSC patients with focal refractory epilepsy ($N = 366$) were randomized to three arms (low or high trough concentrations of Everolimus or placebo), with Everolimus demonstrating significant seizure reduction compared to placebo (placebo 14.9% {95% CI 0.1–21.7} vs. low trough arm 29.3% {95% CI: 18.8, 41.9; $P = 0.003$}, and high trough arm 39.6% {95% CI: 35, 48.7; $P = 0.001$) [13].

Channel subtype-specific modulators (i.e., sodium and potassium) play a key role in initiation and propagation of action potentials in neurons. In disorders such as *SCN8A*-DEE and *KCNQ2*-DEE, modulation of these channels can reduce seizures (e.g. phenytoin or other sodium channel blockers in gain of function *SCN2A*, *SCN8A* and *SCN1A* [59,60]) and very selective modulators are being developed which may have greater benefit and fewer side effects than nonselective therapies [52]. Novel channel subtype-specific modulators are detailed in Table 1.

Memantine is a N-methyl-D-aspartate receptor (NMDAR) antagonist recently used in *GRIN2A*-associated DEEs [23,61]. *GRIN2A* encodes for a subunit of the NMDAR, and variants have been identified in

Table 1. Established and emerging therapies for developmental and epileptic encephalopathies

Drug name	Indications	Mechanism of action	Clinical considerations	Ongoing clinical trial[a]	Level of evidence	References
Precision Therapies						
Everolimus	TSC	mTOR inhibitor, leading to decreased cell growth and metabolism	*Recommended dosing* 5 mg/m2/day with subsequent titration (in increments up to 5 mg) to achieve trough levels of 5–15 ng/mL *Side effects* Stomatitis, diarrhea, vomiting, nasopharyngitis, upper respiratory tract infection, cough, and rash.	No	Class I	[13–15]
Sirolimus	TSC	mTOR inhibitor, leading to decreased cell growth and metabolism	*Side effects* Upper respiratory tract infection, gastrointestinal disturbances, aphthous ulcers, fever, fatigue	No	Class III	[16]
NBI-921352 (XEN 901)	*SCN8A* mutations	Selective Nav1.6 voltage-gated sodium channel blocker, inhibiting sodium currents of excitatory neurons	*Side effects*[b] Dizziness, headache, nausea	Phase 2 randomized, double-blind, placebo-controlled clinical trial. Not yet recruiting (NCT04873869)	NA	[17]
XEN496	*KCNQ2* mutations	Active metabolite of Ezogabine (EZO), Kv7.2/7.3 voltage-gated potassium channel activator, decreases neuronal excitation	*Side effects*[b] Dizziness, oral hypoesthesia, fatigue, depressed mood	Phase 3 randomized, double-blind, placebo-controlled, multicenter study. Recruiting (NCT04639310)	NA	[18,19]
XEN1101	*KCNQ2* mutations	Selective potassium channel (KV7.2/7.3) positive allosteric modulator, decreases neuronal excitability	*Side effects*[b] Dizziness, somnolence, fatigue	Phase 2 randomized, double-blind, placebo-controlled study. Recruiting (NCT03796962)	NA	[20,21]
Memantine	*GRIN2A* mutations	N-methyl-D-aspartate receptor (NMDAR) antagonist, decreasing glutamate neurotransmission	*Side effects (derived from Alzheimer Disease studies in adult)* Dizziness, headache, constipation, vomiting, hypertension	No	Class IV	[22,23]
Anakinra	FIRES, unlicensed use	Human interleukin-1 receptor antagonist that inhibits IL-1α and IL-1β, reduces neuroinflammation	*Side effects* Injection site reaction, vomiting, headache, arthralgia, nasopharyngitis, fever, rarely thrombocytopenia or neutropenia.	No	Class IV	[24–26]
Ketogenic Diet	GLUT-1 deficiency syndrome, Pyruvate dehydrogenase complex deficiency, DS, MAE, SRSE FIRES	High-fat, low-carbohydrate diet. Ketosis mediated decreased glycolysis, anti-inflammatory action, stabilization of neuronal membrane.	*Side effects* Hypoglycemia, hyperlipidemia, weight loss, acute pancreatitis, metabolic acidosis	No	Class IV	[27–29,30▪]
Nontargeted Therapies						
Fenfluramine	DS, LGS, Sunflower Syndrome *CDKL5*-DEE	Serotonergic 5-HT_2 receptor agonist Modulatory activity at σ_1 receptors in vitro and in vivo	*Recommended dosing* 0.2–0.7 mg/kg/day max 26 mg/day If used with concurrent stiripentol 0.4mg/kg/day (max 17 mg/day) *Side effects* Decreased appetite, fatigue, diarrhea, pyrexia	Pilot Open Label for LGS. Active, not recruiting (NCT02823145)	Class I for DS and LGS (unpublished) Class IV for SFS and *CDKL5*-DEE	[31,32,3,34,35,36▪,37–39]

Table 1 (*Continued*)

Drug name	Indications	Mechanism of action	Clinical considerations	Ongoing clinical trial[a]	Level of evidence	References
Stiripentol	DS, SRSE	GABAergic effects, high activity at α3- and δ-subunits; neuroprotective properties. Inhibits LDH leading to neuronal hyperpolarization	*Recommended dosing* 20–50 mg/kg/day; younger children require higher mg/kg doses *Side effects* Drowsiness, anorexia, nausea, reversible neutropenia	No	Class I for DS Class IV for SRSE	[40–43]
CBD	DS, LGS, TSC *CDKL5*-DEE, MAE Aicardi Dup15q syndromes, FIRES	Mechanism not fully understood; negative allosteric modulator of the cannabinoid CB1 receptor	*Recommended dosing* 10–20 mg/kg/day *Side effects* Diarrhea, fatigue, vomiting, somnolence, pyrexia, elevated liver transaminases	Crossover clinical trial for ESES. Recruiting (NCT04721691)	Class I for DS, LGS and TSC Class IV for others	[44–46,47■, 48–50]
Ganaxolone	*CDKL5*-DEE, *PCDH19* TSC, NCSE, CSE	Allosteric modulator of GABA-A receptors	*Side effects* Somnolence, dizziness, fatigue	Expanded access for CDKL5-DD. Available (NCT04678479) RCT for *PCDH19*. Active, not recruiting (NCT03865732) Open label for TSC. Active, not recruiting (NCT04285346) RCT for *CDKL5*-DEE. Active, not recruiting (NCT03572933) RCT for NCSE and CSE. Recruiting (NCT04391569)	Class I for *CDKL5* (unpublished) Class IV for others	[51,52]
Lorcaserin	DS	Selective serotonin receptor (5-HT_{2C}) agonist	*Side effects* Decreased appetite	RCT with open label extension for DS. Recruiting (NCT04572243, NCT04457687)	Class IV for DS	[42]
Soticlestat	DS, LGS CDKL5-DD Dup15q syndromes	First-in-class inhibitor of the enzyme cholesterol 24-hydroxylase	*Side effects* Headache, nausea	Multicenter, Open-label pilot study for *CDKL5*-DEE, Dup15q syndromes. Completed (NCT03694275) (abstract) Phase 2, multicenter, randomized, double-blind, placebo-controlled study in LGS, DS. Completed (NCT03650452)	Class I for DS	[53]
SPN-817	DS	Acetylcholinesterase enzyme inhibitor through Huperzine A	NA	No	NA	[54]
Clemizole (EPX-100)	DS	Histamine receptor antagonist, antiseizure properties through the serotonin pathway	NA	Global, multicenter, randomized, double-blind, placebo-controlled trial. Recruiting (NCT04462770)	NA	[b]

CDKL5-DEE, *CDKL5*-Deficiency Disorder; CSE, convulsive status epilepticus; DS, Dravet Syndrome; FIRES, Febrile Illness-Related Epilepsy Syndrome; GLUT-1, Glucose transporter 1; LGS, Lennox–Gastaut Syndrome; MAE, Myoclonic Atonic Epilepsy; NCSE, nonconvulsive status epilepticus; SRSE, Super-refractory status epilepticus; TSC, tuberous sclerosis complex.
[a]References for ongoing clinical trials for precision and nontargeted therapies are available in Supplementary Table 3, http://links.lww.com/CONR/A64.
[b]Side effects identified in adult studies.

patients with D/EE-SWAS [62]. Future studies are needed to determine its efficacy, safety, and pharmacokinetics in these disorders.

Antisense oligonucleotide modulation

Antisense oligonucleotide (ASO) modulation is a promising therapy that targets altered splicing in the precursor messenger RNA (mRNA), ultimately promoting the generation of productive mRNA [63]. Dravet animal studies identified an ASO that increased expression of productive *SCN1A* transcript in both human cell lines and mouse brains using Targeted Augmentation of Nuclear Gene Output technology, leading to increased production of NaV1.1 protein, with reduction of electrographical seizures and sudden unexpected death in epilepsy [64▪]. With promising preclinical data, *STK-001* emerged as a new investigational ASO for DS, which is currently being evaluated in a multicenter, open-label clinical trial [65].

Genetic therapies

The *SCN1A* gene is too large to incorporate into a viral vector. In Dravet mice, introduction of an adenovirus vector containing a promoter of *SCN1A* led to increased expression of sodium NaV1.1 channels with reduction in frequency and severity of spontaneous seizures, and prolonged survival [66]. *ETX101* is a promising gene therapy for Dravet Syndrome (DS) that will likely begin clinical trials shortly. Unlike ASO therapies, which will need to be administered periodically to maintain efficacy, gene therapy is more 'permanent', requiring only a single administration.

Another precision genetic therapy is *Ataluren*, which reads through premature nonsense stop signals on the mRNA to promote full length, functional proteins. However, this therapy, if efficacious, would be appropriate only for the subset of cases of Dravet syndrome with pathogenic nonsense *SCN1A* variants, as it acts on translation and does not modify transcription or mRNA stability. Unfortunately, a small phase 2 clinical trial in 7 patients with DS with underlying nonsense mutations showed that Ataluren was not effective in reducing seizure frequency, improving cognitive, motor or behavioral function and did not improve quality of life [67].

Immune therapies

Anakinra is recombinant human interleukin-1 receptor antagonist (IL-1RA) targeting IL-1α and IL-1β [68]. In addition to promoting inflammation, IL-1β is a cytokine with ictogenic properties, and its overexpression in neuroglial cells has been documented in animal models with refractory epilepsy [69]. Febrile Infection-Related Epilepsy Syndrome (FIRES) has been associated with decreased expression of intracellular IL-1RA isoforms as well as functional deficiency in the IL-1RA inhibitory activity [70▪]. Several reports suggested potential efficacy in FIRES [24,25]. A recent multicenter retrospective cohort study of 25 children identified a subset whose seizure frequency was measured immediately before and one week after administration of Anakinra and demonstrated reduction of >50% in 11/15 patients. Earlier initiation of Anakinra was also associated with improved short-term outcomes (e.g., decreased duration of mechanical ventilation and length of hospital stay) [26].

Metabolic therapies

Metabolic disorders are uncommon but important causes that require prompt recognition and intervention, if treatment is available. Table 2 shows therapeutic approaches for specific metabolic disorders in pediatric patients [71–83].

Not targeted to pathogenesis

Fenfluramine

Use in DS

Fenfluramine was initially used in photosensitive, self-induced epilepsy [34] but, in 1997 was pulled from the market after reports of cardiac valvulopathy and pulmonary hypertension in persons using it for management of obesity at doses up to 220 mg/d, in combination with phentermine [84]. Nonetheless, a royal decree in Belgium granted approval for compassionate use in DS, and this small cohort demonstrated significant reductions in seizure frequency, without evidence of cardiopulmonary disease at low doses [31,35]. Efficacy was established in two multicenter, randomized, double-blind, placebo-controlled clinical trials. The first evaluated add-on fenfluramine to existing therapies without stiripentol for the treatment of convulsive seizures in DS. Fenfluramine 0.7 mg/kg/day showed a 62.3% greater reduction in mean monthly convulsive seizure frequency (95% CI 47.7–72.8, $P < 0.0001$), and 0.2 mg/kg/day showed a 32.4% reduction in mean monthly convulsive seizure frequency (95% CI 6.2–52.3, $P = 0.0209$) compared with placebo [33▪]. The second evaluated add-on fenfluramine (0.4 mg/kg/day) to regimens containing stiripentol, and demonstrated a 54.0% (95% CI, 35.6–67.2%; $P < 0.001$) greater reduction in mean monthly convulsive

Table 2. Metabolic therapies for selected developmental and epileptic encephalopathies

Drug name	Indications	Mechanism of action	Clinical considerations	Ongoing clinical trial[a]	Level of evidence	References
Cerliponase alfa	Neuronal ceroid lipofuscinosis type 2 (CLN2) disease	Enzyme replacement therapy, active substance is a recombinant human tripeptidyl peptidase-1 (rhTPP1), a lysosomal exopeptidase	*Side effects* Pyrexia, ECG abnormalities, vomiting, seizures, hypersensitivity reactions, headache, hypotension, intraventricular access device-related complications	Multicenter, observational study in the US. Recruiting (NCT04476862)	Class I	[71,72]
Uridine	CAD deficiency	Recycling of pyrimidines, overcoming deficiency of the pyrimidine synthesis pathway	NA	No	Class IV	[73,74]
Pyridoxine	Pyridoxine-Dependent (PDE) (ALDH7A1)-DEE and Pyridox(am)ine 5′-Phosphate Deficiency (PNPO)	Substrate replacement	*Recommended dosing:* In an acutely seizing infant, an initial single 100 mg/dose IV and monitored in the intensive care unit. Oral pyridoxine 15–30 mg/kg/day, divided in two to three doses	No	Class IV	[75–77]
Biotin	Biotinidase deficiency	Substrate replacement	*Recommended dosing:* 5–10 mg oral biotin per day	No	Class IV	[78,79]
Creatine Monohydrate	Cerebral creatine deficiency syndromes (i.e., AGAT, GAMT)	Substrate replacement	*Recommended dosing:* 400–800 mg/kg BW/day in three to six divided doses	No	Class IV	[80,81]
Cyclic pyranopterin monophosphate (cPMP)	Molybdenum cofactor deficiency type A	Substrate replacement	*Side effects:* Fever, respiratory infections, vomiting, gastroenteritis and diarrhea	Phase 2/3, Multicenter, Multinational, Open Label Study. Recruiting (NCT02629393) Phase 2, Multicenter, Multinational, Open-Label, Dose-Escalation Study. Active, not recruiting (NCT02047461)	Class I	[82,83]

AGAT, L-arginine:glycine amidinotransferase; CSE, convulsive status epilepticus; DS, Dravet Syndrome; GAMT, Guanidinoacetate methyltransferase.
[a]References for ongoing clinical trials for metabolic therapies are available in Supplementary Table 3, http://links.lww.com/CONR/A64.

seizure frequency than those receiving placebo [36▪]. Fenfluramine was well tolerated with no observed valvular heart disease or pulmonary arterial hypertension [85▪]. In June 2020, Fenfluramine was approved by the US FDA for treatment of seizures in DS patients aged 2 years and older.

Use in other epilepsy syndromes

Knupp et. al conducted a similarly designed, randomized, placebo-controlled trial of add-on fenfluramine (0.7 mg/kg/day) vs. placebo in LGS that met its primary end-point, with fenfluramine 0.7 mg/kg/day demonstrating with a 19.9% greater reduction in drop seizures compared to placebo. It was also highly effective in reducing generalized tonic-clonic seizures by 46% and 58% in the 0.7 mg/kg/day and 0.2 mg/kg/day fenfluramine groups respectively, compared to worsening of 3.7% in the placebo group [37]. Small open-label studies have also suggested efficacy in CDKL5 [39] and Sunflower syndrome [38].

Stiripentol

Stiripentol (STP) is approved as adjunctive therapy for DS in Europe, Canada, Japan and was approved in the US in 2018. Following a large study evaluating efficacy of stiripentol in a diverse group of epilepsies, which documented particular efficacy in DS [40], a small, double-blind, randomized, placebo-controlled trial of add-on STP (50 mg/kg/day) vs. placebo was performed in children with DS who had inadequate seizure control on valproate and clobazam. After two months of treatment, 71% in the STP arm compared to 5% on the placebo arm were responders [41]. A second small study of similar design in Italy showed a response rate of 66.7% on STP vs. 9.1% on placebo [42]. An important consideration with STP is that when used together with clobazam, STP increases clobazam level approximately two-fold and norclobazam levels by three to five-fold, thus clobazam dose should be reduced if STP is added [86].

Cannabidiol

The therapeutic value of cannabidiol (CBD)-containing products for epilepsy became the focus of research in recent years and led to development of a pharma-grade CBD preparation named Epidiolex/Epidyolex (>98% CBD).

Use in DS

In 2018, the FDA, and in 2019, the European Medicine Agency approved the use of CBD for treatment of seizures in DS, based on a double-blind, randomized controlled trial. 120 children and young adults with DS aged two and older with drug-resistant seizures were randomly assigned to receive add-on CBD (20 mg/kg/d) or placebo over a 14-week treatment period. The median percentage reduction in convulsive seizure frequency was 38.9% with CBD vs. 13.3% with placebo ($P < 0.01$) [44]. In a subsequent open-label extension study, the median reduction from baseline in monthly seizure frequency assessed in 12-week periods up to week 48 ranged from 38–44% for convulsive seizures and 39–51% for total seizures [45].

Use in Lennox–Gastaut syndrome

In the two LGS double-blind placebo-controlled trials, patients ($n = 171$ and 225) were administered add-on CBD at 20 mg/kg/day [48] or 10 or 20 mg/kg/day [87] over a 14-week treatment period. For CBD at 20 mg/kg/day, the median percentage reduction in total seizure frequency was 38.4–41% (vs. 13.7–18.5% for placebo), and monthly median decrease in drop seizures was reported to be 42–44% (vs. 17–22% for placebo). At 10 mg/kg/day, the median percentage reduction in total seizure frequency was similar at 36.4% (vs. 18.5% for placebo), and monthly median decrease in drop seizures was 37% (vs. 17% placebo).

An important consideration with CBD is its potential interaction with other antiseizure medications. CBD increases both clobazam (by 60±80%) and norclobazam (by 500±300%), and thus, reduction of clobazam dose may be needed when adding CBD [88]. Similarly, concomitant use with valproic acid can lead to elevated liver enzymes and therefore should be monitored closely [89].

IMPROVING TREATMENT FOR CHILDREN WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIEs: THE WAY FORWARD

Making a precise diagnosis in a timely manner

The most critical aspect in choosing the optimal treatment is accurately defining seizure type(s), syndrome (if present) and etiology. In an infant or child presenting with clinical features suggesting an evolving DEE, a careful clinical history and physical examination, as well as interictal (+/- ictal) EEG recordings, state-of-the-art imaging, genetic studies (epilepsy gene panel or whole exome/genome sequencing) and selected metabolic investigations should be performed early, which may be facilitated by early consultation with a comprehensive epilepsy center.

Children with DEEs most commonly present with multiple seizure types. Medications should be chosen to target the most impactful seizure type, but ideally would also alleviate other seizure types. In many DEEs, both generalized and focal-onset seizures occur, and caution must be taken to avoid therapies that may help one seizure type, but markedly worsen another.

Although many trials have focused on specific syndromes [33▪,41,87,90–92], as we move into the era of precision therapies, identification of underlying etiology will likely be most impactful on choosing optimal treatment. The hope is that specific treatments can be designed which target the specific pathogenic mechanisms leading to both seizures, as well as the developmental encephalopathy.

Choosing therapy that specifically targets the underlying pathogenic mechanism or etiology

In DEEs due to a surgically resectable, focal lesion, early surgery can be critically important not only to alleviate seizures, but also to prevent progressive encephalopathy and maximize long-term developmental outcome [93,94].

The causal role of specific pathogenic genetic variants is well recognized. However, more work is needed to understand the functional implications of such variants to select treatment [95,96▪]. For example, sodium channel blockers are contraindicated in DS, which is due to severe loss of function *SCN1A* variants [86]. Yet, other early onset epileptic encephalopathies due to gain of function sodium channel variants may respond very favorably [96▪].

Metabolic disorders may be amenable to specific therapies (Table 2) and prompt initiation of targeted therapies is crucial to prevent irreversible neurological decline.

Developing novel animal models of etiology-specific epilepsies to allow rapid testing of new compounds

Over the last decade, new animal models have been developed which are powerful tools for epilepsy research. One of the most important models has been the zebrafish, a vertebrate with a fully sequenced genome and significant genetic homology with humans [97]. These animals can be genetically engineered to create specific models that recapitulate human genetic epilepsies [98]. Seizures can be monitored both behaviorally and electrophysiologically. Such models will facilitate rapid throughput drug screening in a much more economical manner than using mammalian models such as rodents.

Multicenter collaboration amongst clinicians and lay organizations

Although collectively the DEEs comprise a significant proportion of children with drug-resistant epilepsy, each individual DEE is rare – nearly all meet criteria for orphan conditions. Numerous rare epilepsy organizations have been founded by families of affected individuals, often in collaboration with physicians and have not only significantly enhanced our understanding of these rare DEEs but provided an invaluable resource to newly diagnosed families. These organizations provide critical feedback on where research should be focused [99], and access to larger cohorts of persons with these rare conditions, for possible clinical trials. Strong multicenter and international collaboration will be key to enhancing our understanding of how best to treat these conditions.

CONCLUSION

DEEs are a group of heterogeneous disorders associated with poor neurological outcomes significant comorbidities. A tailored approach is needed to modify clinical course and patients' outcomes. Multinational collaborative efforts are needed to evaluate the safety and efficacy of evolving precision and nontargeted therapies.

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Conflicts of interest

EW has participated as a Site Investigator on clinical trials of CBD, Fenfluramine and Ganoxolone, however received no personal reimbursement for these. DW serves on the Data Safety and Monitoring Committees for Neurocrine, Encoded, and Acadia. AV and EB report no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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