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CRITICAL REVIEW – INVITED COMMENTARY

The role of new medical treatments for the management of developmental and epileptic encephalopathies: Novel concepts and results

Cecilie Johannessen Landmark[1,2,3] | **Heidrun Potschka**[4] | **Stéphane Auvin**[5,6] | **Jo M. Wilmshurst**[7] | **Svein I. Johannessen**[2,3] | **Dorothée Kasteleijn-Nolst Trenité**[8] | **Elaine C. Wirrell**[9]

[1]Program for Pharmacy, Department of Life Sciences and Health, Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway

[2]National Center for Epilepsy, Oslo University Hospital, Oslo, Norway

[3]Section for Clinical Pharmacology, Department of Pharmacology, Oslo University Hospital, Oslo, Norway

[4]Institute of Pharmacology, Toxicology, and Pharmacy, Ludwig Maximilian University of Munich, Munich, Germany

[5]Pediatric Neurology Department, Robert Debré Hospital, Public Hospital Network of Paris, Paris, France

[6]Mixed Unit of Research NeuroDiderot U1141, University of Paris, Paris, France

[7]Paediatric Neurology Department, Red Cross War Memorial Children's Hospital, Neuroscience Institute, University of Cape Town, Cape Town, South Africa

[8]Department of Neurosurgery and Epilepsy, University Medical Center Utrecht, Utrecht, the Netherlands

[9]Divisions of Child and Adolescent Neurology and Epilepsy, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Cecilie Johannessen Landmark, Program for Pharmacy, Oslo Metropolitan University, National Center for Epilepsy and Department of Pharmacology, Oslo University Hospital, Oslo, Norway.
Email: cecilie.landmark@oslomet.no

Abstract

Developmental and epileptic encephalopathies (DEEs) are among the most challenging of all epilepsies to manage, given the exceedingly frequent and often severe seizure types, pharmacoresistance to conventional antiseizure medications, and numerous comorbidities. During the past decade, efforts have focused on development of new treatment options for DEEs, with several recently approved in the United States or Europe, including cannabidiol as an orphan drug in Dravet and Lennox–Gastaut syndromes and everolimus as a possible antiepileptogenic and precision drug for tuberous sclerosis complex, with its impact on the mammalian target of rapamycin pathway. Furthermore, fenfluramine, an old drug, was repurposed as a novel therapy in the treatment of Dravet syndrome. The evolution of new insights into pathophysiological processes of various DEEs provides possibilities to investigate novel and repurposed drugs and to place them into the context of their role in future management of these patients. The purpose of this review is to provide an overview of these new medical treatment options for the DEEs and to discuss the clinical implications of these results for improved treatment.

KEYWORDS

antiseizure medications, cannabidiol, Dravet syndrome, drug repurposing, everolimus, fenfluramine, Lennox–Gastaut syndrome, orphan drugs, tuberous sclerosis

1 | INTRODUCTION

The concept of *developmental and epileptic encephalopathy* (DEE) refers to conditions where there is both *developmental encephalopathy*, which is directly due to the underlying etiology of the epilepsy, and *epileptic encephalopathy*, which implies that the epileptic activity itself causes cognitive and behavioral impairment.[1,2] DEEs are rare epilepsies, which may present challenges for enrollment in clinical trials. The largest proportion of DEEs have their onset in infancy and early childhood and are often the result of single gene disorders or acquired or developmental structural causes. DEEs are typically associated with recurrent, severe seizures and electroencephalographic (EEG) abnormalities, often with prominent background slowing and frequent epileptiform activity. However, the burden of the DEEs extends far beyond seizures to include intellectual disability, behavioral challenges including autism spectrum disorder, gait disorders, movement disorders, and other medical issues such as feeding problems and recurrent pneumonia, and holistic care requires managing these nonseizure symptoms. Mortality rates are increased, due both to the underlying neurodevelopmental delay and to seizure-related causes (sudden unexpected death in epilepsy [SUDEP], status epilepticus),[3,4] with SUDEP rates of 9.3 per 1000 person-years in Dravet syndrome (DS).[5]

In young children with DEEs, it is often challenging to disentangle how much of the delay is due to the underlying cause of the epilepsy versus the frequent seizures. In addition, these epilepsies often have onset in early childhood, a critical time in brain development, when key neuronal connections and cognitive networks are forming. Prompt seizure control is key to promote progression of normal brain development.

In recent years, several new antiseizure medications (ASMs) have been introduced to the market, and almost 30 different drugs are available worldwide. ASMs have significant pharmacokinetic variability within and between persons, enhanced by the frequent use of polypharmacy in DEEs.[6–10] Although therapeutic drug monitoring can provide useful clinical guidance, neither laboratory testing nor defined therapeutic ranges are readily available for some of these newer agents.[11] Many drugs used in DEEs have particularly challenging pharmacological properties, with important pharmacokinetic interactions (i.e., stiripentol [STP], valproate [VPA], clobazam [CLB], everolimus, cannabidiol [CBD], and fenfluramine).[9] Such interactions not only are a drawback but may also result in pharmacodynamic synergistic effects and are possible to handle in clinical practice. Repurposing of drugs as well as new strategies targeting the gene abnormalities are emerging and will likely change the treatment paradigm for some DEEs.

Key Points

- Cannabidiol is a new ASM in Dravet and Lennox–Gastaut syndromes, and everolimus is a precision drug for tuberous sclerosis complex
- Fenfluramine has been repurposed as a novel therapy in Dravet syndrome
- Drugs used for specific genetic mutations are an example of applied pharmacogenetics
- New insights into the pathophysiology of DEEs facilitate the investigation of novel and repurposed drugs in future patient management

The purpose of this review is to evaluate data from recent studies to determine the role of new and repurposed ASMs for the management of DEEs in infancy and childhood.

1.1 | Search strategy and selection criteria

This review is based on published articles and searches in PubMed and Google Scholar, up to December 2020, with a focus on recent advances over the past decade. Peer-reviewed articles from internationally recognized journals written in English were included, and primary sources were preferred. The search terms included one or more of the terms antiseizure medications and antiepileptic drugs, and the individual ASMs CBD, everolimus, fenfluramine, quinidine, and STP. Other terms included preclinical and clinical studies, cytochrome P-450, developmental and epileptic encephalopathies, drug interactions, drug repurposing, efficacy, epilepsy, pharmacology, pharmacokinetics, mechanism of action, safety, and tolerance.

2 | NEW MEDICAL TREATMENTS IN DEEs

This main part of the review will cover precision drugs and ASMs, including both novel and repurposed compounds (Figure 1). Recently approved drugs as well as drugs in early and later stages of clinical development are covered. Drugs that have demonstrated recent advances in clinical studies are described in detail in the text, whereas other examples are mentioned in the tables only (Tables 1 and 2). Although patients with DEEs may also benefit from epilepsy surgery or neuromodulation, these therapies are beyond the scope of this article.

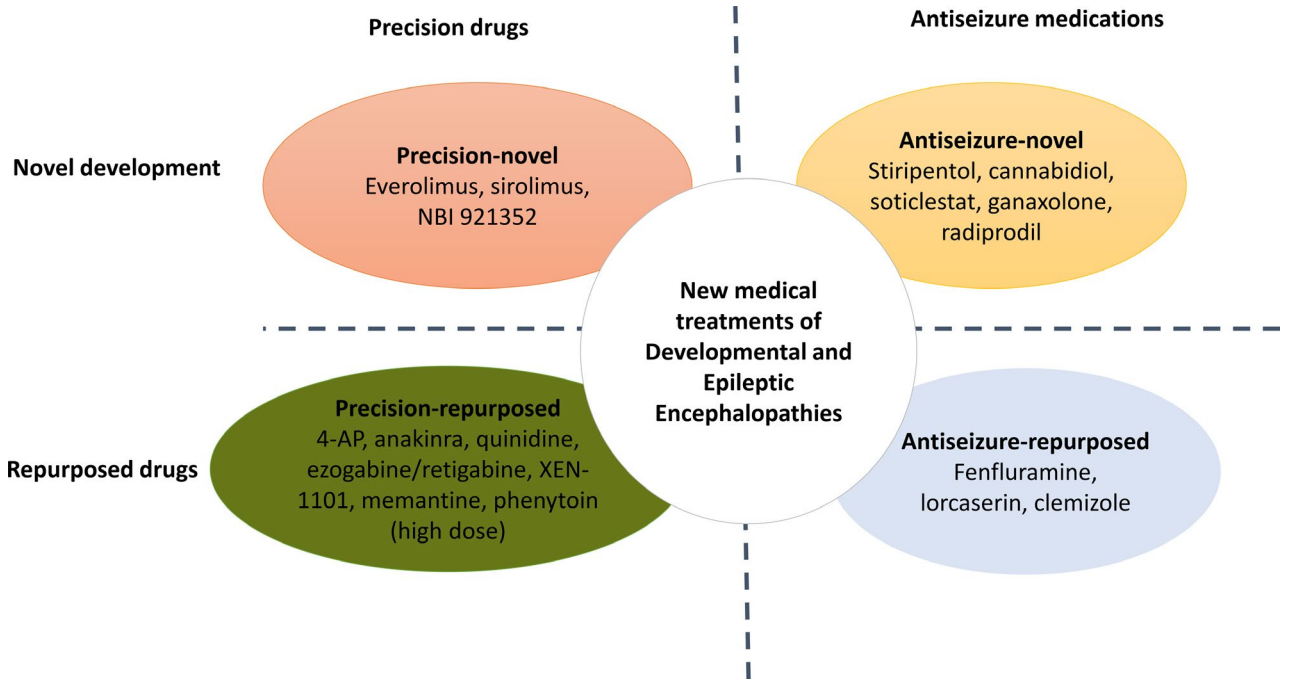

FIGURE 1 A summary of new medical treatments of developmental and epileptic encephalopathies, including precision and antiseizure medications, novel development, and repurposed drugs. The included drugs are described in the text and/or tables

2.1 | Precision drugs

A precision medicine is defined as a treatment that is targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations.[39] Clinical implications for such treatments include considerations of the duration of treatment and the impact on neurodevelopment if early treatment is initiated. Furthermore, the possible efficacy of the pharmacogenetic approach according to the age of expression of the mutation is important, for example, if there is a gain- or loss-of-function mutation at a specific stage in development for certain ion channels or receptors. Advances in genetic technologies have markedly increased our understanding of the pathogenesis of many DEEs as we are increasingly able both to identify the gene and to understand the pathogenic mechanism of how it results in epilepsy. By targeting the underlying pathogenic mechanism, for example, with the use of zebrafish, a precision therapy may mitigate both seizures and the important nonseizure symptoms,[40] given the negative impact of seizures on the developing brain.

2.1.1 | Novel precision therapies, mammalian target of rapamycin inhibitors

Everolimus

Up to 90% of patients with tuberous sclerosis complex (TSC) develop epilepsy, most with onset in the infantile age group, and approximately two thirds become resistant to ASMs. The mammalian target of rapamycin (mTOR) inhibitor everolimus was recently approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as adjunctive therapy for TSC-associated focal seizures in patients older than 2 years. The results of the randomized, double-blind, placebo-controlled (randomized controlled trial [RCT]) Phase 3 EXIST-3 study (NCT01713946)[19,41,42] support add-on everolimus therapy for patients who are drug-resistant to two ASMs.[43]

Everolimus has been developed based on a rational concept considering that TSC is caused by genetic deficiency of negative modulators of the mTOR complex 1 (mTORC1).[44] Mutations in *TSC1* and *TSC2* encoding the proteins hamartin and tuberin result in hyperactivity of mTORC1, leading to abnormal neuronal differentiation and migration with dysmorphic neurons, altered synaptic plasticity, and abnormal lamination, as well as excessive glia activation and inflammatory signaling as hallmarks of TSC-associated brain pathology.[45] mTOR is the core element of mTORC1, which acts as a serine/threonine kinase and serves as a key regulator of cellular function, proliferation, growth, and survival.[46] Everolimus acts as an inhibitor of mTORC1 based on an interaction with FKB12, which forms a complex with mTOR1.[44] As a consequence, there is a reduction in downstream signaling of mTORC1 involving the effectors S6K and 4E-BP1.[44]

Everolimus was initially licensed for management of tuberous sclerosis-associated subependymal giant cell astrocytoma and renal angiomyolipoma.[44,45] A post hoc analysis

TABLE 1 Included drugs, indications, and pharmacological characteristics at the stage of clinical investigation

Drugs used in DEEs	Indication/pathophysiological background (gain- or loss-of-function mutations)	Mechanisms of action	Pharmacokinetic properties and interactions
Precision: novel			
Everolimus	Tuberous sclerosis complex Mutations in *TSC1* and *TSC2* encoding the proteins hamartin and tuberin	mTOR inhibitor. The mutations result in hyperactivity of mTORC1, abnormal cell differentiation, altered plasticity, and inflammatory signaling.	Absorption reduced by food. T_{max} = 1–2 h, protein binding = 74%. Metabolism: CYP3A4/5 $t_{1/2}$ = 30 h, susceptible to drug interactions in combination with enzyme inducers and inhibitors. Substrate for Pgp.
NBI 921352 (XEN901)	*SCN8A* mutations: gain-of-function mutations encoding the $Na_v1.6$ channel causing DEE (EIEE13)	Selective inhibitor of voltage-gated sodium channel subtype $Na_v1.6$, could address the underlying etiology in this condition.	T_{max} = 1–1.5 h, absorption varied with food. Metabolism: CYP3A4, 2C9, 2D6. No significant interaction with phenytoin.
Precision: repurposed			
Anakinra	FIRES	Recombinant human IL-1 receptor antagonist, decreases neurogenic inflammation.	Subcutaneous injection, bioavailability = 95%, $t_{1/2}$ = 4–6 h in adults, renal elimination. Could indirectly affect other ASMs by normalization of CYP activity through effects on cytokines.
Quinidine	*KCNT1* mutations	Decreases excitability. Efficacy was not further confirmed as a valuable approach.	Bioavailability = 70% (45%–100%), T_{max} = 1–3 h, protein binding = 70%, metabolism: CYP3A4 +?, $t_{1/2}$ = 6–11 h
Ezogabine/ retigabine (XEN496)	*KCNQ2* mutations	Specific activator of voltage-gated potassium Kv7.2/7.3 channels, decreases excitatory neurotransmission.	T_{max} = .5–2 h, protein binding = 80%, metabolism: UGTs and N-acetylation, $t_{1/2}$ = 8 h.
XEN1101, new compound similar to retigabine	*KCNQ2* loss of function as a more specific indication; early infantile epileptic encephalopathy type 7 (BFNS)	Specific opener of voltage-gated potassium channels, decreases excitatory neurotransmission.	T_{max} = 4–6 h, enhanced by food, metabolism: CYP3A4, $t_{1/2}$ = 4–10 days. No interaction studies done.
Memantine	*GRIN2* mutations	Noncompetitive NMDA receptor antagonist, decreases glutamatergic neurotransmission.	Bioavailability = 100%, T_{max} = 3–8 h, protein binding = 45%, majority excreted unchanged renally (57%-82%), other non-CYP dependent, $t_{1/2}$ = 60–100 h.
Phenytoin, high dose	*SCN2A* and *SCN8A* mutations, little evidence so far; carbamazepine could also be considered, based on the same mechanism of action	Inhibitor of voltage-gated sodium channels, resulting in a use-dependent block of excitatory neurotransmission.	T_{max} = 1–12 h, protein binding = 92%, metabolism: CYP2C9 and 19, $t_{1/2}$ = 30–100 h, saturation kinetics. Potent enzyme inducer of CYPs and UGTs, affecting various other ASMs.
Antiseizure: novel			
Stiripentol	Dravet syndrome, haploinsufficiency of the voltage-gated sodium channel α subunit NaV1.1	Positive allosteric $GABA_A$ receptor modulator, acting on both the BZD-sensitive γ- and α3-containing $GABA_A$ receptors + BZD-insensitive δ-containing $GABA_A$ receptors, located peri- and extrasynaptically, responsible for tonic inhibition.	Bioavailability unknown, C_{max} = 1.5 h, protein binding = 99%. Metabolism: CYP1A2, 3A4, 2C19, UGT, saturation kinetics, $t_{1/2}$ = 4.5–13 h. Potent enzyme inhibitor of CYP and UGT enzymes, affecting many other ASMs.

(Continues)

TABLE 1 (Continued)

Drugs used in DEEs	Indication/pathophysiological background (gain- or loss-of-function mutations)	Mechanisms of action	Pharmacokinetic properties and interactions
Cannabidiol	Dravet syndrome, Lennox–Gastaut syndrome, tuberous sclerosis complex	GPR55, TRPV1, and adenosine reuptake.	Variable and low absorption (<6% bioavailability, extensive first pass metabolism), increased 3–4-fold by fat-rich meals, C_{max} = 2.5–5 h, protein binding = 99%. Metabolism: CYP2C19, 3A4, UGT1A7, 1A9, 2B7, active metabolite 7-OH-CBD, $t_{1/2}$ = 60 h. Potent enzyme inhibitor of CYP and UGT enzymes, especially increasing N-desmethyl-clobazam by CYP2C19 inhibition.
Radiprodil	Infantile spasm syndrome EE-GRIN2B	Selective allosteric NR2B antagonist of glutamate.	T_{max} = 4 h (range = 3–6 h), mean AUC_{inf} and C_{max} = 2042 h ng ml^{-1} and 89.4 ng ml^{-1}, respectively.
Soticlestat (TAK935/ OV935)	Dravet syndrome	Targets the brain-specific enzyme cholesterol 24-hydroxylase: cholesterol → 24S-hydroxycholesterol (NMDA agonist), decreases excitability.	T_{max} = .25–.5 h, protein binding = 92%, metabolism: CYP3A and UGTs, $t_{1/2}$ = 3.5–4.8 h. No drug interactions studied.
Ganaxolone	CDKL5	Pregnanolone, $GABA_A$-agonist.	T_{max} = 1.5–2 h, $t_{1/2}$ = 7–10 h. Bioavailability issues have been a limitation. AUC and C_{max} increased 2–3-fold with intake of a fat-rich meal. Metabolism through CYP3A4/5, affected by enzyme inducers/inhibitors.
Antiseizure: repurposed			
Fenfluramine	Dravet syndrome	Release of serotonin (5-HT), increases serotonergic signaling via different 5-HT receptors.	T_{max} = 3 h, $t_{1/2}$ = 20 h, metabolism through CYP1A2, 2B6, 2D6, 3A4, 2C9/19, active metabolite nor-fenfluramine. Affected by enzyme inducers/inhibitors.
Lorcaserin	Severe childhood epilepsy (including Dravet syndrome)	Selective 5-HT2C receptor agonist (weight control indication).	T_{max} = 2 h, protein binding = 60%–76%, metabolism: multiple CYPs, $t_{1/2}$ = 12 h, enzyme inducing and inhibiting properties.
Clemizole	Dravet syndrome; histamine 1 antagonist and intracellular inhibitor of HCV protein synthesis	Developed as antiviral drug to treat hepatitis C, used in the 1950–60s.	Minimal PK data available. Oral absorption, CYP3A4-mediated metabolism.

Note: Gene therapies and enzyme replacement therapies are not included in this table.

For some drugs listed as antiseizure, it is actually unknown how broad the spectrum might be, and also for some of them a potential disease-modifying effect cannot be definitely excluded. The information in this table is based on the current state of knowledge, product information for everolimus, cannabidiol, fenfluramine, stiripentol, memantine, and retigabine, and various recent references.[11–18]

Abbreviations: 5-HT, serotonin; ASM, antiseizure medication; AUC , area under the curve; BFNS, benign familial neonatal seizures; BZD, benzodiazepine; C_{max}, maximum concentration; CYP, cytochrome P450; DEE, developmental and epileptic encephalopathy; FIRES, febrile infection-related epilepsy syndrome; GABA, γ-aminobutyric acid; GPR55, G-protein coupled receptor 55; HCV, hepatitis C virus; IL-1, interleukin-1; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; Pgp, P-glycoprotein; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; T_{max}, time to maximum concentration; TRPV1, transient receptor potential vanilloid 1; UGT, uridine diphosphate-glucanosyltransferase.

of the pediatric population (age < 18 years) in the extension trial of the EXIST-3 study found that children younger than 6 years had greater benefit than older children.[42]

Everolimus interacts with many agents that are inhibitors, inducers, or substrates of CYP3A4 and P-gp; patients taking CYP3A4-inducing ASMs such as carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, CLB, and topiramate require a higher starting dose of everolimus.[47] On the other hand, enzyme inhibitors such as erythromycin or ketoconazole will increase the serum concentration

of everolimus.[48] As everolimus is susceptible to many drug interactions, the serum concentration should be monitored. In the EXIST-3 study, the daily doses of the treated groups were therefore based on targeted blood levels of everolimus.

Reported adverse events include stomatitis, diarrhea, nasopharyngitis, pyrexia, and upper respiratory tract infection.[19] Long-term treatment was associated with higher incidence and severity of infections, such as pneumonia, particularly in the younger patients (<6 years); however, the incidence of pneumonia was similar to that in the general population, based on worldwide reports in children younger than 5 years.[42]

Although the EXIST-3 study did not include an infantile age group,[19] small observational case series support beneficial effects for epilepsy in children younger than 2 years, with possible neurocognitive improvement in infants with epileptic spasms and refractory seizures.[49–51] These include a single case report of a 19-month-old infant whose refractory epilepsy and neurocognition improved following everolimus,[49] a case series of four infants with epileptic spasms, three of whom had improved neurocognition,[50] and a cohort of 17 infants, of whom two of four were managed for refractory epilepsy and had improved seizure control.[50] Safety has been explored in a small study ($n = 23$; 19 everolimus, four sirolimus) and considered acceptable in this age group.[52] Larger long-term studies are needed, especially to understand whether this young age group is more vulnerable to respiratory and other infections. Future research should explore whether everolimus could function as a preventative treatment for epilepsy, neurodevelopmental disability, and other systemic manifestations of TSC, particularly in infants and young children.[44,53] Although including subjects younger than 2 years, studies have explored the recommended dosage and hypothesized seizure reduction at 6 mg/m^2.[54]

More recently, various loss-of-function and gain-of-function mutations have been identified in different upstream regulators of mTORC1 comprising different modulators of the GATOR complex. Improved knowledge about various mTORopathies will likely result in an expansion of the therapeutic indications for mTOR inhibitors. Along this line, mTOR inhibitors may be effective in treating other diseases associated with mTOR overactivation, such as type 2b focal cortical dysplasia and other focal epilepsies associated with gain-of-function of mTOR such as mutations in genes such as *DEPDC5*, *MTOR*, *PTEN*, and *GATOR*.[44,55] Considering the adverse effect potential of everolimus, it is of particular interest that efforts are made to develop optimized approaches for improved efficacy and tolerability based on a combined targeting of mTORC1 and mTORC2 or mTORC1, mTORC2, and phosphoinositide 3-kinase.[56]

Sirolimus (rapamycin)

Although most research has focused on everolimus as the mTOR inhibitor promoted for control of epilepsy in settings of mTOR overactivation, other mTOR inhibitors, specifically sirolimus (rapamycin), have been studied.[57–61] The efficacy of rapamycin was described in two case reports of children with TSC, including a 10-year-old girl with a dramatic reduction in seizures after 10 months of rapamycin,[57] and eight children (4–16 years of age) with seizure control in the first year of treatment, but with a relapse in three of them in the second year.[58] After rapamycin withdrawal, three of five children had recurrence of seizures within 6–12 months. Three studies reported on the role of sirolimus for epilepsy therapy.[59–61] Overwater et al. reported on 23 children with TSC and intractable epilepsy (1.8–10.9 years) who were randomly assigned in an open-label add-on study of sirolimus immediately or after 6 months.[59] Intention-to-treat analysis found that the sirolimus treatment group had a 41% seizure frequency decrease (95% confidence interval to −69% to +14%, $p = .11$) compared to the standard-care period. All children had adverse effects, reported as oral sores, diarrhea, and immunosuppression, resulting in five children withdrawing from the study. One year of sirolimus therapy in 91 children with TSC resulted in a response rate of 78% (71/91), 47% (43/91) of whom became seizure-free, with statistical significance in improved seizure control ($p < .001$).[60] The subgroup with drug-resistant epilepsy also had improved control of seizures ($p = .01$). No or minimal adverse effects were reported. The authors noted that age was a critical factor for outcome of epilepsy. Overall, they promoted the use of sirolimus to treat epilepsy in patients with TSC. Another study explored the use of sirolimus for patients with Sturge–Weber syndrome.[61] In a retrospective observational study of six cases who were refractory, the authors reported that seizures were controlled in all patients, with only minor adverse effects. Whereas the data for rapamycin are limited to case reports, there are stronger data to suggest that there is a role for sirolimus in the management of epilepsy for selected etiologies, as shown in a patient with *NPRL3* epilepsy, a mutation associated with focal epilepsy and cortical malformations.[62] Sirolimus could be an important alternative option for settings precluding access to everolimus. One retrospective multicenter study compared everolimus with sirolimus in patients with epilepsy and TSC.[52] The authors commented on the challenges of more adverse events and dosing issues in the sirolimus group compared to those receiving everolimus.

2.1.2 | Other novel precision therapies

With improved understanding of the pathogenesis underlying many of the rare metabolic and genetic epilepsies, there has been increased interest in precision therapies to target these pathways.

Although the concept will not be detailed, as it is not the focus of the text, metabolic epilepsies remain important

TABLE 2 Summary of clinical studies and evidence

ASMs used in DEEs	Disorder	Patients	Outcomes	References
Precision: novel				
EVL	TSC	366 patients with DRE due to TSC, age 2–65 years	Patients randomized 1:1:1 to placebo, and low- and high-dose EVL Response rates: 15.1% on placebo, 28.2% on low-dose EVL ($p = .0077$), and 40.0% on high-dose EVL ($p < .0001$) Serious AEs in 3% on placebo and 14% each in both EVL groups	French et al. (2016)[19]
Precision: repurposed				
Anakinra	FIRES	25 children with FIRES	Multicenter retrospective review Median dose = 5 mg/kg/day 73% exhibited a >50% reduction in seizures after 1 week Adverse effects: 3 DRESS, 2 reversible cytopenias Outcome: 12% mortality; of survivors, 35% had no/mild delay, 35% had moderate delay, and 29% had severe delay	Lai et al. (2020)[20]
Quinidine	KCNT1	20 patients (17 EIMFS, 3 EOEE)	Retrospective analysis of KCNT1 database 20% of children had a >50% reduction in seizures on quinidine and 1 (5%) was seizure-free Adverse effects: prolonged QTc was seen in 47% Best response was seen in cases with variants clustering distal to NADP domain within the RCK2 domain of the protein	Fitzgerald et al. (2019)[21]
Ezogabine/ retigabine	KCNQ2	11 infants and children with KCNQ2 encephalopathy	Retrospective multicenter analysis 11 infants and children treated with ezogabine at doses of 8–40 mg/kg/day 3/4 infants treated prior to 6 months of age improved; all of these had variants in or near the ion-conducting pore region Minimal benefit in cases treated after 6 months of age	Millichap et al. (2016)[22]
Memantine	GRIN2A	Single case report	9-year-old boy with GRIN2A who was commenced on memantine .5 mg/kg/day Seizures decreased from 11.1 to 3.3 per week over treatment period No appreciable change in cognition	Pierson et al. (2014)[23]
Phenytoin (high dose) or high-dose sodium channel agents	SCN2A and SCN8A	12 children with SCN2A encephalopathy	Retrospective study noting improved seizure control in 9/12 cases with sodium channel agents, including 5 with supratherapeutic phenytoin	Howell et al. (2015)[24]
		3 neonates with SCN2A encephalopathy	Retrospective case series noting 2/3 had significant reduction in seizures with phenytoin	Melikishvili et al. (2020)[25]
		5 children with SCN2A DEE	3/5 were found to have GOF variants and phenytoin helpful for all 3	Miao et al. (2020)[26]
		22 persons with SCN8A	Retrospective study showing that the most effective agents were phenytoin (9/12 improved), oxcarbazepine (5/7 improved), and carbamazepine (7/8 improved), often at supratherapeutic doses	Gardella et al. (2018)[27]
		9 children with early onset SCN8A DEE	Retrospective study showing that sodium channel agents were effective in 7/8 cases where they were tried	Kim et al. (2019)[28]

(Continues)

TABLE 2 (Continued)

ASMs used in DEEs	Disorder	Patients	Outcomes	References
Antiseizure: novel				
STP	Dravet syndrome	41 children with Dravet syndrome	Randomized placebo-controlled study of add-on STP (50 mg/kg/day) versus placebo in children on stable clobazam and valproic acid After 2 months, responder rate was 71% for STP versus 5% for placebo ($p < .0001$)	Chiron et al. (2000)[84]
CBD	Dravet syndrome, LGS, TSC		Dravet syndrome: randomized placebo-controlled trial of add-on CBD (20 mg/kg/day) versus placebo in 120 children; the median percent reduction in convulsive seizure frequency was 38.9% with CBD versus 13.3% with placebo ($p < .01$)	Devinsky et al. (2017)[29]
			LGS: randomized, placebo-controlled trial of add-on CBD (20 mg/kg/day or 10 mg/kg/day) versus placebo in 225 patients 2–55 years old with drug-resistant drop seizures; the median percent reduction in drop seizures was 41.9% with 20 mg/kg/day, 37.2% with 10 mg/kg/day, and 17.2% with placebo	Thiele et al. (2018, 2019)[30,31]
			TSC: randomized, placebo-controlled trial of add-on CBD (50 mg/kg/day or 25 mg/kg/day) versus placebo in 224 patients 1–57 years old with drug-resistant focal or generalized seizures; median percent reduction in focal and generalized seizures was 48% on 50 mg/kg/day, 49% on 25 mg/kg/day, and 27% on placebo	Thiele et al. (2019)[32]
Soticlestat	Dravet syndrome, LGS	51 persons with Dravet syndrome 88 persons with LGS	Randomized placebo-controlled trial of add-on soticlestat versus placebo showed a 33.8% median decrease in convulsive seizure frequency with soticlestat versus a 7.0% median increase with placebo ($p = .00007$) Randomized placebo-controlled trial of add-on soticlestat versus placebo showed a 20.6% median decrease in drop seizure frequency with soticlestat versus a 6.0% median reduction with placebo ($p = .1279$)	Unpublished, accessed 1 Dec 2020 from: https://www.takeda.com/newsroom/newsreleases/2020/phase-2-elektra-study-of-soticlestat-tak-935ov935-meets-primary-endpoint-reducing-seizure-frequency-in-children-with-dravet-syndrome-or-lennox-gastaut-syndrome/[33]
Ganaxolone	CDKL5	101 persons with CDKL5 aged 2–21 years	Randomized placebo-controlled trial of ganaxolone (up to 1800 mg/day) versus placebo Ganaxolone was associated with a 32.2% reduction in major motor seizures compared to a 4.0% increase with placebo ($p = .002$)	Bialer et al. (2020)[12]
Radiprodil	ISS		First report in 3 infants with infantile spasm syndrome resistant to combination of steroids and vigabatrin: 1 spasm-free, 2 improved	Auvin et al. (2020)[34]
	GRIN2B-EE		Experimental study suggestive of modification on GOF apathogenic variant when no effect of memantine	Mullier et al. (2017)[35]

(Continues)

TABLE 2 (Continued)

ASMs used in DEEs	Disorder	Patients	Outcomes	References
Antiseizure: repurposed				
Fenfluramine	Dravet syndrome, LGS	119 children aged 2–18 with Dravet syndrome, not on concurrent STP	Randomized placebo-controlled trial of add-on fenfluramine (.7 mg/kg/day or .2 mg/kg/day) versus placebo; median reduction in convulsive seizure frequency was 74.9% with .7 mg/kg/day, 42.3% with .2 mg/kg/day, and 19.2% with placebo	Lagae et al. (2018)[36]
		87 children with Dravet syndrome aged 2–18 years on concurrent STP	Randomized placebo-controlled trial of add-on fenfluramine (.4 mg/kg/day) versus placebo; persons on fenfluramine had a 54% greater reduction in mean monthly convulsive seizure frequency than placebo	Nabbout et al. (2019)[37]
		263 persons with LGS and intractable drop seizures	Randomized placebo-controlled trial of add-on fenfluramine (.7 mg/kg/day or .2 mg/kg/day) versus placebo; median percentage reduction in monthly drop seizures was 26.3% on high-dose fenfluramine, 13.2% on low-dose fenfluramine, and 7.8% on placebo ($p = .003$ comparing high dose to placebo but nonsignificant comparing low dose to placebo)	Knupp et al. (2020)[38]

Abbreviations: AE, adverse event; ASM, antiseizure medication; CBD, cannabidiol; DEE, developmental and epileptic encephalopathy; DRE, drug-resistant epilepsy; DRESS, drug rash, eosinophilia, and systemic symptoms; EIMFS, epilepsy of infancy with migrating focal seizures; EOEE, early onset epileptic encephalopathy; EVL, everolimus; FIRES, febrile infection-related epilepsy syndrome; GOF, gain of function; LGS, Lennox–Gastaut syndrome; QTc, corrected QT; STP, stiripentol; TSC, tuberous sclerosis complex.

differentials to early onset epilepsies and DEEs, and although they are rare, specific therapeutic interventions may prevent both seizures and neurocognitive decline.[63] Such interventions may include provision of a specific substrate, such as the pyridoxine- or pyridoxal-5-phosphate-dependent epilepsies, glucose transporter deficiency type 1 or creatine deficiency syndromes, or enzyme replacement therapies.[64] A high level of clinical suspicion is required to promptly diagnose these conditions early in their course, as many therapies can prevent or attenuate further regression, but do not reverse deterioration that has already occurred.

Moreover, strong efforts are underway to develop selective modulators for specific ion channel subunits affected by genetic variants. Progress has been reported for sodium channel subtype-specific modulators. Selective $Na_V1.6$ inhibition by XEN901 is of interest as a potential precision medicine approach for early infantile epileptic encephalopathy type 13 with a gain-of-function *SCN8A* variant.[12]

DS is due to de novo variants in the *SCN1A* gene, resulting in haploinsufficiency of the voltage-gated sodium channel α subunit NaV1.1. Han et al. identified antisense oligonucleotides that specifically increased the expression of an transcript in human cell lines, as well as in mouse brain.[65] The strategy that is referred to as TANGO (targeted augmentation of nuclear gene output) technology is based on modulation of splicing events with a suppression of nonproductive splicing by antisense oligonucleotides.[65] Testing in a mouse model demonstrated that a single intracerebroventricular dose reduced the incidence of both electrographic seizures and SUDEP, suggesting that such therapies may address important comorbidities as well as improve seizures. A clinical trial is currently underway in children with DS. Such therapies will likely require repeated dosing to maintain efficacy.

An alternate approach has used oligonucleotide-based molecules (AntagoNATs) that interfere with a long-noncoding regulatory RNA, which negatively regulates *SCN1A* expression.[66] Efficacy of this strategy has been indicated by assessment in a mouse model of DS and in fibroblasts from patients with different genetic variants of *SCN1A*.[66]

Additionally, several viral gene therapy models are also being explored.[67] Preclinical work is ongoing in DS, and clinical studies have been performed in several of the neuronal ceroid lipofuscinoses.

In addition to targeted treatments based on the underlying neurobiology, there are also opportunities for therapies that take into account the developmental changes in neurotransmission, in both excitatory and inhibitory pathways. Bumetanide is an inhibitor of NKCC1, and is being investigated for neonatal seizures. By its action on NKCC1, it blocks chloride influx and thus modulates the excitatory action of γ-aminobutyric acid (GABA) in the immature brain.[68,69] Radiprodil, a selective inhibitor of the NR2B subunit of the N-methyl-D-aspartate receptor, is also under

investigation,[34,35] based on the higher expression of NR2B subunits in the developing brain, which results in higher brain excitability through slower kinetics compared to the NR2A subunit that is expressed later in life. With the rapid advances in our understanding of the genes associated with rare epilepsy syndromes, interventions targeting the underlying pathogenic variant are emerging. In patients with haploinsufficiencies, there is an opportunity to upregulate the expression of the functional protein from the intact allele.

2.2 | Repurposed precision therapies

2.2.1 | Anakinra

Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist currently approved for the treatment of rheumatoid arthritis and other inflammatory conditions. In certain epilepsy syndromes, in particular febrile infection-related epilepsy syndrome (FIRES), there is increasing evidence that neurogenic inflammation with a functional deficiency of IL1RA can play a pathogenic role,[70,71] and blockade of IL-1β receptors could inhibit the inflammatory process. Although genetic data from one patient suggest that genetic variants of IL1RN may play a role, more research is necessary to identify the cause of IL1RA deficiency and to further explore the relevance.[71]

Studies of anakinra in human epilepsy have predominantly focused on FIRES, a severe epilepsy syndrome with high mortality and morbidity. The first case of FIRES, a 32-month-old girl treated with anakinra, was published in 2016[72] and since then, several additional case reports or abstracts have been published,[73–78] suggesting potential benefit, as did a recent international retrospective cohort of 25 children with FIRES treated with anakinra.[20] The latency to treatment varied extensively, and neuropsychological data were limited. However, in this international retrospective cohort, 18 (73%) exhibited a greater than 50% reduction in seizures by 1 week of anakinra treatment. Twelve percent of children died, and of survivors, 35% had no/mild cognitive disability, 35% had moderate cognitive disability, and 29% had severe cognitive disability, an outcome that was similar to a previously reported case series of 77 children.[79]

Overall, despite limited data, anakinra was generally well tolerated. Three of 25 children developed so-called DRESS (drug rash, eosinophilia, and systemic symptoms), which was considered to be due to other medications, and they all recovered while continuing on anakinra treatment; two had reversible cytopenias.[20] Anakinra may potentially have a therapeutic role in other epilepsies where neurogenic inflammation plays a significant pathogenic role. Further prospective studies with careful neuropsychological evaluations are needed to more clearly define the role of anakinra in FIRES.

2.3 | Antiseizure medications

ASMs decrease seizure frequency but are not known to be antiepileptogenic. Despite the availability of new drugs during the past decades, the portion of seizure-free patients remains the same.[80] A significant reduction in seizures may nevertheless improve daily functioning. In the recent fenfluramine and CBD studies, caregivers and investigators reported greater improvements in global impression of change in the treatment groups than with placebo,[29,81] and in the fenfluramine study, those on higher dose fenfluramine had greater improvements in their quality of life inventory, executive function, and metacognitive index than those on placebo.[82] Preventative use of vigabatrin administered to 25 infants with TSC who had epileptifom activity on EEG, but no electrical or clinical seizures, was associated with reduced risk and severity of subsequent epilepsy, when compared to 29 TSC infants treated conventionally with vigabatrin for seizures.[83] Some ASMs for DEEs have been used for decades in some countries, such as STP in France and other parts of Europe, and CBD has recently been approved in the United States and Europe.

2.3.1 | Novel ASMs

Stiripentol

STP has been designated as an orphan drug for the management of DS.[84] STP is not a novel drug but has more recently been approved in the United States. It has multiple mechanisms of action; it is a positive allosteric modulator of the $GABA_A$ receptor, acting on both the benzodiazepine-sensitive γ-containing $GABA_A$ receptors and on the benzodiazepine-insensitive δ-containing $GABA_A$ receptors, which are located peri- and extrasynaptically and are responsible for mediating tonic inhibition.[85] Based on the high abundance of the α3 subunit during brain development, it has been suggested that this subunit preference makes STP particularly interesting for management of pediatric epilepsies.[86,87] The combination of STP and benzodiazepines enhances GABAergic neurotransmission. Furthermore, STP inhibits lactate dehydrogenase, leading to neuronal hyperpolarization.[88] Lactate connects the glial and neuronal metabolic energy systems.[89] Thus, an inhibition of lactate dehydrogenase by STP might have relevant consequences for neuronal energy balance and excitability. STP has also been shown to be neuroprotective and reduces cell injury in the hippocampal CA1 region in rodent models.[90,91] Additionally, STP has pharmacokinetic effects on several other ASMs. Importantly, in DS, when combined with CLB, there are increased levels of both CLB, and the active metabolite desmethyl CLB, due to inhibition of CYP2C19 and CYP3A4.[9,87] The dose of CLB is typically reduced to approximately .2 mg/kg/day.

The best evidence for efficacy of STP is in DS. In the STICLO study,[83] an RCT, STP was added to CLB and VPA. Those receiving STP experienced a 69% reduction in seizure frequency from baseline (7% increase in those on placebo). Other retrospective analyses confirmed efficacy: 9%–17% seizure freedom, 57%–89% with a >50% reduction in seizure frequency, with significant reductions in seizure duration, frequency of status epilepticus, use of rescue medication, and number of emergency room visits.[92–95] Efficacy may be somewhat lower when STP is started during adolescence or adulthood, with responder rates of 23% at 36 months.[96] Limited data suggest that STP may have an additional role in the treatment of status epilepticus,[97–99] focal epilepsy, and other types of genetic epilepsies starting early in life.[100] The dose of STP is typically 20–50 mg/kg/day divided into two equal doses. STP exhibits a lower clearance with higher body weight, and thus younger, smaller children need a higher dose per kilogram than do teens and adults.[101] The FDA and EMA mandate that STP should be used in combination with CLB, and most patients also use it with VPA. Adverse effects of STP such as somnolence, fatigue, ataxia, and decreased appetite are dose dependent. A complete blood count and liver enzymes should be monitored at baseline, and then every 6 months while the patient is on therapy.

2.3.2 | Cannabidiol

Although there is a long-standing interest in possible antiseizure effects of phytocannabinoid preparations,[13] a comprehensive drug development program assessing efficacy of CBD in DS, Lennox–Gastaut syndrome (LGS), tuberous sclerosis, and infantile spasms was only initiated a few years ago.[102–104]

CBD has a complex pharmacodynamic profile comprising an interaction with several target sites, including different ionotropic and metabotropic receptors, ion channels, and transporters.[13,105,106] The compound has a very low affinity at the endocannabinoid receptors CB1 and CB2.[105] Different targets that might be relevant for antiseizure effects of CBD include modulation of the G-protein coupled receptor 55 (GPR55), agonistic effects on the transient receptor potential vanilloid 1 (TRPV1) coupled to calcium concentration influx, and adenosine reuptake.[107] In addition, changes in intracellular calcium may in turn affect gene expression patterns, with an impact on the cellular functional state, and adenosine serves as an endogenous anticonvulsant. In experiments in acute seizure models, genetic deficiency of TRPV1 or GPR55 limited the antiseizure effects of CBD.[13,107]

CBD has a challenging pharmacokinetic profile, with low and variable bioavailability (<6%), also affected by fat-rich food, 99% protein binding, and metabolism through CYP2C19 and 3A4.[13,108] CBD has shown efficacy in placebo-controlled, randomized trials in DS, LGS, and tuberous sclerosis in doses of 10–25 mg/kg.[29–31,109] In two trials with DS subjects (n = 120), a median reduction of 40% of convulsive seizures was observed with CBD 20 mg/kg. The time frame was up to 48 weeks including the open label extension phase.[29,109] A median reduction in drop seizures and total seizures was seen in the two studies with patients with LGS (n = 171 and n = 225) up to 48 weeks with CBD 10–20 mg/kg.[29–31] The study with TSC patients is yet to be published, but preliminary data are shown in Table 2.[32] Open-label studies have suggested effectiveness in children with CDKL5 deficiency disorder, Aicardi syndrome, and Dup15q syndrome,[110] and case reports in other epileptic syndromes.

Safety data from these controlled trials show a clear dose dependency of adverse effects including somnolence, diarrhea, appetite loss, and fatigue/lethargy. Liver enzymes aspartate aminotransferase and alanine aminotransferase increase to more than threefold in patients who use VPA concomitantly and may settle spontaneously or require withdrawal of CBD in some cases.[109] CBD is a strong enzyme inhibitor and causes drug interactions, for example, at the CYP2C19 step with CLB, resulting in severalfold increase in the active metabolite desmethyl CLB, with a risk of excessive adverse effects.[111,112] If the patient is already using STP, further enzyme inhibition is unlikely.[113] Recently, a one- to threefold increase in the serum concentrations of brivaracetam was seen in patients who added CBD due to inhibition of the same enzyme.[113] Use of therapeutic drug monitoring could be considered for patients initiating CBD, particularly if possible symptoms of toxicity develop. Also, the pharmacokinetics of CBD is variable and unpredictable, and it is used in polytherapy, resulting in possible toxicity due to interactions.[14,15]

Other novel ASMs that are currently in development include drug candidates that can be considered first-in-class drug candidates with a novel mechanism of action. One example is soticlestat (TAK935/OV935); this targets the brain-specific enzyme cholesterol 24-hydroxylase, which generates 24S-hydroxycholesterol from cholesterol.[114] Clinical studies are currently ongoing to assess the efficacy of soticlestat in children with DS and LGS (Table 2).

2.3.3 | Repurposed ASMs

Fenfluramine

Fenfluramine was initially marketed in the United States in 1973 as an appetite suppressant and was frequently combined with the monoamine oxidase inhibitor phentermine to prolong its effect. However, reports of possible valvular heart disease and pulmonary hypertension emerged in the 1980s, and the

drug was withdrawn from the market based on results from a case–control study.[115] Casaer and Boel reported significant benefit with fenfluramine in 22 children with self-induced photosensitive epilepsy; 27% achieved complete seizure freedom, and another 45% experienced a greater than 90% reduction in seizures.[116] In 2012, Ceulemans et al. reported that 70% of their case series of 12 DS patients achieved seizure freedom with fenfluramine.[117]

The pharmacological profile indicates that fenfluramine is a multitarget drug. It enhances serotonin (5-HT) release, increasing serotonergic signaling via different 5-HT receptors.[118] Fenfluramine causes a rise in extracellular serotonin exceeding that triggered by traditional 5-HT reuptake inhibitors.[119] The active metabolite nor-fenfluramine has a high affinity for 5-HT_{2B} and 5-HT_{2C} receptors.[120] Whereas activation of 5-HT_{2C} receptors mediates appetite suppression, activation of 5-HT_{2B} receptors seems to be involved in drug-induced hypertrophy of cardiac valves.[121] Fenfluramine has been combined with different receptor antagonists in a zebrafish mutant model, and the findings indicated a role of 5-HT_{1D} and 5-HT_{2C} receptors in its antiseizure effects. Interestingly, the study also demonstrated contribution of the sigma-1 receptor.[120] The sigma-1 receptor is a highly interesting target site with an intracellular localization in the endoplasmic reticulum, mitochondria, and nuclear membrane, which could affect neuroprotection and inflammation.[122,123] However, the question of whether fenfluramine can exert disease-modifying effects beyond a mere antiseizure effect still requires further investigation. The current state of knowledge suggests that fenfluramine's mechanism of action combines an enhancement of serotonergic neurotransmission with a positive allosteric modulation of the sigma-1 receptor.

Based on experience in the Belgium cohort and knowledge about the pharmacological characteristics, a drug development program was initiated to further assess efficacy and tolerability of fenfluramine in controlled clinical studies. Two Phase 3, randomized, placebo-controlled studies in DS have confirmed its efficacy. The first study included 119 DS patients, aged 2–18 years, with refractory convulsive seizures, but without use of STP.[81] Cases were randomized 1:1:1 to fenfluramine .7 mg/kg/day (up to a dose of 26 mg), fenfluramine .2 mg/kg/day, or placebo, with percentage reduction in convulsive seizure frequency as primary outcome measure. The median seizure reduction was significantly higher in both fenfluramine groups compared to placebo (74.9%, 42.3%, and 19.2%, respectively). The second study, which had identical entry criteria, except that patients had to be on STP, included 87 cases, who were randomized 1:1 to fenfluramine .4 mg/kg/day (to a maximum of 17 mg/day) or placebo.[37] The doses were lower here than in the first study due to concomitant use of the enzyme inhibitor STP. Patients treated with fenfluramine achieved a 54% greater reduction in mean monthly convulsive seizure frequency than those receiving placebo. With fenfluramine, 54% of patients demonstrated a 50% or greater and 35% a greater than 75% reduction in monthly convulsive seizure frequency versus 5% and 2%, respectively, with placebo.

The efficacy and tolerability appear to be maintained in the long term. Of 232 DS patients who entered the open-label extension study, the median reduction in seizure frequency was similar in patients less than 6 (−75.7%) and 6 or more years old (−64.7%), with a median follow-up of 256 days (range = 46–634).[124]

A clinical trial was also performed in LGS patients, aged 2–35 years, with drug-resistant drop seizures.[36] Patients were randomized 1:1:1 to fenfluramine .7 mg/kg/day, fenfluramine .2 mg/kg/day, or placebo. Only the higher dose gave a significantly greater reduction in drop seizures (26.5% vs. 7.8% on placebo, $p = .0012$). Similarly, more patients had a greater than 50% reduction in drop seizures on the higher dose of fenfluramine (25% at .7 mg/kg/day vs. 10% in the placebo group).

Fenfluramine was also studied in a small open-label trial in five patients, aged 4–25 years, with drug-resistant seizures associated with Sunflower syndrome.[125] The initial dose was .2 mg/kg/day, titrated to a maximum of .7 mg/kg/day or 26 mg/day. Overall, patients experienced a median reduction in convulsive seizure frequency of 74%. The most common adverse effects include decreased appetite, diarrhea, fatigue, lethargy, somnolence, and weight loss. Importantly, no cardiac valvulopathy or pulmonary hypertension has been noted so far. FDA has mandated surveillance echocardiograms every 6 months for all children treated with fenfluramine.

Other repurposed drug for DEEs, including DS, are lorcaserin and clemizole (Table 1).

3 | EXPERT OPINION AND CONCLUSIONS

The drug development landscape is evolving, from the development of a few drugs targeting a large number of patients (mainly those with focal onset and/or generalized tonic–clonic seizures with idiopathic generalized epilepsy) to numerous candidate drugs for orphan epilepsies.[126] This change is likely due to a saturation of the market, with an abundance of medications for focal onset seizures, resulting in decreased financial incentives to develop further such medications. However, this evolution of the drug development landscape results into a unique opportunity for pediatric onset epilepsies that have been underinvestigated for years. This is particularly true for rare DEEs, where few if any drugs are approved for specific use. The progress in genetics and molecular biology has also provided new insights in the understanding of the neurobiology of many of these disorders, allowing the development of precision medicine in the epilepsy field. Precision medicine refers to tailored or personalized treatment, and

usually starts with in vitro or in vivo data followed by a proof-of-concept study in patients. New drug candidates are also arising from the repurposing of existing compounds, either based on clinical observation (e.g., fenfluramine in DS) or choosing a product with a known mechanism of action to target the neuropathological mechanism. However, for some of these compounds, the results so far are scarce or conflicting. Furthermore, various genetic treatments will possibly be the future of precision medicine in DEEs.

In recent years, everolimus has been the first example of an ASM developed based on the neurobiology of disease. Despite a positive trial, the Phase 3 study results are less robust than hoped for with a precision medicine, instead being similar to what is usually seen in Phase 3 RCTs of drugs for focal onset seizures. However, everolimus is not truly an antiseizure medication, but rather has a possible disease-modifying effect. Thus, early treatment initiation may be of benefit, and there is a need for clinical studies in younger children with DEEs. In addition to everolimus improving seizures, data suggest it has an impact on cognition and in other tuberous sclerosis-associated neuropsychiatric disorders. Moreover, experimental data suggest that precision medicines such as mTOR inhibitors in the TSC model might not be a unique way to reduce seizures. In TSC1 KO^{GFAP} mice, the use of an anti-inflammatory compound (IL1B and CXCL10 inhibitor) significantly reduces seizures during a window of time of brain development.[127] Another example of precision medicine that went from the laboratory to clinical practice is the use of quinidine for *KCNT1*-related epilepsy. Recent data have been disappointing, suggesting the absence of clear correlation between a positive effect on quinidine on the potassium influx and the clinical response in patients with the same pathogenic variant.[128] These two examples demonstrate the importance of assessing theoretical precision therapies in actual patients, measuring the outcome of important comorbidities in addition to seizures.

Although designing a precision therapy based on the neurobiological mechanism of disease is enticing, it is not the only way to successfully develop new compounds. The success with fenfluramine in DS reminds us that clinical observations or exploratory trials might lead to highly successful drug development. Clinical efficacy, mechanism of action, pharmacokinetic properties, drug–drug interactions, and adverse effect profile are key for development and prescription of any drug. Currently, all the trial designs accepted by the regulatory agencies have focused on antiseizure properties; however, it will be key to also establish how to demonstrate effectiveness of a precision therapy on the natural history of the disease, focusing on both seizures and comorbidities.

CONFLICT OF INTEREST

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Dorothée Kasteleijn-Nolst Trenité proposed the idea for this review. All authors contributed to the development and evaluation of the manuscript and approved the final version.

ORCID

Cecilie Johannessen Landmark https://orcid.org/0000-0002-0877-8912
Heidrun Potschka https://orcid.org/0000-0003-1506-0252
Stéphane Auvin https://orcid.org/0000-0003-3874-9749
Jo M. Wilmshurst https://orcid.org/0000-0001-7328-1796
Svein I. Johannessen https://orcid.org/0000-0001-7087-6655
Dorothée Kasteleijn-Nolst Trenité https://orcid.org/0000-0002-6659-2614
Elaine C. Wirrell https://orcid.org/0000-0003-3015-8282

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