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REVIEW ARTICLE

Recent Advances in the Management of Seizures in Children

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Abstract
Childhood epilepsies comprise a group of heterogeneous conditions associated with diverse aetiologies, seizure severities/types, comorbidities, degrees of impairment and prognoses. Seizures are refractory to antiseizure medications (ASMs) in around one-third of cases. Alternatives to medication, for example surgical resection, are not always feasible, implying that new treatments are needed. In the past decade, new ASMs have been approved for specific childhood-onset epilepsy syndromes, notably cannabidiol for Lennox–Gastaut syndrome (LGS), Dravet syndrome (DS) and tuberous sclerosis complex (TSC); fenfluramine for LGS and DS; everolimus for TSC; and ganaxolone for cyclin-dependent kinase-like deficiency disorder. However, seizure freedom with these medications has rarely been achieved in randomised controlled trials. Alongside ASM development, and surgical strategies such as laser interstitial therapy, neurostimulation modalities have evolved towards responsive systems, such as autostimulation vagus nerve stimulation (VNS) and responsive neurostimulation, and non-invasive devices such as transcutaneous VNS and transcranial direct current stimulation; these have achieved similar decreases in seizure frequency to traditional neurostimulation in some studies. However, data for paediatric epilepsy are limited. Focused ultrasound is being developed not only for seizure focus ablation but also for other approaches to seizure control. In parallel with these developments, accumulating research in the areas of genetic testing, including genetic and related therapies designed to correct or compensate for underlying genetic causes of seizures, suggests that these technologies may have the potential to transform epilepsy treatment in the future. This review summarises major recent developments and current research in the treatment of epilepsy in children.

1 Introduction

Childhood epilepsy syndromes vary from the relatively benign and self-limiting, such as self-limited epilepsy with centrotemporal spikes (SeLECTS), to the more severe developmental and epileptic encephalopathies, such as Dravet syndrome (DS) and Lennox–Gastaut syndrome (LGS), which are typically associated with life-long impairment and comorbidities.

The incidence of epilepsy in children is estimated as 41–187/100,000 [1]. In 20–30% of cases, epilepsy remains

Key Points

New antiseizure medications (ASMs), including cannabidiol, everolimus, fenfluramine and ganaxolone have shown efficacy for seizures in childhood-onset epilepsies such as Lennox–Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex

Despite encouraging seizure frequency reductions and response rates with these ASMs, seizure freedom was rarely achieved in the pivotal trials, implying new pharmacological options are still needed

Advances in neurostimulation technologies include personalised adaptive systems such as responsive neurostimulation and closed-loop vagus nerve stimulation (VNS), and less invasive approaches such as transcranial direct current stimulation and transcutaneous VNS

Future treatment strategies for childhood epilepsy are likely to be influenced by continuing advances in emerging technologies such as genetic therapy and focused ultrasound

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drug-resistant [2], defined by the International League Against Epilepsy as 'failure of adequate trials of two tolerated and appropriately chosen and used [antiseizure medication (ASM)] schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom' [3]. The proportion of drug-resistant cases has remained largely constant [4], despite the accelerated development of new ASMs over the past three decades [5, 6]. Several of the recent ASMs have novel antiseizure mechanisms of action (MOA) [7], distinct from the voltage-gated sodium channel and γ-aminobutyric acid (GABA) modifying actions of established ASMs such as valproate, carbamazepine and lamotrigine. In some cases, for example cannabidiol, antiseizure effects are multi-modal or only partially understood. The mainstay of treatment for the majority of individuals remains the first- and second-generation medications; first-line treatments for childhood-onset epilepsies in the NICE guidance include sodium valproate for DS and LGS, vigabatrin in combination with prednisolone for infantile spasms, lamotrigine or levetiracetam for SeLECTS, and levetiracetam or sodium valproate for epilepsy with myoclonic-atonic seizures [8] (Fig. 1). Since 2024, the UK Medicines and Healthcare products Regulatory Agency (MHRA) advises that sodium valpraote should not be started in women or men under the age of 55 years unless there is agreement independently by two specialists that there is no other effective and tolerated treatment, or unless there are compelling reasons that the reproductive risks associated with valproate do not apply [9]. This extends the previous advice that valproate should be avoided in women and girls of childbearing potential.

In this article we summarise developments in diagnostic strategies and new therapeutic interventions in the treatment of seizures in childhood epilepsy, with a particular focus on ASMs, including newly approved ASMs, ASMs in an advanced stage of development, and medications repurposed from other indications. The review also provides an overview of recent advances in non-pharmacological treatments, including surgical interventions and neuromodulation. Improvements in genetic testing, the application of artificial intelligence (AI) and machine learning models to support electroencephalogram (EEG) analysis and other technological innovations are discussed briefly but are not the main focus of the review.

Diagnostic strategies and therapeutic interventions for inclusion were identified through a search in PubMed covering the 5-year period to 21 January 2025 (see the supplementary information for search terms), recent review articles relevant to the subject and the authors' own experience. A more focused literature search was conducted for each of the included interventions to identify the salient studies reporting antiseizure efficacy findings in children.

Epilepsy management extends far beyond treating seizures, but this review is focused specifically on advances in seizure control.

2 Diagnostic Strategies

2.1 Magnetic Resonance Imaging (MRI) and Electroencephalogram (EEG) Analysis

Examination of MRI and EEG by clinical experts remains current practice to assist in the confirmation of the diagnosis and type of epilepsy. However, such specialist skills are not always readily available. Furthermore, brain activity between seizures can be normal and it is often difficult to capture a clinical seizure during the investigation. Machine learning/AI is already showing much promise in improving seizure detection and seizure prediction on EEG and/or MRI [10, 11] with applications extending to evaluation and planning for epilepsy surgery [12].

Novel mobile and portable EEG solutions have been developed in recent years but are not yet fully integrated into routine clinical practice. Whilst there is high interest amongst clinicians, widespread adoption would require more research with validation studies, and enhanced communication between researchers, companies and clinicians [13].

2.2 Genetic Testing

Genetic testing can inform clinical treatment decisions in 12–80% of genetic diagnoses [14, 15]. For example, the ketogenic diet has demonstrated efficacy in SLC2A1-related epilepsy and epilepsies due to SCN1A, KCNQ2, STXBP1 and SCN2A mutations, but is less effective in patients with CDKL5 mutations [14, 16]. Greater understanding of the role of gain-of-function (GOF) and loss-of-function (LOF) mutations in epilepsy pathogenesis is beginning to inform ASM choice. For example, in epilepsies associated with SCN1A LOF mutations, in which seizures are the result of impaired inhibitory interneuron function of the sodium channel Nav1.1, the use of sodium channel blocking agents may lead to exacerbation, and ASMs with alternative antiseizure MOAs are the recommended first-line options. Conversely, sodium channel blocking agents, including phenytoin and the new ASM cenobamate, which act via inhibition of persistent sodium currents, have demonstrated efficacy in epilepsies associated with SCN8A GOF variants [17–20]. Research in this area has also informed rational repurposing of medications not previously indicated for seizures: for example, quinidine has shown some efficacy for KCNT1-related epilepsy [21], although it may not be effective in all cases [22]. Genetic diagnoses in patients with epilepsy may

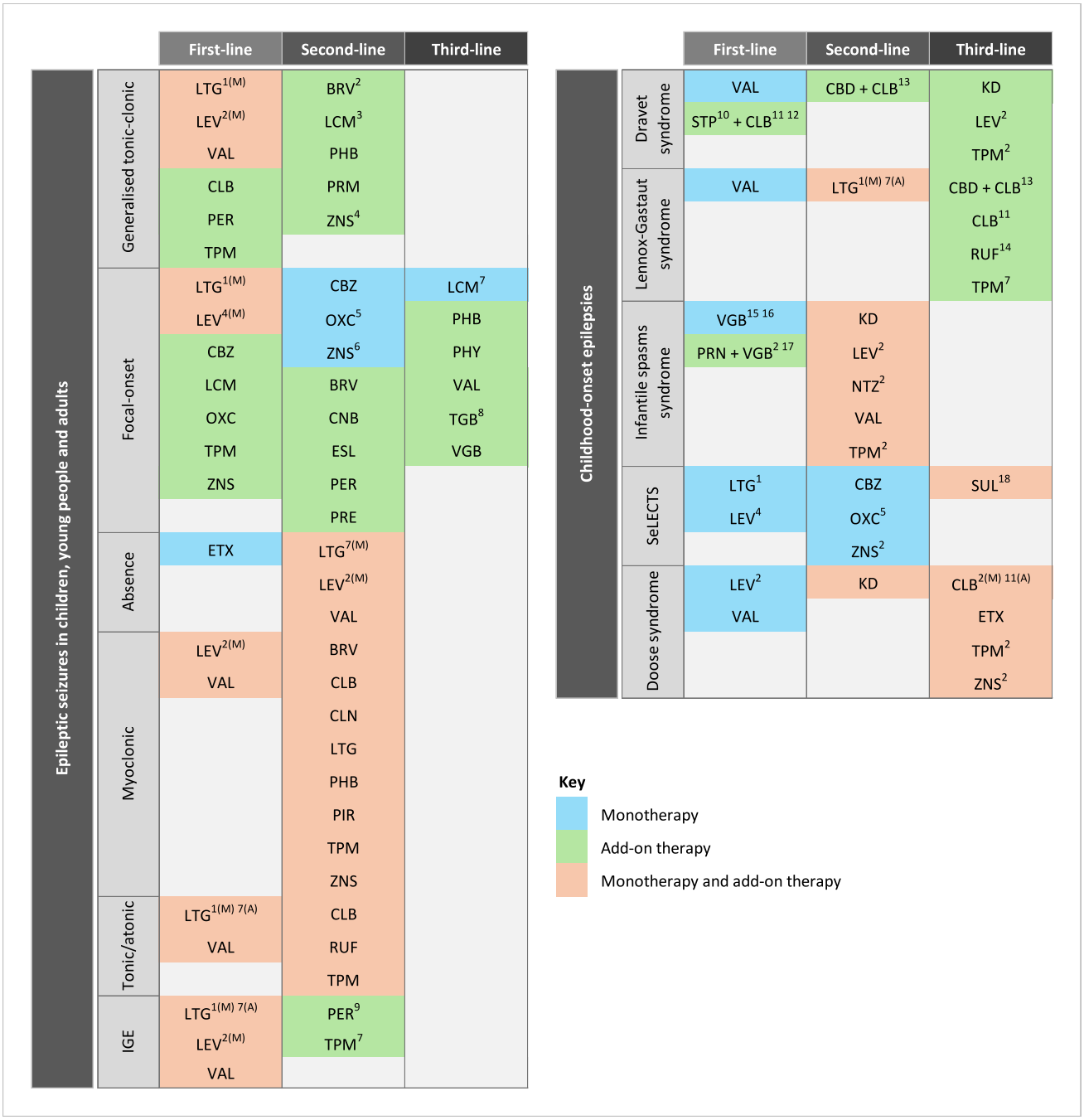

Fig. 1 NICE recommended therapies for seizures in epilepsy. (M) applies to medication as monotherapy, (A) applies to medication as add-on therapy. [1]Off-label in children < 13 years. [2]Off-label in adults and children. [3]Off-label in children < 4 years. [4]Off-label in children and young people < 16 years. [5]Off-label in children < 6 years. [6]Off-label in children. [7]Off-label in children < 2 years. [8]Off-label in children < 12 years. [9]Off-label in children < 7 years. [10]STP off-label when started in adults > 18 years. [11]CLB off-label in children < 6 months. [12]Triple therapy with VPA. [13]If child > 2 years. [14]Off-label in children < 1 year. [15]Infantile spasms due to tuberous sclerosis. [16]In children with high risk of steroid-related side effects. [17]If infantile spasms not due to tuberous sclerosis. [18]Not licensed in the UK. *BRV* brivaracetam, *CBZ* carbamazepine, *CLB* clobazam, *CNB* cenobamate, *ESL* eslicarbazepine acetate, *ETX* ethosuximide, *IGE* idiopathic generalised epilepsy, *KD* ketogenic diet, *LCM* lacosamide, *LEV* levetiracetam, *LTG* lamotrigine, *OXC* oxcarbazepine, *PER* perampanel, *PHY* phenytoin, *PIR* piracetam, *PRE* pregabalin, *PRM* primidone, *PRN* prednisolone, *RUF* rufinamide, *SeLECTS* self-limited epilepsy with centrotemporal spikes, *STP* stiripentol, *SUL* sulthiame, *TGB* tiagabine, *TPM* topiramate, *VAL* sodium valproate, *VGB* vigabatrin, *ZNS* zonisamide

also influence prognosis and lead to decreased hospitalisations [14].

2.3 Wearable Devices

Digital technology and wearable devices, aside from mobile and portable EEGs, have also become available. The option of relaying an automatic notification on detection of a seizure to designated people or services is starting to become available. However, until concerns about accuracy, data confidentiality (particularly for children) and technical support are satisfactorily addressed, adoption into clinical management will be limited. Consideration of these factors do not appear to limit the willingness of people with epilepsy to use digital technology for long-term seizure monitoring [23].

3 Therapeutic Interventions

3.1 Recently Approved Antiseizure Medications for Paediatric Epilepsy

3.1.1 Cannabidiol

Cannabidiol (CBD) is a non-psychoactive constituent of cannabis with multiple apparent antiseizure MOAs, which are thought to include antagonism of the G-protein-coupled receptor 55 (GPR55), desensitisation of the transient receptor potential of vanilloid type 1 (TRPV1) channels and adenosine reuptake, among others [24]. However, the precise MOA and hierarchy of antiseizure effects in humans is still uncertain. CBD was approved in 2018 in the USA and 2019 in the EU/UK for seizures associated with LGS and DS, and subsequently, in 2020, for seizures associated with tuberous sclerosis complex (TSC) (Table 1) [25, 26]. In DS, the pivotal randomised controlled trial (RCT) [27] reported a median decrease in monthly convulsive seizure frequency of 38.9% from baseline with adjunct CBD compared with a 13.3% decrease with adjunct placebo. The adjusted median percentage difference between CBD and placebo groups was 22.8 (95% confidence interval [CI] 5.4–41.1; $p = 0.01$) (Table 2; Fig. 2). In LGS, in the first of two pre-licensing RCTs (GWPCARE3) [28], the median decrease in monthly drop seizure frequency was 41.9% with high-dose CBD (20 mg/kg), 37.2% with low-dose CBD (10 mg/kg) and 17.2% with placebo. The estimated median differences between CBD and placebo were 21.6% (95% CI 6.7–34.8; $p = 0.005$) for the higher dose and 19.2% (95% CI 7.7–31.2; $p = 0.002$) for the lower dose. In the second RCT (GWPCARE4) [29], the median decrease in drop seizures was 43.95% with 20 mg/kg CBD and 21.8% with placebo. The estimated median difference between groups was 17.21% (95% CI 4.09–30.32; $p = 0.0135$) (Table 3). In TSC, in the pivotal RCT (GWPCARE6) [30], adjunct CBD was associated with a 47.5% decrease in TSC-associated seizures at a dose of 50 mg/kg and a 48.6% decrease at a dose of 25 mg/kg compared with 26.5% for placebo. The difference between CBD and placebo was 28.5% (95% CI 11.9–42.0; $p = 0.002$) for high-dose CBD and 30.1% (95% CI 13.9–43.3; $p < 0.001$) for the lower dose (Table 4).

CBD is an inhibitor of cytochrome P450 (CYP) 2C19 implying the potential for pharmacokinetic interactions with other medications. Notably, CBD increases the plasma concentration of norclobazam, the active metabolite of clobazam. Meta-analysis of the RCT data show both enhanced antiseizure effects and greater frequency of adverse events related to somnolence, rash, pneumonia and aggression in the subgroup of individuals receiving both drugs [31–33]. Estimates derived from an analysis of pooled data from all four RCTs in LGS and DS indicated both a greater reduction in seizure frequency in the CBD + clobazam subgroup (treatment ratio [TR] = 0.59; 95% CI 0.52–0.68; $p < 0.0001$) than for CBD without clobazam (TR = 0.85; 95% CI 0.73–0.98; $p = 0.0226$), and a higher odds ratio for response (CBD + CLB 2.51; 95% CI 1.69–3.71; $p < 0.0001$; CBD − CLB 2.40; 95% CI 1.38–4.16; $p = 0.0020$). Approval for CBD in Europe reflects these findings, with CBD only licensed in combination with CLB [34]. In the USA, CBD is approved as monotherapy for seizures in LGS, DS and TSC [25].

Common adverse events reported in the RCTs of CBD and other ASMs in this section (everolimus, fenfluramine and ganaxolone) are shown in Fig. 3.

3.1.2 Everolimus

Tuberous sclerosis complex is a genetic disorder associated with loss of function mutations in the TSC1 or TSC2 genes responsible for encoding hamartin and tuberin, respectively. In TSC, loss of normal inhibitory effects on the mammalian target of rapamycin (mTOR) signalling pathway mediated by these proteins results in dysregulated cell growth in the form of characteristic benign tumours affecting the brain, skin, heart, lungs and kidneys [35–37]. Epilepsy in TSC is common: seizures occur in around 84% of cases [38]. Everolimus (EVE) is an mTOR inhibitor which was approved in 2018 in the USA and UK for the treatment of TSC-related benign brain and renal tumours (subependymal giant cell astrocytoma and renal angiomyolipoma), and TSC-associated focal-onset seizures with or without secondary generalisation from the age of 2 years [39, 40]. In the EU, EVE is designated an ‘orphan medicine’ for TSC [41]. The pivotal phase 3 RCT, the EXIST-3 trial [42], reported a statistically significant decrease in seizure frequency and

Table 1 Summary of licensing and pivotal studies for cannabidiol, fenfluramine, soticlestat, ganaxolone and everolimus in Dravet syndrome, Lennox–Gastaut syndrome, cyclin-dependent kinase-like 5 deficiency disorder and tuberous sclerosis complex

	Licensed indications			Pivotal studies				
ASM	ES	USA	EU/UK	Study	Design	Country	Main inclusion criteria	N^a	Primary efficacy outcome
CBD	DS	Seizures associated with DS in patients 1 year of age and older	Adjunctive therapy for seizures associated with DS in conjunction with CLB in patients 2 years of age and older	Devinsky (2017) [27]	Multicentre, double-blind, placebo-controlled RCT 4-week baseline, 14-week treatment period (2-week dose escalation, 12-week maintenance), 10-d taper and 4-week safety follow-up CBD dose: 20 mg/kg/d	Multinational	Age 2–18 years; established diagnosis of DS; treatment with ≥ 1 existing ASM; ≥ 4 convulsive seizures during 28-d baseline period	120	Percentage change from baseline in 28-d convulsive seizure frequency compared with placebo during 14-week treatment period
	LGS	Seizures associated with LGS in patients 1 year of age and older	Adjunctive therapy for seizures associated with LGS in conjunction with CLB in patients 2 years of age and older	Devinsky (2018) [28]	Multicentre, double-blind, placebo-controlled RCT 4-week baseline, 14-week treatment period (2-week dose escalation, 12-week maintenance), 10-d taper and 4-week safety follow-up CBD dose: 20 mg/kg/d or 10 mg/kg/d	Multinational	Age 2–55 years; slow (< 3 Hz) spike-and-wave pattern on EEG; ≥ 2 generalised seizure types including drop seizures (atonic, tonic or tonic–clonic) for ≥ 6 months; treatment with 1–4 concomitant ASMs; ≥ 2 drop seizures per week during 28-d baseline period	225	Percentage change from baseline in 28-d drop seizure frequency compared with placebo during the 14-week treatment period
				Thiele (2018) [29]	Multicentre, double-blind, placebo-controlled RCT 4-week baseline, 14-week treatment period (2-week dose escalation, 12-week maintenance), 10-d taper and 4-week safety follow-up CBD dose: 20 mg/kg/d	Multinational	Age 2–55 years; clinical diagnosis of LGS; slow (< 3 Hz) spike-and-wave pattern on EEG; ≥ 2 generalised seizure types including drop seizures (atonic, tonic or tonic–clonic) for ≥ 6 months; failure of ≥ 2 ASMs; ≥ 2 drop seizures per week during 28-d baseline period	171	Percentage change from baseline in 28-d drop seizure frequency compared with placebo during the 14-week treatment period

Table 1 (continued)

	Licensed indications			Pivotal studies					
ASM	ES	USA	EU/UK	Study	Design	Country	Main inclusion criteria	*N*[a]	Primary efficacy outcome
	TSC	Seizures associated with TSC in patients 1 year of age and older	Adjunct therapy for seizures associated with TSC in patients 2 years of age and older	Thiele (2021) [30]	Multicentre, double-blind, placebo-controlled RCT 4-week baseline, 16-week treatment period (4-week dose escalation, 12-week maintenance), 10-d taper and 4-week safety follow-up CBD dose: 50 mg/kg/d or 25 mg/kg/d	Multinational	Age 1–65 years; clinical diagnosis of TCS; ≥ 8 TSC-associated seizures during 28-d baseline period	224	Change from baseline in TSC-associated seizures including focal motor seizures with or without impairment of awareness, focal seizures evolving to bilateral motor seizures and generalised seizures (tonic–clonic, tonic, clonic or atonic) compared with placebo during the 16-week treatment period
FFA	DS	Seizures associated with DS in patients 2 years of age and older	Adjunct therapy for seizures associated with DS in patients 2 years of age and older	Lagae (2019) [47]	Parallel phase 3, multicentre, double-blind, placebo-controlled RCTs 6-week baseline period, 14-week treatment period (2-week dose escalation, 12-week maintenance), 2-week taper and 3–6-month safety follow-up or continuation in OLE FFA dose: 0.8 mg/kg/d or 0.2 mg/kg/day (max 30 mg/d)[b]	Multinational	Age 2–18 years; clinical diagnosis of DS; treatment-resistant seizures; ≥ 4 convulsive seizures (hemiclonic, tonic, clonic, tonic/atonic, generalised tonic–clonic or focal with observable motor signs) in a 4-week period during the 12 weeks pre-baseline; stable ASM regimen for ≥ 4 weeks	119	Change from baseline in 28-d convulsive seizure frequency compared with placebo during 14-week treatment period

Table 1 (continued)

	Licensed indications			Pivotal studies					
ASM	ES	USA	EU/UK	Study	Design	Country	Main inclusion criteria	*N*[a]	Primary efficacy outcome
	LGS	Seizures associated with LGS in patients 2 years of age and older	Adjunct therapy for seizures associated with LGS in patients 2 years of age and older	Knupp (2022) [48]	Multicentre, double-blind, placebo-controlled RCT 4-week baseline, 14-week treatment period (2-week dose escalation, 12-week maintenance), taper or continuation in OLE FFA dose: 0.7 mg/kg/d or 0.2 mg/kg/d	Multinational	Age 2–35 years; Epilepsy Study Consortium-confirmed diagnosis of LGS; onset of seizures at age 11 years or younger; multiple seizure types including tonic and tonic/atonic seizures; stable treatment with 1–4 concomitant ASMs; stable 4-week seizure baseline with ≥ 2 drop seizures (generalised tonic–clonic, secondary generalised tonic–clonic, tonic, atonic or tonic/atonic) per week; abnormal cognitive development; slow (< 2.5 Hz) spike-and-wave pattern on EEG	263	Percentage change from baseline in 28-d Epilepsy Study Consortium-confirmed drop seizure frequency with 0.7 mg/kg/d FFA compared with placebo during the 14-week treatment period
SOT	DS/LGS	NA	NA	Hahn (2022) [79]	Phase 2, multicentre, double-blind, placebo-controlled RCT 4 to 6-week screening/baseline period, 20-week treatment period (8-week dose escalation, 12-week maintenance), taper or continuation in OLE SOT dose: 300 mg BID (≥ 60 kg) or weight-based dosing (< 60 kg)	Multinational	Age 2–17 years; clinical diagnosis of DS or LGS; weight ≥ 10 kg; inadequate response to ≥ 2 ASMs; stable treatment with 1–4 concomitant ASMs; ≥ 3 convulsive seizures (DS) or ≥ 4 drop seizures (LGS) per month at baseline	141	Change from baseline in convulsive seizure frequency (DS) or drop seizure frequency (LGS) compared with placebo in combined patient population during 12-week maintenance period

Table 1 (continued)

	Licensed indications			Pivotal studies					
ASM	ES	USA	EU/UK	Study	Design	Country	Main inclusion criteria	*N*[a]	Primary efficacy outcome
GNX	CDD	Seizures associated with CDD in patients 2 years of age and older	'Orphan medication' status for seizures in children from 2 to 17 years of age with CDD (EU)	Knight (2022) [53]	Phase 3, multicentre, double-blind, placebo-controlled RCT 6-week baseline, 17-week treatment period (4-week dose escalation, 13-week maintenance), taper or continuation in OLE GNX dose: Max 63 mg/kg/d (weight ≤ 28 kg) or 1800 mg/day (weight > 28 kg)	Multinational	Age 2–21 years; pathogenic or probable pathogenic CDKL5 variant; history of early-onset seizures; unresponsive to ≥ 2 appropriate ASMs; ≥ 16 major motor seizures (bilateral tonic, generalised tonic–clonic, bilateral clonic, atonic or focal to bilateral tonic–clonic) per 28 d in 8-week pre-screening period; stable treatment with ≤ 4 concomitant ASMs	101	Percentage change from baseline in median 28-d major motor seizure frequency compared with placebo during 17-week double-blind treatment phase
EVE	TSC	Focal-onset seizures associated with TSC in patients 2 years of age and older	Adjunct treatment of focal-onset seizures associated with TSC in patients 2 years of age and older (UK) 'Orphan medication' for adjunct treatment of focal-onset seizures associated with TSC in patients 2 years of age and older (EU)	French (2016) [42]	Phase 3, multicentre, double-blind, placebo-controlled RCT 8-week baseline, 18-week core phase (6-week dose escalation, 12-week maintenance), taper or continuation in OLE EVE dose: adjusted on the basis of patient characteristics to achieve target concentration of 3–7 ng/mL (low-exposure) or 9–15 ng/mL (high-exposure)	Multinational	Age 2–65 years; confirmed diagnosis of TSC; treatment-resistant seizures; ≥ 16 seizures during 8-week baseline period; no continuous 21-day seizure-free period during baseline; stable treatment with 1–3 concomitant ASMs for ≥ 12 weeks pre-randomisation	366	Median change from baseline in seizure frequency and response rate (≥ 50% reduction in seizure frequency) compared with placebo during 12-week maintenance period

ASM antiseizure medication, *CBD* cannabidiol, *CDD* cyclin-dependent kinase-like 5 deficiency disorder, *DS* Dravet syndrome, *EEG* electroencephalogram, *ES* epilepsy syndrome, *EVE* everolimus, FFA fenfluramine, *GNX* ganaxolone, *LGS* Lennox–Gastaut syndrome, *NA* not applicable, *OLE* open-label extension, *RCT* randomised controlled trial, *SOT* soticlestat, *TSC* tuberous sclerosis complex

[a]Randomised

[b]Base equivalent doses of 0.69 mg/kg/d and 0.17 mg/kg/d, max. 25.9 mg/day

Table 2 Efficacy outcomes for RCTs of cannabidiol, fenfluramine and soticlestat in Dravet syndrome

ASM	Study	Intervention group	Median % reduction in convulsive seizure frequency[a]	Estimated median % difference versus PLB (95% CI)	*p* value	≥ 50% reduction in convulsive seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	≥ 25% reduction in convulsive seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	≥ 75% reduction in convulsive seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	100% reduction in convulsive seizure frequency (%)	*p* value
CBD	Devinsky (2017) [27]	CBD 20 mg	38.9	22.8 (5.4 to 41.1)	0.01	43.0	2.00 (0.93 to 4.30)	0.08		2.10 (1.01 to 4.35)	0.05		2.21 (0.82 to 5.95)	0.11		0.08
		PLB	13.3			27.9									0.0	
FFA	Lagae (2019) [47]	FFA 0.7 mg	74.9	62.3 (47.7 to 72.8)	< 0.0001	68.0	15.0 (4.5 to 50.0)	< 0.0001	90.0	22.3 (6.0 to 84.0)	< 0.0001	50.0	55.1 (6.0 to 526.0)	0.0005	8.0	
		FFA 0.2 mg	42.3	32.4 (6.2 to 51.3)	0.0209	38.0	4.8 (1.5 to 15.0)	0.0091	67.0	4.1 (2.0 to 11.0)	0.0041	23.0	12.0 (1.4 to 102.0)	0.0229	8.0	
		PLB	19.2			12.0			35.0			2.0			0.0	
SOT	Hahn (2022) [79]	SOT	33.76	45.95 (19.99 to 68.51)	0.0007	30.8						19.2			3.8	
		PLB	(7.04)			0.0						0.0			0.0	

ASM antiseizure medication, *CBD* cannabidiol, *CI* confidence interval, *FFA* fenfluramine, *PLB* placebo, *SOT* soticlestat

[a]Results for full randomised treatment period (dose escalation plus maintenance phase)

Fig. 2 Primary efficacy outcomes for pivotal trials of cannabidiol, fenfluramine, soticlestat and everolimus in (**A**) Lennox–Gastaut syndrome, (**B**) Dravet syndrome and (**C**) tuberous sclerosis. *CBD* cannabidiol, *EVE* everolimus, *FFA* fenfluramine, *PLB* placebo, *SOT* soticlestat, *TSC* tuberous sclerosis complex

Table 3 Efficacy outcomes for RCTs of cannabidiol, fenfluramine and soticlestat in Lennox–Gastaut syndrome

ASM	Study	Intervention group	Median % reduction in drop seizure frequency[a]	Estimated median % difference versus PLB (95% CI)	*p* value	≥ 50% reduction in drop seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	≥ 25% reduction in drop seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	≥ 75% reduction in drop seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	100% reduction in drop seizure frequency (%)
CBD	Devinsky (2018) [28]	CBD 20 mg	41.9	21.6 (6.7 to 34.8)	0.005	39.0	3.85 (1.75 to 8.47)	< 0.001				25.0	12.33 (2.76 to 55.13)		0.0
		CBD 10 mg	37.2	19.2 (7.7 to 31.2)	0.002	36.0	3.27 (1.47 to 7.26)	0.003				11.0	4.55 (0.93 to 22.22)		0.0
		PLB	17.2			14.0						3.0			0.0
	Thiele (2018) [29]	CBD 20 mg	43.9	17.2 (4.1 to 30.3)	0.0135	44.0	2.57 (1.33 to 4.97)	0.0043	64.0	2.3 (1.24 to 4.26)	0.0081	20.0	2.75 (1.07 to 7.01)	0.0273	0.0
		PLB	21.8			24.0			44.0			8.0			0.0
FFA	Knupp (2022) [48]	FFA 0.7 mg	26.5	19.9 (8.7 to 31.0)	0.001	25.0		0.02			0.007			NS	0.0
		FFA 0.2 mg	14.2	10.5 (−4.0 to 25.0)	0.09	28.0		0.005			0.04			NS	1.0
		PLB	7.6			10.0									1.0
SOT	Hahn (2022) [79]	SOT		14.8 (−4.6 to 34.5)	0.1279	16.3						11.6			0.0
		PLB				13.3						0.0			0.0

ASM antiseizure medication, *CBD* cannabidiol, *CI* confidence interval, *FFA* fenfluramine, *PLB* placebo, *SOT* soticlestat

[a]Results for full randomised treatment period (dose escalation plus maintenance phase)

Table 4 Efficacy outcomes for RCTs of cannabidiol and everolimus in tuberous sclerosis complex

ASM	Study	Intervention group	Median % reduction in TSC-associated seizure frequency	Estimated median % difference versus PLB (95% CI)	*p* value	≥ 50% reduction in TSC-associated seizure frequency (%)	Odds ratio versus PLB (95% CI)	*p* value	≥ 25% reduction in TSC-associated seizure frequency (%)	≥ 75% reduction in TSC-associated seizure frequency (%)	100% reduction in TSC-associated seizure frequency (%)
CBD	Thiele (2021) [30]	CBD 50 mg[a,b]	47.5	28.5 (11.9 to 42.0)	0.002	40.0		0.02		16.9	0.0
		CBD 25 mg	48.6	30.1 (13.9 to 43.3)	< 0.001	36.0		0.07			1.0
		PLB	26.5			22.0				0.0	0.0
EVE	French (2016) [42]	EVE 9–15 ng/mL[c]	39.6		< 0.0001	40.0	3.9 (2.1 to 7.3)	< 0.0001	70.0		3.8
		EVE 3–7 ng/mL	29.3		0.0028	28.2	2.2 (1.2 to 4.2)	0.0077	52.1		5.1
		PLB	14.9			15.1			37.8		0.8

ASM antiseizure medication, *CBD* cannabidiol, *CI* confidence interval, *EVE* everolimus, *PLB* placebo

[a]Results for full randomised treatment period (dose escalation plus maintenance phase)

[b]All countable focal motor seizures with or without loss of awareness, focal seizures evolving to bilateral motor seizures and generalised seizures (tonic–clonic, tonic, clonic and atonic)

[c]Results for core (maintenance) treatment period

Fig. 3 Frequency (%) of treatment-emergent adverse events reported in ≥ 10% of participants in randomised, placebo-controlled trials of cannabidiol, everolimus, fenfluramine and ganaxolone. *CBD* cannabidiol, *EVE* everolimus, *FFA* fenfluramine, *GNX* ganaxolone, *PLB* placebo

higher response rate (≥ 50% reduction in seizure frequency from baseline) with EVE compared with placebo, the two primary endpoints. Participants with high-exposure EVE (9–15 ng/mL) had a 39.6% (95% CI 35.0–48.7%) median decrease in seizure frequency compared with a 14.9% (95% CI 0.1–21.7%) decrease with placebo ($p < 0.0001$). Low-exposure EVE (3–7 ng/mL) was associated with a median decrease in seizure frequency of 29.3% (95% CI 18.8–41.9%; $p = 0.0028$ versus placebo). Response rates were 15.1% (95% CI 9.2–22.8%) with placebo, 40.0% (95% CI 31.5–49.0%) for high-exposure EVE ($p < 0.0001$ versus placebo) and 28.2% (95% CI 20.3–37.3%) for low-exposure EVE ($p = 0.0077$ versus placebo) (Table 4).

3.1.3 Fenfluramine

Fenfluramine (FFA) is an amfetamine derivative originally indicated as an anti-obesity drug and recently repurposed as an ASM for seizures in LGS and DS, having previously been withdrawn from the market owing to concerns over an association with pulmonary hypertension and valvular heart disease. The antiseizure effects are thought to depend primarily on dual interactions at serotonin and sigma-1 receptors, resulting in enhancement of GABAergic inhibitory signalling and suppression of sigma-1-mediated excitatory signalling [43]. FFA is licensed in the USA for the treatment of seizures in DS and LGS from the age of 2 years [44]. In the EU and UK, it is approved as an adjunct treatment for the same indications [45, 46]. In DS, FFA was associated with a median decrease in monthly convulsive seizure frequency of 74.9% at a dose of 0.7 mg/kg and 42.3% at a dose of 0.2 mg/kg compared with 19.2% for placebo in the pivotal RCT [47]. The median percentage difference between FFA and placebo was 62.3 (95% CI 47.7–72.8; $p < 0.0001$) for the higher FFA dose and 32.4 (95% CI 6.2–52.3; $p = 0.0209$) for the lower dose (Table 2). In the pivotal RCT in LGS [48], median drop seizure frequency decreased by 26.5% and 14.2% with FFA 0.7 mg/kg and 0.2 mg/kg, respectively, compared with 7.6% with placebo. The estimated median percentage difference between FFA and placebo was 19.9 (95% CI 8.7–31.0; $p = 0.001$) with the higher dose but did not reach statistical significance with the lower dose (10.5; 95% CI 4.0–25.0; $p = 0.09$) (Table 3).

3.1.4 Ganaxolone

Ganaxolone (GNX), a synthetic analogue of the neurosteroid allopregnanolone, is a positive allosteric modulator of the $GABA_A$ receptor complex [49, 50]. It was approved in 2022 in the USA for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) from the age of 2 years [51]. In the EU it was granted 'orphan medicine' status for seizures in CDD in 2019 [52]. In a phase 3 RCT in children and young people with CDD [53], GNX resulted in a median 30.7% decrease in major motor seizure frequency per 28 d compared with 6.9% with placebo ($p = 0.0036$). The estimated median difference between GNX and placebo was 27.1% (95% CI

9.6–47.9%). GNX has also been investigated as a treatment for seizures associated with TSC. However, preliminary results of a phase 3 RCT (TrustTSC) announced in October 2024 showed no difference between GNX and placebo in median percent change from baseline in 28 d TSC-associated seizure frequency (GNX 19.7%; placebo 10.2%; $p = 0.09$) [54].

3.2 Medications Under Investigation for Paediatric Epilepsy

3.2.1 Carisbamate

Carisbamate (CBM) is an alkyl-carbamate which is thought to act via inhibition of voltage-gated sodium channels and modification of calcium ion signalling [55, 56]. CBM is a US Food and Drug Administration (FDA)-designated 'orphan drug' for seizures in LGS [57] and infantile spasms [58]. A placebo-controlled RCT of adjunct CBM in children and adults with LGS (the LGS DISCOVER trial; NCT05219617) is currently in progress, with the first stage due for completion in June 2025 and an open-label extension to follow in June 2026.

3.2.2 Cenobamate

Cenobamate (CNB) is voltage-gated sodium channel inhibitor of the persistent sodium current, and a positive allosteric modulator of $GABA_A$ receptors at a binding site distinct from benzodiazepines [59]. It was licensed in the USA in 2019, and the EU and UK in 2021, as an adjunct therapy for focal-onset seizures in adults [60–62] following two placebo-controlled RCTs in which CNB was associated with dose-dependent percentage decreases in focal-onset seizure frequency of up to 56%, and ≥ 50% response rates, up to 64% at maintenance doses [63, 64]. Small, open-label studies have suggested CNB may be a safe and effective treatment for paediatric focal and focal-onset seizures [65, 66], paediatric drug-resistant epilepsy [67], seizures in SCN8A-associated DEEs [18] and TSC-associated epilepsy [68] with response rates of 60%, 37.5%, 66% and up to 59%, respectively. RCTs in children and adolescents with focal seizures (NCT05067634) and adolescents and adults with primary generalised tonic–clonic seizures (NCT03678753) are currently in progress (Table 4).

3.2.3 Neural Regeneration Peptide 2945

Neural regeneration peptide 2945 (NRP2945) is a synthetic, 11-mer peptidomimetic which has demonstrated neuroregenerative, anti-inflammatory and antiseizure effects in preclinical trials [69, 70]. Subsequent to a phase 1 tolerability study in healthy volunteers, and a small phase 2a proof-of-concept study in genetic generalised absence epilepsy [71], NRP2945 was designated an orphan drug for the treatment of seizures in LGS, predicated on evidence suggesting restoration of thalamic inhibitory function may be possible [72]. Phase 1/2 studies in LGS and juvenile myoclonic epilepsy are planned [73].

3.2.4 Soticlestat

Soticlestat (SOT) is a novel small-molecule inhibitor of the cytochrome P450 (CYP) enzyme cholesterol 24-hydroxylase (CYP46A1/CH24H) responsible for catalysing the conversion of cholesterol to 24S-hydroxycholesterol [74]. 'Ectopic' expression of CYP46A1 in reactive astrocytes and microglia due to neurodegeneration or brain insults has been implicated in decreased cholesterol in the plasma membrane leading to increased extracellular glutamate and a corresponding increase in excitatory glutamatergic activity [75]. SOT acts to maintain plasma membrane cholesterol by inhibition of CYP46A1-mediated conversion to 24-hydroxycholesterol [76]. SOT was granted orphan drug status in the USA in 2017 [77] for the treatment of seizures in DS and LGS, and in the EU in 2021 for seizures associated with LGS [78]. In the ELEKTRA phase 2 RCT [79], adjunct SOT was associated with a statistically significant decrease compared with placebo in convulsive seizure frequency in DS (median difference 45.95%; 95% CI 19.99–68.51%; $p = 0.0007$), but not in drop seizure frequency in LGS (median difference 14.81%; 95% CI −4.62 to 34.47%; $p = 0.1279$). In preliminary results from the subsequent phase 3 SKYLINE and SKYWAY studies, the differences between SOT and placebo for convulsive seizures in DS and drop seizures in LGS, respectively, did not reach statistical significance [80]. Publication of the full efficacy findings from these studies is still pending. In addition to the studies in DS and LGS, ARCADE, a recent open-label pilot study in individuals with epilepsy associated with chromosome 15q duplication (Dup15q) syndrome or with CDD [81] suggested SOT may be effective for motor seizures in CDD but was associated with an increase in motor seizures in individuals with Dup15q syndrome. Total seizure frequency decreased from baseline in both groups. Re-evaluation of the efficacy findings for the studies in DS and LGS resulted in development of SOT being discontinued in January 2025 [82].

3.2.5 STK-001

STK-001 is an antisense oligonucleotide therapy in development for the treatment of seizures in DS and has been granted orphan drug status for this indication by the US FDA and European Medicines Agency (EMA). STK-001

is an example of a disease modifying agent; it is a messenger RNA (mRNA) modulator, specifically designed to upregulate expression of the sodium channel Nav1.1 protein through enhancement of productive *SCN1A* mRNA [83]. Data for 19 children and adolescents (aged 2–18 years) with DS from two completed multicentre, phase 1/2a studies showed decreases from baseline in convulsive seizure frequency 3 months and 6 months following the last dose were 43% and 57%, respectively, for those receiving a single 70mg dose, and 85% and 74%, respectively, for those who received two or three doses [83]. An open-label extension study (NCT04740476) is currently in progress [83]. A further open-label study (NCT04442295) is investigating the safety and pharmacokinetics of a single dose and multiple ascending doses.

3.3 Other Recent Developments in ASM therapy

3.3.1 Expansion of Approval for Brivaracetam for Focal-Onset Seizures

Brivaracetam (BRV), is a racetam derivative closely related to the established ASM levetiracetam, with selective high affinity for the synaptic vesicle protein 2A (SV2A) [84, 85]. Inhibition of excitatory neurotransmitter release resulting from this interaction is thought to be responsible for the antiseizure effects, but the precise antiseizure MOA is unknown [84, 85]. BRV received initial marketing approval for the treatment of focal-onset seizures in individuals aged 16 years and over in 2016. This has now been expanded to children and infants from the age of 1 month in the USA (since 2021) [84], and children from the age of 2 years in the UK/EU as an adjunct therapy (since 2022) [86, 87]. Three 12-week, dose-ranging, double-blind, randomised, placebo-controlled trials (RCTs) in adults and older adolescents (≥ 16 years) were conducted [88–90] in which the primary efficacy outcome was percent reduction in baseline-adjusted focal-onset seizure frequency compared with placebo. In the first study reported by Ryvlin et al. [88], BRV 100 mg/day was associated with a statistically significant greater reduction in focal-onset seizure frequency (diff. versus placebo 11.7%; $p = 0.037$), but the difference between placebo and BRV doses of 20 mg/day and 50 mg/day BRV did not reach statistical significance (diff. versus placebo 6.8%, $p = 0.239$; and 6.5%, $p = 0.261$, respectively). In the study by Biton et al. [89], BRV was superior to placebo at the 50 mg/day dose (diff. 12.8%; $p = 0.025$), but not at doses of 5 mg/day (diff. −0.9%; $p = 0.885$) or 20 mg/day (diff. 4.1%; $p = 0.492$). Finally, Klein et al. [90] reported that BRV was superior to placebo at doses of 100 mg/day (diff. versus placebo 22.8%; 95% CI 13.3–31.2; $p < 0.001$) and 200 mg/day (diff. versus placebo 23.2%; 95% CI 13.8–31.6; $p < 0.001$). Subsequent open-label studies have provided efficacy data for paediatric samples. In a phase 2a study in 80 children aged from 1 month to < 16 years [91], the ≥ 50% response rate for all seizure types was 21.3% for the total sample, and 29.7% for those with a history of focal seizures and no primary generalised seizures. In a subgroup of children with a history of focal seizures, the response rate was 20.0% for those aged < 4 years, and 36.4% for those aged 4 to < 16 years. Data from a phase 3 study in 247 children between the ages of 1 month and < 17 years [92] showed a median decrease in 28-days adjusted focal seizure frequency of 62.9% and a ≥ 50% response rate for all seizure types of 50.9% in those aged 2 years and older. In those aged under 2 years, the median decrease in 28-days focal seizure frequency was 96.9% and the ≥ 50% response rate for all seizure types was 68.2%. No statistical analyses were reported for these results.

3.3.2 Expansion of Approval of Perampanel for Focal-Onset Seizures

Perampanel (PER) is a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist, first approved in 2012 as an adjunct treatment for focal-onset seizures with or without secondary generalisation in adults and children from the age of 12 years [93–95]. Licensing was later expanded to include adjunct treatment of primary generalised tonic–clonic seizures from the age of 12 years in the USA [93] and 7 years in the UK/EU [94, 95]. The FDA approved PER as monotherapy for focal-onset seizures in 2017 [93], and a further update in 2018 extended licensed use to children from the age of 4 years [93–95]. Efficacy for focal-onset seizures was demonstrated in three RCTs [96–98]. Pooled analysis of data from these studies [99] showed median decreases in focal-onset seizure frequency of 23.3%, 28.8% and 27.2% for adjunct PER doses of 4 mg, 8 mg and 12 mg, respectively, compared with 12.8% for placebo (all $p < 0.05$ versus placebo). Response rates (> 50% decrease in seizure frequency) were 28.5%, 35.3% and 35.0%, respectively, for the three PER doses, compared with 19.3% for placebo (all $p < 0.05$ versus placebo). A single RCT in which percent change from baseline in primary generalised tonic–clonic seizures was the primary efficacy outcome [100] reported a decrease of 76.5% with PER compared with 38.4% with placebo ($p < 0.0001$). The response rate (≥ 50% decrease in tonic–clonic seizure frequency) was 64.2% for PER and 39.5% for placebo ($p = 0.0019$). The recently reported phase 4 PROVE study has provided data on long-term retention, efficacy, safety and tolerability during routine clinical care [101, 102]. Separate analyses of data for participants aged < 4 years, 4 to < 12 years, 12 to < 18 years, and ≥ 18 years, showed median percent decreases in seizure frequency during months 10–12 of 95.8%, 79.3% and 70.8%, respectively, for the 4 to < 12 years, 12 to < 18 years and ≥ 18 years groups (no data were available for the < 4 years group). In the paediatric age groups,

the decrease in seizure frequency in early treatment (months 1–3) was 33.3% for those aged < 4 years and 26.0% for those aged 4 to < 12 years. Overall, 24-month retention rates were 35.7%, 42.0%, 53.5% and 47.8%, respectively [101, 102]. No statistical analyses were reported for these outcomes. Adverse events, commonly abnormal behaviour, irritability, aggression and seizures, were cited as a primary reason for discontinuation in 19.5%, 20.2%, 22.4% and 25.8% of enrollees in the < 4 years, 4 to < 12 years, 12 to < 18 years and ≥ 18 years age groups, respectively. Inadequate therapeutic effect was a primary reason for discontinuation in 22.0%, 16.3%, 14.6% and 12.0%, respectively. However, for the majority of participants, PER was introduced as a third- or fourth-line treatment, suggesting a high degree of refractory epilepsy [101, 102].

3.3.3 FDA Approval of Stiripentol for Seizures Associated with DS

Stiripentol (STP), an α-ethylene alcohol, acts via positive allosteric modulation of ligand-gated $GABA_A$ receptors, potentiation of GABA neurotransmission and inhibition of voltage-gated sodium and calcium channels [103, 104]. The antiseizure properties have been recognised since the late 1970s [104], and the drug has been licensed in the EU since 2007 for the treatment of generalised tonic–clonic seizures in DS in combination with clobazam and valproate [105]. FDA approval was granted in 2018 for the treatment of seizures in DS from the age of 6 months in combination with clobazam [106]. The two pivotal RCTs were published in the early 2000s [107, 108]. In brief, these studies reported median decreases in generalised tonic–clonic or clonic seizures of 91% (versus 5% with placebo; $p < 0.0001$) [107] and 81% (versus 9% with placebo; $p = 0.0094$) [106], respectively, and response rates (> 50% decrease in generalised tonic–clonic or clonic seizure frequency) of 71% [107] and 67% [106], respectively.

3.3.4 Vigabatrin as Preventive Therapy for Seizures in Tuberous Sclerosis Complex

Vigabatrin (VGB) is a second generation ASM licensed as an adjunct treatment for focal-onset seizures with or without secondary generalisation and as monotherapy in the treatment of infantile spasms (West syndrome) [109–111]. In recent years, research on new therapies for seizures in TSC has focused on preventive interventions with the aim of disrupting the progression of detectable early signs of epileptiform activity on EEG and subsequent electrographic seizures to clinical epilepsy. A mixed RCT and open-label trial conducted in Europe and Australia as part of the long-term prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy-tuberous sclerosis complex (EPISTOP) project [112], compared the effect of intervention with VGB after electrographic or clinical seizure onset, with preventive treatment with VGB initiated immediately on detection of epileptiform EEG activity before detection of seizures in infants aged ≤ 4 months with TSC. Preventive treatment was associated with a longer time interval to the first clinical seizure than conventional reactive treatment coinciding with the first detected electrographic or clinical seizure. In the RCT cohort, the median time to a first clinical seizure was 364 d (95% CI 223–535 days) in infants who received preventive VGB compared with 124 d (95% CI 33–149 days) in those who received conventional treatment. In the open-label cohort, the median time to a first clinical seizure was 426 d (95% CI 258–628 days) with preventive VGB, compared with 106 days (95% CI 11–149 days) with conventional treatment. At follow-up at 24 months, pooled analysis of data from the RCT and open-label trial showed a statistically significant reduced risk of development of clinical seizures (OR = 0.21; $p = 0.032$), drug-resistant epilepsy (OR = 0.23; $p = 0.022$) and infantile spasms (OR = 0; $p < 0.001$) in those who received preventive treatment compared with conventional treatment. Despite these promising findings, evaluation of neurodevelopmental outcomes showed no statistically significant differences between preventive and conventional treatment groups in the incidence of neurodevelopmental delay (32% versus 18% in pooled analysis) or risk of autistic features (25% versus 41% in pooled analysis) at 24 months [112]. The subsequent phase 2b PREVeNT trial [113] reported a similar lack of improvement in neurocognitive outcomes at 24 months with early vigabatrin treatment, and no statistically significant difference between early vigabatrin and placebo groups in the incidence of focal seizures and drug-resistant epilepsy, although as with the EPISTOP trial, the incidence of infantile spasms was lower and time to onset of infantile spasms was greater in the vigabatrin group.

3.3.5 Rescue Medicine for Seizure Clusters

Midazolam (MDZ) nasal spray was approved in 2019 as acute treatment for seizure clusters and acute repetitive seizures in children from the age of 12 years [114]. A nasal spray formulation of diazepam (DZP) followed in 2020 with approval for use in children from the age of 6 years [115]. In a phase 3 RCT [116] and a long-term open-label extension [117] in children and adults who underwent outpatient treatment with MDZ nasal spray for focal or generalised seizure clusters, the rate of seizure termination within 10 min with no recurrence within the subsequent 10 min to 6 h was statistically higher with MDZ than placebo ($p = 0.0109$). There

are no RCT data specifically for the nasal spray formulation of DZP, but exploratory analysis of paediatric data from a long-term, phase 3, open-label safety study [118] using a proxy measure of effectiveness found that, of 1634 treated seizure clusters, 186 (11.4%) required a second dose to be administered within 24 h of the first dose, suggesting that in the majority of cases, seizure clusters resolved with a single application. Because these acute treatments have not been compared in comparative trials with the well-established treatment of buccal midazolam [119, 120], it is not yet possible to state whether they represent advances in treatment.

4 Neurostimulation and Surgical Interventions

Vagus nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS), are palliative therapies for medically refractory seizures, which can be considered (usually in addition to existing ASMs) if a patient is not considered a viable candidate for resective surgery. VNS, DBS and RNS are approved for focal-onset seizures in adults, but only VNS is approved for use in children (from the age of 4 years). There are limited paediatric data for DBS and RNS.

Of particular recent interest are responsive 'closed-loop' systems, of which autostimulation VNS and RNS are examples, which increase stimulation on detection of physiological or electrographic markers of seizure onset, and external devices such as transcutaneous VNS (tVNS) and transcranial direct current stimulation (tDCS), which circumvent the need for invasive surgery.

4.1 Responsive Neurostimulation (RNS)

RNS involves intracranial implantation of the electrical pulse generator and a combination of strip or depth electrodes at the stimulation targets of interest, usually corresponding to the seizure onset zone. Separate electrodes record electrographic signals or deliver the stimuli when electrical activity exceeds an algorithmically determined threshold characteristic of that associated with seizure onset. Stimulation parameters and activation thresholds are calculated individually by prior analysis of each patient's historic electrocorticography data. Long-term, ambulatory EEG data recorded by RNS devices might also be used to localise seizure foci to guide future resective surgery where feasible.

Response rates (≥ 50% reduction in seizure frequency) for RNS based on published data for children and adolescents are between 65 and 80% [121–123], and the median decrease in seizure frequency is around 75% [121, 124]. Case reports have described high percentage decreases in seizure frequency in typically drug-resistant paediatric epilepsy syndromes [125] such as LGS [126] and TSC [127], including, in some cases, where previous surgical interventions had failed. Serious AEs (infection, haemorrhage, stroke and device malfunction) occur at a similar rate to that reported in adults [128], with around 8% reporting infection associated with device implantation [121].

Currently, there are very limited prospective data for paediatric RNS [123]. Prospective open-label studies in individuals with paediatric drug-resistant focal epilepsy (NCT04839601), paediatric idiopathic generalised epilepsy (NCT05147571) and LGS (NCT05339126) are in progress.

4.2 Autostimulation VNS

In contrast to standard VNS in which stimulation follows a repeating, predefined pattern, autostimulation (closed-loop) VNS is designed to abort incipient seizures by amplification of stimulation in response to preictal cardiac changes [129]. A retrospective comparison of closed-loop and standard VNS for paediatric drug-resistant epilepsy showed no difference in response rates at 1 year but a trend towards greater response with closed-loop VNS after 2 years [130]. A chart review reporting outcomes in 55 children and young adults with predominantly generalised seizures [131] found a mean reduction in seizure frequency at 12 months of 56.0% with closed-loop VNS devices, compared with 41.6% for open-loop devices. In a larger cohort of 71 children and adolescents with LGS [132], the response rate (> 50% decrease in seizures) with closed-loop VNS at 6, 12 and 24 months was 55.0%, 67.7% and 65.0%, respectively. While these results suggest similar efficacy for closed-loop VNS as for open-loop systems, and no new safety concerns were reported, more data are needed, specifically for paediatric epilepsy, to clarify whether closed-loop VNS might offer greater benefit than open-loop systems in long-term treatment, perhaps for specific situations.

4.3 Transcutaneous VNS (tVNS)

tVNS is a newer technology which does not require device implantation. Instead, electrical pulses are delivered externally to the auricular branch of the vagus nerve via VNS devices placed in one or both ears (taVNS), or alternatively to the cervical path of the vagus nerve via a handheld VNS device (tcVNS). Data for tVNS in epilepsy, in particular for tcVNS, remain limited, especially for paediatric patients. Controlled studies of taVNS in mixed age samples have reported statistically significant decreases in seizure frequency from baseline, and when compared with sham VNS at 6–12 months [133–135]. In these studies, decreases in monthly seizure frequency of up to 51% [134] were reported; however, paediatric data were not separately analysed. An uncontrolled prospective study in an exclusively paediatric sample with focal or generalised seizures [136] reported a mean decrease in seizure frequency of 54% after 16 weeks ($p < 0.05$) that remained

unchanged at 24 weeks. Response rate (> 50% reduction in seizure frequency) was also 54% from week 16.

While tVNS may be more acceptable to young patients and their carers, and is likely to present lower practical barriers to adoption than implanted devices, there are currently no tVNS devices specifically adapted for use in children, and optimal stimulation parameters and treatment protocols are yet to be established [137].

4.4 Transcranial Direct Current Stimulation (tDCS)

tDCS is a non-invasive system in which neurostimulation is delivered via scalp placement of electrodes through which a continuous weak electrical current is passed diffusely through the skull and into the cortex. tDCS has shown efficacy for seizures in drug-resistant paediatric focal [138, 139] and generalised epilepsies, including LGS [140]. In an early study in children with focal-onset seizures [139], tDCS was associated with a statistically significant decrease in epileptogenic EEG discharge frequency immediately following a single 20-min treatment, and at 24 h and 48 h post-treatment. A statistically significant decrease in seizures was also detected 4 weeks after treatment but was considered to be clinically negligible. A later study in 22 children with LGS [140] reported a statistically significant decrease in seizure frequency with active tDCS compared with sham tDCS at each day during the 5 consecutive day treatment period ($p = 0.004$ to $p < 0.001$), and at intervals of 1, 2, 3 (all $p < 0.001$) and 4 weeks ($p = 0.002$) after treatment. The reduction in seizure frequency from baseline at weeks 1, 2, 3 and 4 following treatment was 89.75%, 81.16%, 72.39% and 55.96%, respectively. A subsequent open-label, single-blind study in 24 children and adolescents with LGS [141] reported a median decrease in all seizures of 68% during the first 2 weeks following ten 30-min tDCS sessions conducted on consecutive weekdays over a 2-week period ($p = 0.002$). However, median seizure frequency was increased with respect to baseline at 1 month (+62%) and 2 months post-treatment (+109%). Most recently, a randomised, double-blind, sham-controlled study in 18 children and adolescents with drug-resistant focal epilepsy [138] reported a statistically significant reduction in seizure duration from baseline in the active tDCS group ($p = 0.024$) following completion of 5 consecutive days of 20-min daily stimulation. However, the frequencies of clinical seizures and spike-and-wave discharges on EEG showed no statistically significant change from baseline, or statistically significant difference between active and sham tDCS groups, either on completion of the treatment phase or at follow-up 1 month post-treatment.

4.5 Laser Interstitial Thermal Therapy (LITT)

LITT is a less invasive surgical alternative to craniotomy. It has been deployed in ablative surgery targeting, for example, deep brain epileptic foci [142] or cortical tubers in TSC, and in disconnection procedures such as CC in LGS. The technique involves stereotactically placed fibreoptic catheters through which thermal energy is directed at the target tissue. A review of published case series in paediatric epilepsy patients reported Engel class I outcomes (freedom from disabling seizures) in 57.5% [143] of cases with various epilepsy aetiologies and seizure foci; efficacy has been reported for seizures associated with hypothalamic hamartomas [144], cortical dysplasia [145] and tuberous sclerosis [146, 147], among others [144, 148–150], in some cases in individuals who had undergone prior resective surgery [145, 146]. In one recent study, however, previous epilepsy surgery was associated with the failure of LITT to improve seizure outcomes [151]. In comparison with open CC, LITT has achieved comparable rates of favourable Engel outcomes in paediatric generalised epilepsies [152, 153]. However, in individuals with other surgical targets for LITT, lower rates of seizure freedom at 1 year post-surgery have been reported compared with open surgery [154, 155]. There is also some evidence that the therapeutic effect of LITT may diminish over time [156]. Advantages of LITT over other surgical options are related to its less invasive nature, shorter hospital stay, lower blood loss and fewer surgical complications, albeit with typically longer time in surgery [152–154, 157]. Owing to its relative precision, LITT may be a more viable alternative to open craniotomy where the seizure focus is adjacent to eloquent cortex or associated with a lesion situated within eloquent cortex [150, 158], reducing the risk of surrounding tissue damage and long-term adverse neurocognitive outcomes. The aim in such cases is to remove or destroy the lesion tissue only, while preserving function of the eloquent tissue. If this is achieved, it should be possible to avoid additional functional deficits.

4.6 Combined Strategies

Combining neurostimulation modalities (dual-device neurostimulation), or initiating neurostimulation after surgical resection or corpus callosotomy, has shown promise in difficult-to-treat cases where, for example, VNS or surgical interventions alone have not achieved substantial improvement in seizures. A small observational study [159] in a mixed age sample of 11 individuals with refractory generalised epilepsy, 10 with LGS, reported double the number of responders when DBS devices were used in conjunction with previously implanted VNS devices compared with VNS only. Among those who had not responded to VNS, 4/7 had > 50% reduction in seizure frequency with combined VNS-DBS. The four individuals who had previously responded to VNS had a > 50% additional decrease in seizure frequency

with combined VNS-DBS. While these findings suggest combined VNS-DBS may represent an effective new treatment strategy in some individuals, the findings should be interpreted with some caution given the small sample size and lack of comparison with a DBS treatment only group. Notable decreases in seizure frequency have also been achieved with combined VNS-RNS. The findings from a retrospective chart review in seven paediatric patients [160] showed that all seven had decreases of 75–99% in the frequency of disabling seizures according to electroclinical criteria, and 4/7 had a > 50% decrease based on self-reports and/or caregiver reports. These apparent successes, albeit in a very small number of individuals so far, suggest further investigation is warranted. Similarly, limited case reports and case series in mixed age samples have suggested VNS after initial CC may achieve enhanced control of residual seizures, and in some cases seizure freedom, in difficult-to-treat epilepsies including LGS and West syndrome [161, 162], but these data require further confirmation.

5 Therapeutic Strategies in Early Development

5.1 Focused Ultrasound (FUS)

FUS involves precision transfer of energy in the form of ultrasonic waves capable of reaching deep tissue targets [163, 164]. Ultrasound has existing therapeutic medical applications in the treatment of nephrolithiasis (kidney stones), uterine fibroids, prostate disorders and pain associated with bone cancer. More recently, transcranial ultrasound has been investigated as a possible treatment for various neurological and psychiatric disorders, for example Alzheimer disease, Parkinson disease and obsessive-compulsive disorder [164]. In epilepsy, three potential applications are the subject of pre-clinical and clinical research: high-intensity (> 100 watts/cm^2) focused ultrasound (HIFU) for ablative procedures; low-intensity (< 100 watts/cm^2) focused ultrasound (LIFU) for neuromodulation; and low-to-moderate frequency ultrasound as a means of breaching the blood–brain barrier to allow ingress of ASM molecules or otherwise promote greater focal ASM uptake [163, 164]. Clinical efficacy data for the use of focused ultrasound in epilepsy are still very limited. A recent systematic review by Khaboushan et al. [163] identified seven case reports and small case series involving a total of 20 individuals who underwent either ultrasonic ablation ($n = 8$) or modulation ($n = 12$) procedures. Of those undergoing ablation, four were reported to be seizure-free for ≥ 12 months, with some decrease in seizure frequency reported in the other four. Modulation resulted in a decrease in seizure frequency in seven individuals and 12-month seizure freedom in one other individual [163]. Adverse effects included headache, dizziness, nausea and vomiting. Temporary neurological deficits in the form of memory impairments were reported in two individuals. Currently, there are no data on the use of focused ultrasound in children with epilepsy.

5.2 Genetic and Related Therapies

The underlying cause of epilepsy is unknown in around 75% of individuals [165]. Recent advances in genetic sequencing suggest that genetic aetiologies might account for many of these cases [165], which implies that advances in gene therapy may have particular relevance for potential future treatment strategies. Genetic and related technologies under investigation include, among others; antisense oligonucleotide targeting of messenger RNA transcription; viral vector therapies, for example to deliver gene supplementation in epilepsies associated with LOF mutations; and gene editing technologies such as CRISPR-Cas9 in which the Cas9 enzyme is recruited to sever double-stranded DNA at a specified location, or precipitate activation or repression of target genes adjacent to a guide RNA binding site [166, 167]. The current stage of development of RNA modulation and gene modifying techniques and their application in genetic epilepsies has been reviewed by Walker [166] and Cai et al. [167]. Most research in this area remains at the pre-clinical phase; however, clinical studies investigating the use of antisense oligonucleotides to increase expression of the sodium channel subunit NaV1.1 in DS (for example, STK-001 – see above) and viral vector delivery of MECP2 gene supplementation in Rett syndrome are in progress [166, 167]. While barriers remain for the feasible clinical application of many of the techniques currently being investigated, there is the potential for genetic therapies to transform future models of epilepsy treatment, either by correcting or compensating for the underlying genetic causes of seizures, or by enabling precision ASM therapy, simultaneously enhancing antiseizure efficacy while minimising adverse effects.

6 Conclusions

ASMs remain the cornerstone of treatment for seizures for most children and young people with epilepsy. In the last 5–10 years, new ASMs, including CBD, FFA and GNX, have been approved for paediatric use, including for seizures in typically difficult-to-treat developmental and epileptic encephalopathies such as LGS, DS, TSC and CDD. In addition, several potential ASMs, including some with novel antiseizure MOAs, are at various stages of development. Seizure freedom is the ultimate goal of ASM therapy but remains elusive in up to one-third of cases despite the introduction of new ASMs. While few individuals achieved freedom from drop seizures and/

or major convulsive seizures in the RCTs of CBD and FFA in LGS, DS and TSC, substantial decreases in seizure frequency and notable 50% response rates were reported. New neurostimulation paradigms, in particular, responsive systems such as RNS and autostimulation VNS, may offer improved seizure control in medically refractory cases, but there are currently little published data on the use of these technologies in children with epilepsy. Non-invasive systems, such as tVNS and tDCS, offer practical advantages over standard VNS, DBS or RNS, most notably the avoidance of surgery to implant and maintain the devices. These considerations are likely to be of particular relevance for younger patients and their families. However, paediatric data are very limited. In general, optimal treatment parameters and potential biomarkers for responses to neurostimulation systems in children with epilepsy are yet to be firmly established. Furthermore, there are very few data on the relative efficacies of VNS, DBS, RNS and tDCS, or between these interventions and other second-line therapies, such as the ketogenic diet, on which to base clinical decisions. Combining neurostimulation modalities, for example VNS and DBS, has shown promise in small samples, but more data, in particular on long-term safety and efficacy, are needed.

Diagnostic procedures and seizure prediction have been influenced and improved with advances in machine learning and device technology and these approaches can be expected to be refined further in the future. Of particular recent interest is the combination of research in genetic epilepsies and its application in personalised treatment approaches to seizure management. While individualised therapy is not yet a proposition in most cases, increased understanding of genetic aetiologies in epilepsy and the prospect of further advances in this field, in parallel with novel ASM development and drug repurposing for seizures, suggest these might become increasingly valuable strategies in the future.

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Conflict of interest R.F.M.C. was a principal investigator in a GW Pharma sponsored trial of cannabidiol for the treatment of Lennox–Gastaut syndrome. He has received honoraria from, has provided paid consultation for, and has awarded educational grants from Jazz Pharmaceuticals and UCB. F.M.C.B. is an Editorial Board member of *Pediatric Drugs*. F.M.C.B. was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. F.M.C.B. and M.J.V. have no competing interests to declare that are relevant to the topics covered in this article.

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