REVIEW ARTICLE

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Challenges and advances in the treatment of drug-resistant epilepsy

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Abstract

Introduction and Objective. Drug-resistant epilepsy (DRE) is a serious therapeutic challenge, as approximately 30% of epileptic patients do not achieve sustained seizure control despite using at least two appropriately selected antiepileptic drugs. Although pharmacotherapy is the basis of treatment, some patients need new solutions. The aim of this study is to present current therapeutic options for DRE, as well as promising drugs being tested in clinical trials.

Review Methods. The review article was compiled mainly on the basis of the PubMed database and the ClinicalTrials.gov website. Most of the articles included were published between 2018–2025.

Brief description of the state of knowledge. In recent years, new therapeutic approaches have been investigated. Among a variety of treatment strategies studied, add-on therapy, dietary approaches including ketogenic diet (KD) and continuously improved neurostimulation techniques (DBS, VNS, RNS) are interventions of high clinical significance. Add-on therapy involves introducing additional drugs to the treatment regimen in order to reduce the number and severity of seizures, improve quality of life, prolong seizure-free periods and increase safety. Moreover, numerous international clinical trials on drugs and other treatments for DRE are being conducted, the results of which in the near future may possibly become available to a wider group of patients.

Summary. Due to drug resistance in the treatment of epilepsy, there is a constant need to search for new, complex therapeutic methods that ensure better control of the disease.

Key words

seizures, epilepsy, drug resistant epilepsy

INTRODUCTION

Epilepsy poses one of the most frequent neurological disorders globally, affecting about 70 million people at all ages [1]. Seizures are caused by inappropriate synchronous neuronal firing in a specific brain region or throughout the entire brain, resulting in temporary changes in muscular tone or movement, perceptions, behaviours, or states of consciousness. The causes of epileptic seizures vary depending, among other things, on the age of the patient. In children, genetics, cortical development abnormalities and prenatal damage are the main causes, while in adults brain infections, injuries and tumours play significant roles. A separate group consists of the elderly, in whom epilepsy results from neurodegenerative disorders, brain tumours and head traumas. Epilepsy can be classified according to the cause (idiopathic, symptomatic, cryptogenic) and type of seizures. Based on the type of seizures, the simplest classification includes generalized and focal seizures, with focal seizures being predominant [2].

The current treatment for epilepsy is mainly pharmacotherapy. Despite the availability of numerous drugs tailored to specific types of seizures, approximately one-third of patients do not respond sufficiently to treatment, developing drug-resistant epilepsy (DRE), referred as failure in sustained control of seizures despite proper administration of at least two antiepileptic drugs [3]. In order to achieve disease control, these patients may require complex and individually tailored therapy by means of different techniques, with the focus on add-on therapy, dietary interventions, neuromodulation techniques, and emerging medications under clinical trials. The presented scoping review also takes into account severe types of childhood-onset DRE. The review – unlike previous reviews – integrates the latest findings from 2023–2025, such as the results from phase III clinical trials of new pharmaceuticals, innovative cellular therapies, as well as revised guidelines for severe childhood-onset epilepsies. Additionally presented is an interdisciplinary viewpoint by integrating pharmacotherapy, nutritional approaches, neuromodulation, and translational treatments, thereby providing extensive resources.

Pharmacotherapy. Anti-seizure medications (ASMs) are one type of epilepsy treatment which offers symptom managemen in the form of seizure suppression. Nonetheless, one-third of epileptic patients do not respond to ASMs or other therapies, resulting in DRE [1].

Recurrent seizures are caused by excessive nervous system hyperexcitability. While the pharmacology of currently marketed ASMs is not fully understood, they aim to restore the balance of neuronal excitation and inhibition. The most significant mechanisms of AMSs activity include

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Table 1. Antiseizure drugs used as supplementary treatment in focal epilepsy, approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) with summary of molecular targets [1, 5, 6].

Drug generation	ASM	Voltage-gated Na^+ channels	LVA Ca^{2+} channels	HVA Ca^{2+} channels	Voltage-gated K^+ channels	GABA-A receptors	GABA Turnover	Glutamate receptors	Carbonic anhydrase	Synaptic vesicle protein 2A
First	Sodium valproate	++	++				++			
	Carbamazepine	+++								
Second	Gabapentin	+		++			+			
	Lamotrigine	+++		++						
	Oxcarbazepine	+++								
	Levetiracetam			+		+				+++
	Topiramate	++		++	+	++		++	+	
	Pregabalin			++						
	Vigabatrin						+++			
	Tiagabine						+++			
	Zonisamide	+++	++						+	
	Felbamate	++		++		++		++		
Third	Eslicarbazepine acetate	+++								
	Perampanel							+++		
	Lacosamide	+++							+	
	Rufinamide	+++								
	Retigabine				+++					
	Cenobamate	+++				++				

ASM, antiseizure medication; GABA, gamma-aminobutyric acid; HVA, high voltage-activated; LVA, low voltage-activated

regulation of voltage-gated ion channels, increase of gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission, and weakening of glutamate-mediated excitatory neurotransmission [4]. Table 1 highlights the main pharmacological targets of ASMs in focal epilepsy management [1, 5, 6]. Zhang et al. [1] compared three generations of ASMs approved as adjunctive therapy in focal epilepsy, with focus on their safety and efficacy. They found that all ASMs had a substantially higher ≥50% response rate when compared with placebo. Cenobamate (CNB), in comparison to placebo, demonstrated the greatest likelihood of attaining seizure independence. Moreover, CNB was found to improve seizure freedom throughout the maintenance phase (21% vs 1%; $p<0.0001$). The researchers also revealed that CNB showed the greatest efficacy of all three generation ASMs, which may result from its dual complementary mechanism of action affecting both excitatory and inhibitory neurotransmission.

The research also investigated patient retention rate, which indicates treatment efficacy and tolerability. The second- and third-generation ASMs demonstrated higher patient retention at the study's conclusion compared to placebo, indicating greater acceptance of the newer ASMs. Interestingly, levetiracetam (LEV), when compared with other drugs, had a reduced risk of incidence for total treatment-emergent adverse events (AEs) [1].

Research by Deng et al. to assess ASMs as add-on therapy in drug-resistant focal epilepsy, showed tiagabine (TGB) showed the most optimal therapeutic result, followed by topiramate (TPM), oxcarbazepine (OXC) and LEV [3].

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are severe forms of childhood-onset epilepsy, characterized by drug-resistant seizures as well as developmental and cognitive impairments. Seizures occur throughout life and seizure freedom is rare in both syndromes, patients therefore receive different ASMs over the years [7].

An International DS Consensus released recommendations for managing DS, recommending valproate (VPA) as the first-line ASM, while additional ASMs can be used simultaneously as first- or second-line choices. As far as LGS is concerned, experts propose VPA as the first-line ASM regimen, followed by lamotrigine (LTG). Other ASMs are approved as additional lines of treatment [8]. Figure 1 [9] illustrates lines of therapy for DS treatment. Pharmacological treatment for newly diagnosed or suspected LGS patients is demonstrated in Figure 2 [8]. Fenfluramine (FFA) is now approved in the US for managing seizures associated with DS and LGS in children ≥2 years old, as well as an add-on medication in the EU, UK, and Japan. It reduces seizures via activating serotonin and positively modulating sigma-1 receptors. FFA has shown short- and long-term seizure effectiveness in DS and LGS patients, with a special utility in lowering generalized tonic–clonic seizure (GTCS) frequency from baseline [8]. Benzodiazepines, such as clonazepam (CZP) or clobazam (CLB), however, should be used with caution because of a risk of tolerance, reliance, and cognitive/

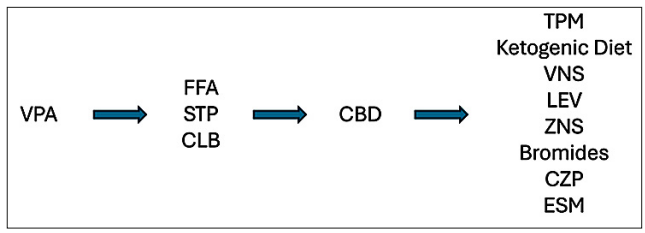

Figure 1. Lines of therapy for DS treatment. CBD, cannabidiol; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; FFA, fenfluramine; LEV, levetiracetam; STP, stiripentol; TPM, topiramate; VNS, vagus nerve stimulation; VPA, sodium valproate; ZNS, zonisamide

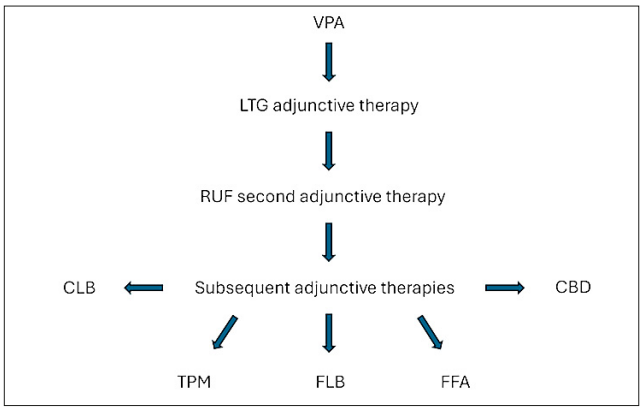

Figure 2. Pharmacological treatment for newly diagnosed or suspected LGS patients. CBD, cannabidiol; CLB, clobazam; FFA, fenfluramine; FLB, felbamate; LTG, lamotrigine; RUF, rufinamide; TPM, topiramate; VPA, sodium valproate

behavioural AEs, such as sustained absence seizures or cluster seizures. Importantly, high-dose benzodiazepines may cause drowsiness and increase the risk of tonic seizures [7]. EMA licensed cannabidiol (CBD) is an adjuvant treatment for LGS and DS seizures in patients aged ≥2 years, in combination with CLB, while in the US, CBD is approved for LGS and DS treatment in patients aged ≥1 years. CBD is connected to long-term reductions in both drop and total seizure frequency maintenance [10].

In a Phase 4 retrospective chart review study [11], 92 patients with LGS and 15 patients with DS aged ≥2 years were treated for ≥3 months in order to evaluate the effectiveness and tolerability of CBD without CLB. During the 12-month study, median seizure reductions in LGS patients ranged from 6.2%-20.9% at each time point. Additionally, 30% of patients who remained on therapy after 12 months reported a > 50% seizures reduction. After 12 months of therapy, the average number of seizure-free days in LGS patients increased by 1.7 days, compared to baseline [11].

Ethosuximide is approved as a part of absence seizures treatment and should be implemented with an ASM dedicated to generalized tonic-clonic and tonic/atonic seizures, since it is ineffective for these types [7].

Dietary interventions. The complexity of DRE underscores the need for ongoing exploration of novel therapeutic strategies. Among the established approaches for managing drug-resistant seizures, the ketogenic diet (KD) has gained increasing attention. Although its popularity has grown over time, the precise mechanisms underlying its efficacy remain incompletely understood [12, 13].

Ketogenic dietary therapies (KDT) are nutritional interventions characterized by a high fat content, adequate protein intake, and markedly reduced carbohydrate consumption. This macronutrient composition lowers the tone the lower esophageal sphincter, delays gastric emptying, and facilitates intestinal transit. Patients are maintained in a state of chronic ketosis while allowing for normal growth and development. As a non-pharmacological intervention, KDT has evolved into several variants, including the classical ketogenic diet (cKD) – with a fat:protein:carbohydrate ratio of 4:1:8 – the less restrictive Atkins diet, and regimens emphasizing medium-chain triglyceride intake [13, 14]. The therapeutic effects of KDs are thought to result, at least in part, from ketone bodies generated in significant quantities during ketosis. These metabolites have been shown to possess potential anti-inflammatory properties, enhance gut microbiota diversity, with beneficial effects on the gut–brain axis, and reduce reactive oxygen species (ROS) levels. The principal ketone bodies produced during ketosis are acetone, beta-hydroxybutyrate, and acetoacetate [14].

Most meta-analyses and randomized controlled trials evaluating KDs in neurological disorders have focused on paediatric populations. One of the few studies involving adults published in 2025 [14], examined the feasibility and efficacy of a modified Atkins diet (MAD) in patients with psychogenic non-epileptic seizures (PNES). PNES are characterized by subjective disturbances of consciousness and involuntary movements not associated with epileptic activity. This randomized trial, conducted at the National Institute of Neurology and Neurosurgery'"Manuel Velasco Suárez' (INNN-MVS) in Mexico, aimed to determine whether a 6-week MAD could be successfully implemented in adults with PNES, and whether it could maintain ketosis. Outcomes were compared with those from a low-calorie diet (CD), focusing on seizure frequency and selected mental health parameters. The study enrolled 17 outpatients with documented PNES, aged ≥17 years (mean age ~28 years), who were randomized to MAD (n = 12) or CD (n = 5, including the only male participant). The MAD group consumed a diet low in carbohydrates, whereas the CD group followed a regimen rich in complex carbohydrates with a standard macronutrient distribution. Outcomes included the Montgomery-Åsberg Depression Rating Scale (MADRS), the Hamilton Anxiety Rating Scale (HAM-A), daily PNES frequency, urinalysis, and metabolic parameters such as lipid profile.

Results demonstrated a significant reduction in seizure frequency in the MAD group ($p = 0.04$; Hedges' $g = 0.5$), along with improvements in depressive and anxiety symptoms (MADRS: $p = 0.005$; HAM-A; $p = 0.02$) and a mean weight loss of 2.5 kg ($p < 0.001$). AEs were mild and required no intervention, indicating good tolerability. These findings suggest that MAD may substantially reduce PNES frequency; however, due to the small sample size and other limitations, larger, well-controlled trials are needed for confirmation [14].

A larger and more demographically diverse study was published in 2023 by the All India Institute of Medical Sciences (AIIMS) in New Delhi, India, in collaboration with neurologists and clinical dietitians [15]. The trial investigated whether MAD combined with standard drug therapy (SDT) would be more effective in reducing DRE seizures than SDT alone. The prospective, randomized controlled trial enrolled 160 patients (80 adults, 80 adolescents) aged 10–55 years with DRE. Inclusion criteria required ≥2 seizures per month despite treatment with at least 3 ASMs at maximal tolerated doses, and no dietary therapy that might confound outcomes. Participants were randomized to receive MAD plus SDT (intervention group) or SDT alone (control group). The primary endpoint was a >50% reduction in seizure frequency at 6 months; secondary outcomes included quality of life (QoL) measures and AEs. The >50% seizure reduction was achieved by 26.2% of MAD patients versus 2.5% in the control group ($p < 0.001$), with complete seizure remission in 5% of MAD participants. QoL improved, and AEs were generally mild and infrequent. Adjunctive use of MAD in adolescents and adults with DRE resulted in clinically meaningful improvements compared with pharmacotherapy

alone, with additional psychological benefits. The diet was well tolerated and easier to implement than the cKD. Its macronutrient distribution was approximately 65% fat, 25% protein, and 10% carbohydrates, with no caloric or protein restriction [15].

In summary, dietary therapies such as MAD offer an effective and well-tolerated adjunctive option for managing DRE in adolescents and adults. They may serve as practical alternatives to the cKD, particularly for patients ineligible for or unwilling to undergo surgical intervention. Further research is warranted to identify neurophysiological and genetic biomarkers predictive of response, which could facilitate earlier initiation and individualized risk–benefit assessment.

KDs are emerging as a valuable complement to pharmacological treatment in adults with chronic epilepsy and refractory status epilepticus. Current evidence supports their feasibility, tolerability, and efficacy in adults, although more randomized controlled trials are needed. Most potential AEs are mild or manageable, but strategies to improve dietary adherence remain essential [16].

Neurostimulation. Neurostimulation represents an established therapeutic modality involving the application of electrical stimulation to specific structures of the nervous system, with the primary aim of attenuating epileptiform activity [17]. The principal therapeutic goal is the reduction of seizure frequency, most commonly assessed using the 50% responder rate-defined as the proportion of individuals who achieve at least a 50% reduction in baseline seizure frequency [18]. Among the various neuromodulatory strategies investigated to date, 3 modalities have been most extensively studied in the treatment of DRE: open-loop vagus nerve stimulation (VNS), open-loop deep brain stimulation (DBS), and closed-loop responsive neurostimulation (RNS) [17]. These are the only neuromodulatory interventions that have been evaluated in adequately powered, double-blind, randomized controlled trials, and have received regulatory approval for the treatment of focal DRE [18].

Each modality utilizes an implanted neurostimulator and electrodes, but differs in its mechanism of action, stimulation paradigm, and anatomical targets. Neurostimulation constitutes a particularly important therapeutic option for patients with DRE who are not candidates for resective epilepsy surgery. This includes individuals with epileptogenic foci located within eloquent cortical areas, or cases in which seizure onset zones cannot be localized despite comprehensive non-invasive multimodal assessment or invasive electrophysiological monitoring [19]. Table 2 presents a comparison of different neuromodulation techniques [17, 19].

Table 2. Comparison of neurostimulation techniques [17, 19]

Feature	VNS	DBS	RNS
Stimulation type	Open-loop (continuous)	Open-loop (continuous)	Closed-loop
Implant location	Chest (stimulator) + vagus nerve electrode	Chest (stimulator) + thalamic electrodes (ANT/CM)	Cranial implant + intracranial electrodes
Effectiveness	≥50% seizure reduction in ~50% of patients	11-76% reduction; strong data from SANTE trial	~44% at 1 year, 53% at 2 years; 68% of children ≥50% reduction
Common side effects	Voice changes, cough, implant site infection	Mood/memory issues, infection, implant site pain	Infection (~12% long-term); ~50% require device removal

ANT, anterior nucleus of the thalamus; CM, centromedian nucleus of the thalamus; DBS, deep brain stimulation; RNS, responsive neurostimulation; SANTE, Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy trial; VNS, vagus nerve stimulation

VNS. VNS is a neuromodulatory therapy that involves delivering intermittent electrical impulses to the vagus nerve, typically via a surgically-implanted pulse generator placed in the chest wall, with leads connected to the left cervical vagus nerve [20]. Since 1997, when the Food and Drug Administration (FDA) approved VNS for adults with focal epilepsy, its use has expanded to children as young as 4 years and, off-label, even to infants under one year, with comparable outcomes [21]. The efficacy of this method has been extensively evaluated in both adult and paediatric populations. In 2021 meta-analysis by Jain and Arya, which included 99 studies and 3,474 pediatric patients, found that 56.4% of children achieved a ≥50% reduction in seizure frequency-comparable to results observed in adult cohorts [22].

Beyond seizure reduction, long-term follow-up studies have demonstrated that VNS is associated with improvements in QoL, including enhanced mood, alertness, and social functioning [23]. Nevertheless, surgical complications, although relatively uncommon, have been reported. In a large observational series with over 2 decades of follow-up, complications occurred in approximately 9% of patients. These included implant site infections, haematomas, and vocal cord palsy [24].

DBS. DBS involves the implantation of electrodes into specific thalamic nuclei, most commonly the anterior nucleus (ANT) or centromedian nucleus (CM), to modulate seizure activity in patients with DRE. A pulse generator implanted in the chest delivers programmed electrical impulses to the targeted thalamic nucleus. Although various targets have been explored (e.g., subthalamic nucleus, pulvinar), the ANT and CM nuclei of the thalamus are currently considered the most promising sites for DBS in epilepsy treatment [25].

ANT-DBS has shown particular efficacy in managing focal and secondarily generalized seizures [26], while CM-DBS is especially effective in patients with generalized epilepsy and LGS [27]. The strongest evidence supporting the efficacy of ANT-DBS comes from the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial, a large, multicentre, double-blind, randomized controlled study, in which the majority of adult DRE patients achieved a seizure reduction greater than 50% [28]. Additional clinical studies have reported encouraging-albeit variable-responses, with seizure reductions ranging from 11.5%-76%. Furthermore, ANT-DBS has demonstrated potential neuroprotective effects by reducing neuronal loss, suppressing local immune responses, inducing molecular changes in hippocampal neurons, and modulating glucose metabolism in the brain [26].

Although the majority of DBS studies focus on adults, evidence is also emerging in paediatric populations. A recent systematic review identified 52 children who received ANT or CM-DBS, among whom ≥50% seizure frequency reduction was observed in 9 of 14 patients following ANT-DBS, and 31 of 38 patients following CM-DBS [29].

The most common serious device-related complication is implant site infection. While rarely leading to meningitis or intracranial infection, hardware removal is often required. Additionally, up to 20% of patients report implant site pain. Mood disturbances and memory impairment were the most frequently reported stimulation-related AEs in the SANTE trial [28].

RNS. RNS is a closed-loop neuromodulatory therapy for DRE. The implanted device, connected to intracranial electrodes, continuously monitors brain activity and delivers targeted stimulation upon detecting epileptiform patterns. Unlike DBS or VNS, RNS responds only to abnormal activity, reducing interference with normal function and making it suitable for seizures from eloquent cortical areas [30].

In a pivotal randomized controlled trial by Morrell et al. [31], patients in the stimulation group experienced a significantly greater reduction in seizure frequency, compared to controls (37.9% vs. 17.3%). Continued follow-up demonstrated progressive improvement, with a mean seizure reduction of 44% at one year and 53% at 2 years [31].

Paediatric data, although more limited, are also encouraging. Panov et al. [32] reported that among 22 children followed one year post-implantation, 68.2% experienced a ≥50% seizure reduction, and 11 children (50%) had seizure reductions exceeding 75% [32].

Ongoing research aims to broaden the indications for RNS [33]. The FDA-approved NAUTILUS trial is currently investigating the efficacy of responsive thalamic stimulation in patients aged 12 and older with idiopathic generalized epilepsy, including those experiencing tonic-clonic, myoclonic, or absence seizures, who have not responded to at least two ASMs [33].

In terms of safety, long-term data from a 9-year prospective study indicated a 4% risk of infection per surgical procedure, with at least one infection occurring in 12% of patients. Approximately half of these cases required device removal [34].

PROMISING CLINICAL TRIALS

NRTX-1001. This multicentre, single arm, open label clinical trial [35] aims to evaluate the safety and preliminary effectiveness of a single dose of inhibitory nerve cells, known as interneurons (NRTX-1001), into both temporal lobes of people with drug-resistant bilateral mesial temporal lobe epilepsy (MTLE). NRTX-1001 originates from a human stem cell line that has been transformed into high-purity inhibitory interneurons that generate GABA. This compound is supposed to prevent the development and progression of seizures.

Patients enrolled in the study will receive a single stereotactic CT- or MRI-guided intracerebral infusion of human interneurons into both temporal lobe areas of the brain. Safety, tolerability, and impacts on epilepsy symptoms will be evaluated at about quarterly intervals over a period of 2 years following the administration of NRTX-1001. Serious adverse effects (SAE), as well as change in frequency of clinical seizures, will be assessed 12 months after treatment [35]. Preliminary findings from the Phase 1/2 research revealed a significant median seizure decrease and absence of cognitive impairment. Several patients had substantial improvements in cognition assessment scores.

Due to promising data from ongoing phase 1/2 studies, it was decided to conduct a Phase 3 EPIC study. Positive trial findings might result in providing the first disease-modifying therapy for epilepsy [36].

Azetukalner (XEN1101). Nerve excitability depends on several factors, including the work of ion channels. A promising therapeutic target for epilepsy are potassium channels, thus an innovative drug, a potent Kv7 potassium channel opener – azetukalner – is currently under investigation for neurological disorders such as epilepsy and major depressive disorder.

Xenon's Phase 3 epilepsy programme consists of 2 current identical clinical studies, X-TOLE2 and X-TOLE3. These trials include adults with focal onset seizures (FOS) who receive up to 3 ASMs, yet still experience seizures. The aims of the studies are to assess the clinical effectiveness, safety, and tolerability of azetukalner when used as a supplementary treatment for FOS. Patients are randomized into 3 groups: an experimental group receiving 25 mg of XEN1101 per day, an experimental group receiving 15 mg of XEN1101 per day, and a placebo group receiving placebo taken once-daily. The baseline period lasts up to 9.5 weeks in order to evaluate seizures frequency, followed by 12-week double blind period (DBP). After completing the DBP, eligible patients can enroll in an open-label extension (OLE) trial for up to 3 years as a continuation of treatment. The primary efficacy endpoint measures the median percentage change in the number of focal seizures monthly, from the baseline to DBP, comparing XEN1101 with placebo [37].

Zorevunersen. Zorevunersen is a novel medication under study for DS, which is a genetic epileptic syndrome, frequently resistant to antiepileptic drugs. Levels of the sodium channel Nav1.1 protein are reduced in DS patients. Therefore, zorevunersen aims to elevate the levels of functional SCN1A messenger RNA (mRNA), hence boosting the production of the sodium channel Nav1.1 protein.

EMPEROR [38] is a global, multicentre, randomized, double-blind, sham-controlled, parallel group Phase 3 trial to evaluate the safety, tolerability and efficacy of zorevunersen in patients with DS. The study is comprised of 2 groups: experimental and sham. Experimental group patients receive 2 loading doses of 70 mg zorevunersen, followed by 2 maintenance doses of 45 mg for a period of 52 weeks, while sham group patients undergo a lumbar puncture with CSF withdrawal. The primary outcome measure is the change in the frequency of motor seizures. Additional endpoints concern clinical condition, cognitive and behavioural changes, and QoL. The trial is currently recruiting, with a completion date set for 2027 [38, 39].

Cannabinoids. Another clinical trial is CAN-DRE [40] which will explore the effects of cannabinoids on seizure reduction in adults and children (from 2-years-old) with DRE. Effectiveness of cannabinoids in reducing seizure frequency will be measured as the number of seizures monthly, from baseline to maintenance. The second aim of the research is to determine if CBD works better as an isolation or as a CBD-enriched cannabis herbal extract (CHE). Moreover, throughout the trial, AEs and dose limiting toxicities will be reported. Participants will be divided into 3 groups: placebo group, receiving tetrahydrocannabinol [THC]-free and CBD-

free oil, CBD Isolate, receiving oil containing 100 mg of CBD and 0 mg of THC per 1 mL, and CBD-CHE, receiving 100 mg of CBD and 3 mg of THC per 1 mL. The study is promising, as some small, open-label, uncontrolled trials have demonstrated that CBD-enriched CHE decreased the frequency of seizures [40].

Soticlestat. A new drug being tested is soticlestat, a selective inhibitor of the enzyme cholesterol 24-hydroxylase (CYP46A1). This enzyme, primarily found in the brain, converts cholesterol into a compound known as 24S-hydroxycholesterol (24HC). Soticlestat inhibits CYP46A1, lowering the levels of 24HC in the brain, which is supposed to help reduce neuronal excitability and possibly manage seizures [41].

ENDYMION 2 [42] is the phase 3, open-label, multicentre extension of earlier studies. Participants were drawn from 2 previous double-blind, randomized phase 3 trials of soticlestat as adjunctive treatment in DS (SKYLINE trial) and LGS (SKYWAY trial). Both studies evaluated the efficacy and safety of soticlestat compared to placebo, with co-administration of regular antiepileptic drugs. Patients who completed one of these studies and met the requirements were eligible for an open-label extension phase (ENDYMION 2) to continue receiving the active medication. The study plan assumes a 2-week dose titration period, based on body weight, followed by a period of dose maintenance for about 4 years, and ultimately a gradual dose reduction within one week, and treatment completion. The primary goal is a long-term evaluation of safety and tolerability in paediatric and young adult patients, as well as palatability in the paediatric population. The study completion date is predicted to be in 2026 [42].

Moreover, a number of multicentre clinical trials on neuromodulation in DRE are being conducted. These trials are registered and have official indications in the treatment of DRE; however, ongoing studies are aimed at, for instance, comparison of different techniques, long-term safety investigation, evaluation of utility in specific patients, and improvement of the stimulation effect [43].

CONCLUSIONS

The study enhances the current literature by investigating both established therapies and the latest advancements, focusing on new strategies presently under investigation. Owing to the inclusion of various treatment techniques, the intention of the current review was to support the development of more individualized approaches to DRE treatment. Although pharmacotherapy remains the cornerstone of epilepsy treatment, approximately one-third of patients develop DRE. Newer ASMs demonstrate improved safety and efficacy profiles, with CNB showing the highest rates of seizure remission. Dietary interventions, particularly KD and its modifications, serve as valuable adjunctive therapies, contributing to seizure reduction and improvements in QoL, although their long-term effectiveness is often limited by adherence challenges. Neurostimulation techniques, including VNS, DBS and RNS, provide important therapeutic alternatives for patients in whom resective surgery is not feasible. Of particular note, RNS enables adaptive, real-time modulation of epileptogenic activity, allowing targeted intervention at the onset of seizure activity.

Emerging treatment strategies, such as gene therapies, neuronal transplantation, ion channel modulators, and cannabinoids, show promise for disease modification and may significantly expand therapeutic options for severe epileptic syndromes in the future. Despite these advances, managing DRE remains a major clinical challenge.

Key limitations include the lack of predictive biomarkers for therapy response, difficulties in maintaining long-term dietary interventions, the risk of complications associated with neurostimulation techniques, and the high costs of novel pharmacological and biological therapies.

Moving forward, it will be crucial to develop personalized treatment strategies, enhance access to innovative therapies, and implement multimodal interventions that integrate pharmacological, non-pharmacological, and experimental approaches to maximize patient outcomes.

REFERENCES

1. Zhang H, Ou Z, Zhang E, et al. Efficacy and safety of add-on antiseizure medications for focal epilepsy: A network meta-analysis. Epilepsia Open. 2024;9(4):1550–1564. https://doi.org/10.1002/epi4.12997
2. Falco-Walter J. Epilepsy-Definition, Classification, Pathophysiology, and Epidemiology. Semin Neurol. 2020;40(6):617–623. https://doi.org/10.1055/s-0040-1718719
3. Deng NJ, Li XY, Zhang ZX, et al. Effectiveness and safety of single anti-seizure medication as adjunctive therapy for drug-resistant focal epilepsy based on network meta-analysis. Front Pharmacol. 2025;16(April):1–22. https://doi.org/10.3389/fphar.2025.1500475
4. Sills GJ, Rogawski MA. Mechanisms of action of currently used antiseizure drugs. Neuropharmacology. 2020;168:107966. https://doi.org/10.1016/j.neuropharm.2020.107966
5. Rugg-Gunn YFJ, Stapley HB. Epilepsy 2019. From Bench To Bedside: A Practical Guide To Epilepsy. 17th ed. Oxford, 2019.
6. Sankar R, Ferrari L. Clarification of the Mechanism of Action of Cenobamate (P9–9.012). Neurology. 2025;104(7_Supplement_1). https://doi.org/10.1212/WNL.0000000000208526
7. Auvin S, Arzimanoglou A, Falip M, et al. Refining management strategies for Lennox–Gastaut syndrome: Updated algorithms and practical approaches. Epilepsia Open. 2025;10(1):85–106. https://doi.org/10.1002/epi4.13075
8. Wirrell EC, Lagae L, Scheffer IE, et al. Practical considerations for the use of fenfluramine to manage patients with Dravet syndrome or Lennox–Gastaut syndrome in clinical practice. Epilepsia Open. 2024;9(5):1643–1657. https://doi.org/10.1002/epi4.12998
9. Dravet Syndrome Foundation. The Diagnosis and Treatment of Dravet Syndrome. https://dravetfoundation.org/hcp-resources/diagnosis-and-treatment. (access: 2025.08.20).
10. Wechsler RT, Burdette DE, Gidal BE, et al. Consensus panel recommendations for the optimization of EPIDIOLEX® treatment for seizures associated with Lennox–Gastaut syndrome, Dravet syndrome, and tuberous sclerosis complex. Epilepsia Open. 2024;9(5):1632–1642. https://doi.org/10.1002/epi4.12956
11. Nabbout R, Arzimanoglou A, Auvin S, et al. Retrospective chart review study of use of cannabidiol (CBD) independent of concomitant clobazam use in patients with Lennox-Gastaut syndrome or Dravet syndrome. Seizure. 2023;110(January):78–85. https://doi.org/10.1016/j.seizure.2023.05.003
12. Su TY, Hung PL, Chen C, et al. Graph theory-based electroencephalographic connectivity and its association with ketogenic diet effectiveness in epileptic children. Nutrients. 2021;13(7). https://doi.org/10.3390/nu13072186
13. Nassar MF, Shata MO, Awadallah SM, et al. Impact of L-carnitine supplementation on gastric emptying and bowel function in pediatric ketogenic diet therapy: a clinical trial. Sci Rep. 2024;14(1):1–8. https://doi.org/10.1038/s41598-024-78779-4
14. Janssen-Aguilar R, la Portilla JG de, Martínez-Juárez IE, et al. The impact of ketogenic diet on the frequency of psychogenic non-epileptic seizures (PNES): A feasibility randomized pilot study. Epilepsia Open. 2025;10(2):602–608. https://doi.org/10.1002/epi4.13131
15. Manral M, Dwivedi R, Gulati S, et al. Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy: A

Randomized Controlled Trial. Neurology. 2023;100(13):E1376–E1385. https://doi.org/10.1212/WNL.0000000000206776
16. Williams TJ, Cervenka MC. The role for ketogenic diets in epilepsy and status epilepticus in adults. Clin Neurophysiol Pract. 2017;2:154–160. https://doi.org/10.1016/j.cnp.2017.06.001
17. Touma L, Dansereau B, Chan AY, et al. Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis from the ILAE Surgical Therapies Commission. Epilepsia. 2022;63(6):1314–1329. https://doi.org/10.1111/epi.17243
18. Ryvlin P, Rheims S, Hirsch LJ, et al. Neuromodulation in epilepsy: state-of-the-art approved therapies. Lancet Neurol. 2021;20(12):1038–1047. https://doi.org/10.1016/S1474-4422(21)00300-8
19. Gouveia FV, Warsi NM, Suresh H, et al. Neurostimulation treatments for epilepsy: Deep brain stimulation, responsive neurostimulation and vagus nerve stimulation. Neurotherapeutics. 2024;21(3). https://doi.org/10.1016/j.neurot.2023.e00308
20. Fan JJ, Shan W, Wu JP, et al. Research progress of vagus nerve stimulation in the treatment of epilepsy. CNS Neurosci Ther. 2019;25(11):1222–1228. https://doi.org/10.1111/cns.13209
21. Muthiah N, Joseph B, Varga G, et al. Investigation of the effectiveness of vagus nerve stimulation for pediatric drug-resistant epilepsies secondary to nonaccidental trauma. Child's Nerv Syst. 2023;39(5):1201–1206. https://doi.org/10.1007/s00381-022-05817-9
22. Jain P, Arya R. Vagus Nerve Stimulation and Seizure Outcomes in Pediatric Refractory Epilepsy. Neurology. 2021;96(22):1041–1051. https://doi.org/10.1212/WNL.0000000000012030
23. Englot DJ, Hassnain KH, Rolston JD, et al. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav. 2017;66:4–9. https://doi.org/10.1016/j.yebeh.2016.10.005
24. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr. 2016;18(1):97–104. https://doi.org/10.3171/2016.1.PEDS15534
25. Yan H, Wang X, Zhang X, et al. Deep brain stimulation for patients with refractory epilepsy: nuclei selection and surgical outcome. Front Neurol. 2023;14. https://doi.org/10.3389/fneur.2023.1169105
26. Bouwens van der Vlis TAM, Schijns OEMG, Schaper FLWVJ, et al. Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. Neurosurg Rev. 2019;42(2):287–296. https://doi.org/10.1007/s10143-017-0941-x
27. Warsi NM, Yan H, Suresh H, et al. The anterior and centromedian thalamus: Anatomy, function, and dysfunction in epilepsy. Epilepsy Res. 2022;182:106913. https://doi.org/10.1016/j.eplepsyres.2022.106913
28. Salanova V, Sperling MR, Gross RE, et al. The SANTÉ study at 10 years of follow- up: Effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021;62(6):1306–1317. https://doi.org/10.1111/epi.16895
29. Khan M, Paktiawal J, Piper RJ, et al. Intracranial neuromodulation with deep brain stimulation and responsive neurostimulation in children with drug-resistant epilepsy: a systematic review. J Neurosurg Pediatr. 2022;29(2):208–217. https://doi.org/10.3171/2021.8.PEDS21201
30. Wong S, Mani R, Danish S. Comparison and Selection of Current Implantable Anti-Epileptic Devices. Neurotherapeutics. 2019;16(2):369–380. https://doi.org/10.1007/s13311-019-00727-2
31. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77(13):1295–1304. https://doi.org/10.1212/WNL.0b013e3182302056
32. Panov F, Ganaha S, Haskell J, et al. Safety of responsive neurostimulation in pediatric patients with medically refractory epilepsy. J Neurosurg Pediatr. 2020;26(5):525–532. https://doi.org/10.3171/2020.5.PEDS20118
33. Haneef Z, Skrehot HC. Neurostimulation in generalized epilepsy: A systematic review and meta-analysis. Epilepsia. 2023;64(4):811–820. https://doi.org/10.1111/epi.17524
34. Nair DR, Laxer KD, Weber PB, et al. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology. 2020;95(9). https://doi.org/10.1212/WNL.0000000000010154
35. ClinicalTrials.gov. A Phase 1/2 Study of NRTX-1001 Neuronal Cell Therapy in Drug-Resistant Bilateral Mesial Temporal Lobe Epilepsy (MTLE). https://www.clinicaltrials.gov/study/NCT06422923?term=Drug Resistant Epilepsy treatment&sort=StudyFirstPostDate&page=5&rank=50. (access: 2025.08.27).
36. Neurona Therapeutics. Neurona Unveils Phase 3 EPIC Study for NRTX-1001 Cell Therapy in Epilepsy. https://www.neuronatherapeutics.com/news/press-releases/022025. (access: 2025.08.25).
37. Xenon Pharmaceuticals Inc. Azetukalner for Focal Onset Seizures. https://www.xenon-pharma.com/product-pipeline/azetukalner-fos. (access: 2025.08.27).
38. ClinicalTrials.gov. A Double-blind Study Evaluating the Efficacy, Safety, and Tolerability of Zorevunersen in Patients With Dravet Syndrome. https://www.clinicaltrials.gov/study/NCT06872125?term=stk-001&rank=1. (access: 2025.08.27).
39. Chilcott E, Díaz JA, Bertram C, et al. Genetic therapeutic advancements for Dravet Syndrome. Epilepsy Behav. 2022;132:108741. https://doi.org/10.1016/j.yebeh.2022.108741
40. ClinicalTrials.gov. CANnabinoids for Drug Resistant Epilepsy (DRE) in Adults and Children (CAN-DRE). https://www.clinicaltrials.gov/study/NCT07023744?term=Drug Resistant Epilepsy treatment&sort=StudyFirstPostDate&rank=4#more-information. (access: 2025.08.27).
41. Kondo S, Murthy V, Asgharnejad M, et al. A review of the putative antiseizure and antiepileptogenic mechanisms of action for soticlestat. Epilepsia. 2025;66(5):1394–1405. https://doi.org/10.1111/epi.18287
42. ClinicalTrials.gov. A Study of Soticlestat as an Add-on Therapy in Children and Adults With Dravet Syndrome or Lennox-Gastaut Syndrome. https://www.clinicaltrials.gov/study/NCT05163314?term=soticlestat&rank=5. (access: 2025.08.27).
43. Li Q, Shan Y, Wei P, et al. The comparison of DBS and RNS for adult drug-resistant epilepsy: a systematic review and meta-analysis. Front Hum Neurosci. 2024;18(June):1–13. https://doi.org/10.3389/fnhum.2024.1429223