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Therapeutic Innovation in DRE: Filling the Unmet Need with Emerging Modalities

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Abstract:
Background: Epilepsy - one of the most commonly known neurological disorders, is affecting over 50 million people worldwide. Despite advances in pharmacotherapy, about 30% of patients continue to experience uncontrolled seizures. This disease proved to be linked to cognitive decline, and higher mortality, confirming the need for effective therapeutic alternatives.
Aim of the review: The aim of this paper is to provide a comprehensive review and analysis of current, scientifically proven treatments for drug-resistant epilepsy and drugs along with potential therapies under clinical trials.
Material and methods. A systematic literature search was conducted using the PubMed, Google Scholar, Cochrane Library databases and the ClinicalTrials.gov website. Following removal of duplicates and relevance screening, 49 studies published from 2020 onwards with key studies included regardless of the publication date.
Results: Newer-generation agents such as cenobamate, lacosamide, brivaracetam, and perampanel offer novel mechanisms and improved safety, while ganaxolone, padsevonil, and carisbamate are promising but yet in trials. Surgical interventions remain highly effective for selected patients, whereas minimally invasive techniques like MRI-guided laser ablation have broadened treatment options. Neuromodulatory approaches such as VNS, DBS, RNS should be utilized in inaccessible epileptogenic foci. Dietary interventions, particularly the ketogenic diet and its variants, show efficacy through different mechanisms. Experimental therapies, including gene-based interventions, interneuron transplantation, and immunomodulation, alongside biomarker-guided strategies, signal a shift toward individual medicine.
Conclusions: DRE remains a major challenge, but therapeutic progress is evident. New treatments should be observed for adverse effects and for both adjunctive therapy and drug's isolated effects.

Keywords: Drug resistant epilepsy, Anticonvulsants, Neurosurgery, Neuromodulation, Ketogenic Diet, Cenobamate

Introduction

Epilepsy is one of the most prevalent chronic neurological conditions that affects vast numbers of people worldwide - recent estimates indicate that in 2021, there were approximately 51.7 million people with epilepsy globally (idiopathic and secondary combined) (Feigin, V. L., 2025). Even though a wide range of antiepileptic drugs (AEDs) is available, approximately 30% of patients treated pharmacologically experience seizures (Fattorusso et al., 2021). This form of the disease, defined by the International League Against Epilepsy (ILAE), is called drug-resistant epilepsy (DRE). There are thought to be 4 patterns of DRE - 1) de novo - where disease is uncontrolled right from the start; 2) disease is well-controlled initially but later its management proves difficult; 3) fluctuating pattern, where the epilepsy shifts between being well-managed and unmanageable; or 4) A scenario where the epilepsy initially does not respond to medication but eventually does so over time (Kwan et al., 2010). DRE poses a significant clinical and therapeutic challenge, correlating with a higher risk of adverse outcomes such as cognitive decline, and increased mortality (Löscher et al., 2020). From a public health standpoint, it generates significant economic and social costs, underscoring the urgent need to search for alternative and effective treatments (Evans et al., 2025).

1. Pharmacotherapy

In the treatment of drug-resistant epilepsy, the optimization of pharmacotherapy plays a key role, often employing newer-generation antiepileptic agents with novel mechanisms of action and a more favorable safety profile.

1.1 Cenobamate

Cenobamate (CNB) is among the most recently approved antiseizure medications used in DRE pharmacotherapy. It has been demonstrated that cenobamate has two distinct mechanisms of action. One of them is inhibition of persistent sodium current (InaP) in the neurons (Błaszczyk et al., 2024). InaP has been linked to epilepsy, due to its ability to amplify neuronal response to excitation which can lead to burst firing of neurons and induction of seizures. Increased INaP in inhibitory interneurons can also result in their excessive stimulation and eventual depletion, diminishing their capacity to suppress excitatory neurons. Consequently, excitability of the neural network is heightened and triggering epileptic episodes (Wengert & Patel, 2021). Another mechanism that distinguishes CNB from other antiseizure medications (ASM) is GABA-A receptor positive allosteric modulation, with binding sites different from benzodiazepines. As a result, the neuronal cell membrane becomes hyperpolarised and less susceptible to excitation, therefore reducing the possibility of seizure. Moreover CNB does not induce a tolerance mechanism, which allows for long term use of this drug (Steinhoff, 2021). There are studies discussing adverse effects of CNB - Badr et al. revealed that 38% of patients included in the study reported adverse effects with the most common being somnolence. This research also indicated that retention rate of CNB pharmacotherapy was approximately 72%. Primary drivers for discontinuing treatment with CNB were lack of meaningful seizure reduction (89%) and occurrence adverse effects (55%) (Badr et al., 2025).

1.2 Lacosamide

Lacosamide (LCM) is another novel AED, which binds to sodium channels similarly to drugs such as carbamazepine, phenytoin and lamotrygine. The unique way that LCM works is by encouraging the gradual inactivation of voltage-gated sodium channels. Neuronal membranes of affected neurons show diminished hyperexcitability, therefore less nervous stimuli are passed on and as a result less seizures occur (Carona et al., 2021). An alternative LCM's mechanism that has not been thoroughly explored involves its ability to bind with collapsin response mediator protein 2 (CRMP2). The phosphorylation of CRMP2 is associated with alterations in the structure of granule cells, which have been noted in individuals affected by temporal lobe epilepsy (Carona et al., 2021; Danzer, 2017). There are no certain studies indicating mechanism linking LCM and CRMP2 so far, hence more research is needed to confirm or exclude this hypothesis. LCM particularly effective in add-on therapy of focal epilepsy - Babar et al. analysis concluded that using LCM in add-on therapy significantly reduces seizure frequency compared to placebo. This review demonstrates that most common adverse effects of the drug are: abnormal co-ordination (Relative risk of 6.12) blurred vision (Relative risk of 4.65) and diplopia (Relative risk of 5.59) (Babar et al., 2021).

1.3 Brivaracetam

Brivaracetam (BRV) is an AED structurally similar to the already well-known drug - levetiracetam (LEV) thus both of them are classified as racetams and bind to the same protein - synaptic vesicle protein 2A (SV2A). The newer BRV however is much more selective and uses a different binding site or binds to SV2A when it is in a different conformational state, in comparison with LEV (Hwang & Kim, 2025). Modulation of SV2A protein results in reduced ability to release neurotransmitters into synapse, which by not-yet fully understood mechanism reduces seizure-generating activity of affected neurons (Klein & Bourikas, 2024). BRV, unlike LEV, can permeate the blood-brain barrier more rapidly, leading to a more immediate management of seizures. BRV was also suspected to inhibit sodium voltage-gated channels, but after further studies this theory was rejected (Hwang & Kim, 2025). Surya et al. review has summarised the efficacy of BRV and demonstrated that most patients reported moderate reduction in seizure frequency (defined as 21-50% reduction), with 20% of patients achieving complete freedom from epileptic episodes. This review also brought up that the full potential of BRV is hard to assess due to the fact that line of therapy influences the possibility of achieving seizure freedom, and BRV was mostly administered as second-line or later therapy, while only about 10% of patients received it as a first-line option (Surya et al., 2024). Brandt et al. meta-analysis reported that BRV is generally well tolerated, with minimal discontinuation attributed to adverse events. The most frequent adverse events were somnolence, dizziness, fatigue, headache, and nausea, and primarily appeared in the first few weeks of treatment. Importantly, compared to levetiracetam, BRV was associated with fewer rates of adverse behavioral and psychiatric effects such as mood change or irritability which makes it a possible alternative for patients with an intolerance to LEV (Brandt et al., 2020).

1.4 Perampanel

Perampanel (PMP) is the first selective, noncompetitive antagonist of glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA). Binding to allosteric sites on AMPA receptors results in dampening of the glutamatergic neurotransmission on postsynaptic excitatory synapses thus reducing excessive neuronal excitability (Yamamoto et al., 2022). Steinhoff et al. review indicates that, when used in add-on therapy with other AEDs, PMP can provide meaningful seizure reduction in patients with drug-resistant epilepsy. However, in addition to its efficacy, PMP has been associated with a relatively higher incidence of behavioral adverse events compared to several other commonly used AEDs. The review found that 9.2% of patients treated with PMP experienced irritability, 5.8% exhibited aggression, and 4.3% had other behavioral disturbances. Most of these events' severity was mild to modern and could often be managed by adjusting administered doses, without requiring the treatment to be stopped (Steinhoff et al., 2021). These findings are supported by a Cochrane review, which also confirmed the efficacy of perampanel as adjunctive therapy, but noted a higher rate of treatment discontinuations due to adverse events compared to placebo. Both studies highlight the importance of monitoring patients for potential adverse effects, particularly in the context of add-on therapy (Bresnahan et al., 2023).

1.5 Drugs in clinical trials

Numerous innovative antiepileptic drugs are currently under development or evaluation in clinical trials as a treatment for DRE and other specific types of epilepsy, offering better seizure control beyond existing options. XEN110 is a selective Kv7.2/7.3 potassium channel modulator, which has shown promising phase II results in patients with focal epilepsy and demonstrated significant seizure reduction and a favorable safety profile (Klein et al., 2023). Padsevonil, a compound targeting synaptic vesicle protein 2 (SV2) isoforms similarly to BRV and additionally modulating GABA-A receptors, has completed phase II and III trials. Although its primary efficacy endpoints were not consistently met, the drug showed encouraging signals in responder rates and seizure control (Toledo et al., 2020; Gasior et al., 2020). Ganaxolone is a synthetic analog of allopregnanolone and positive allosteric modulator of GABA-A receptors, has demonstrated efficacy in rare epileptic encephalopathies such as CDKL5 deficiency disorder and tuberous sclerosis complex in phase II–III studies (Villanueva et al., 2021; Curatolo et al., 2023). Carisbamate, currently investigated in a phase III randomized trial for treatment of Lennox–Gastaut syndrome, demonstrated clinically significant reductions in seizure frequency. This drug’s multimodal mechanism is thought to involve both sodium channel modulation and GABAergic effects. Carisbamate might prove to be a beneficial treatment option for patients suffering from syndromic epilepsies, resistant to standard treatment (Devinsky et al., 2022). These innovative drugs broaden the scope of potential treatments by targeting mechanisms not sufficiently addressed by current ASMs, consequently offering hope for improved outcomes in treatment of DRE.

2. Neurosurgery

Surgical procedures remain a cornerstone in the treatment of DRE. To qualify for such surgery patients must have a well-localized epileptogenic zone, evidenced by neuroimaging and videoelectroencephalogram (EEG) recordings, must undergo neuropsychological and psychiatric assessment and seizures should significantly impair quality of their life or pose safety risks (Rugg-Gunn et al., 2020). The most common procedure - anterior temporal lobectomy with amygdalohippocampectomy, remains the gold standard for mesial temporal lobe epilepsy associated with hippocampal sclerosis. Long-term follow-up data indicate that approximately 65% of patients remain free from epileptic incidents, with 73.6% achieving this outcome initially, demonstrating enduring effectiveness of resective surgery over decades (Lagae et al., 2022). Another type of surgical procedure is lesionectomy, which involves resection of small lesions such as cavernomas, foci of cortical dysplasia and some indolent tumors, which proved to be epileptogenic. The most damaging surgical intervention in the treatment of DRE is hemispherotomy. Hemispherotomy inevitably leads to substantial neurological impairment, such as hemiplegia and hemianopia, therefore it is best suited for those with pre-existing impairment (Rugg-Gunn et al., 2020).

Early surgical intervention is particularly important in pediatric populations, as uncontrolled seizures can lead to abnormal development. Panelli et al. systematic review including 68 studies reported overall one-year seizure freedom rate of 64.8%, with hemispheric surgery showing a higher rate (74.7%) than temporal lobe (73.3%) or extratemporal surgeries (60.2%) (Panelli et al., 2023).

In recent years, a shift toward utilizing less intrusive methods like MRI-guided laser interstitial thermal therapy (LITT) occured. This technique allows for precise ablation of the epileptogenic focus while minimizing damage to surrounding brain structures. Ali et al. meta-analysis reported seizure freedom in 55% of patients who underwent this treatment, with major complications around 2.3% and reoperations at 14.3% (Ali et al., 2025). LITT is particularly valuable for patients with deep-seated lesions or those with higher surgical risk. LITT might produce better results regarding cognitive abilities when contrasted with conventional resections, although subtle impairments in memory and executive function may still occur depending on the ablation site (Trimmel et al., 2023).

3. Neuromodulation

Neuromodulatory therapies have become a valuable option in managing DRE, presenting different alternatives to its management when surgical intervention is not viable. Vagus nerve stimulation (VNS) modulates seizures through activation of afferent vagal fibers projecting to the nucleus tractus solitarius and further to brainstem structures including the locus coeruleus and raphe nuclei. This pathway has been associated with increased release of norepinephrine and serotonin, modulation of pro-inflammatory cytokines, and enhancement of blood–brain barrier integrity (Moroșanu et al., 2023). Crucially, VNS has been shown to desynchronize pathological hypersynchronous neuronal activity and promote more efficient network organization in drug-resistant epilepsy patients, observable via magnetoencephalography as reduction in functional connectivity within theta and alpha frequency bands (Li et al., 2022).

Clinically, VNS yields responder rates (≥50% seizure reduction) between 45–65%, with improvements in mood and quality of life, and side effects such as hoarseness or dyspnea generally being manageable (Wu et al., 2020).

Another form of neuromodulatory therapy is Deep brain stimulation (DBS), which targets the anterior nucleus of the thalamus (ANT), is approved for focal DRE and has been shown to significantly reduce seizure propagation by disrupting thalamocortical networks. Five-year data reveal substantial responder rates (~68%) and seizure freedom in approximately 19%, with some series documenting dramatic reductions in status epilepticus incidence - from 28.8% pre-implant to 1.9% post-implant (Talbot et al., 2025; Firtinidou, A, 2024).

Responsive neurostimulation (RNS) systems - implantable devices that detect seizure-like activity and deliver targeted stimulation - offer real-time, closed-loop control. Long-term data (up to 9 years) show median seizure frequency reduction of 75%, a 73% responder rate, seizure freedom in ~18% of patients for at least 1 year, durable quality of life improvements, and low SUDEP rates (Nair et al., 2020). Real-world retrospective cohort studies acknowledge these outcomes, demonstrating seizure reduction trajectories that improve over time, with good safety profiles and even utility in super-refractory status epilepticus (Heilbrun et al., 2023; Ernst, L. D., 2023). VNS, ANT-DBS, and RNS provide different ways to manage seizures in people with DRE. VNS by neuromodulation of ascending systems, ANT-DBS - through thalamocortical circuits, and RNS- through closed-loop feedback.

Interventional Modality	**Responder Rate (≥50% Seizure Reduction)**	**Seizure-Free Rate**
Resection (Temporal Lobectomy)	High (Usually 70% long-term)[27]	Approx. **65%**(long-term perspective) [27]
LITT (Laser Interstitial Thermal Therapy)	High, but slightly lower than conventional resection [29]	Approx. **55%** [29]
RNS (Responsive Neurostimulation)	Approx. **73-75%** (after 9 years) [36]	Approx. **18%** (for at least 1 year, after 9 years) [37]
DBS (Deep Brain Stimulation)	Approx. **68%** (after 5 years) [34]	Approx. **19%** (after 5 years) [34]
VNS (Vagus Nerve Stimulation)	Approx. **45-65%** [33]	Low (significantly below 10%) [33]

4. Ketogenic Diet

The ketogenic diet (KD), along with its variations like the modified Atkins Diet (MAD), is emerging as a promising treatment strategy for drug-resistant epilepsy (DRE) in both children and adults. Clinical data indicates notable efficacy, with approximately 60% of pediatric patients on KD and 53% on MAD achieving a significant seizure reduction of 50% or more, and a subset of patients even reaching complete seizure freedom, all while successfully maintaining acceptable growth and lipid profiles (El-Shafie, A. M., 2023). Possible mechanism of KD is inducing metabolic changes that are key to its antiepileptic effect: elevation of circulating ketone bodies as alternative energy substrates, enhancement of mitochondrial efficiency and biogenesis, and crucially, attenuates oxidative stress by decreasing reactive oxygen species and upregulating antioxidant pathways. Furthermore, the diet powerfully modulates neurotransmitter balance by boosting inhibitory GABA synthesis and diminishing excitatory glutamatergic signaling, with preclinical evidence suggesting that the ketone β-hydroxybutyrate may directly exert an inhibitory influence on AMPA receptor activity, thereby stabilizing neuronal excitability (Rudy et al., 2020). Notably, KD is also linked to changes in the gut microbiome - studies on animals demonstrate that specific bacteria associated with KD for e.g. Akkermansia, Parabacteroide, convey seizure protection both on animals on a KD and animals on normal diet after microbiota transplant (Ruskin et al., 2021), and human data show KD-induced enrichment in beneficial microbial bacteria, which may correlate with better seizure control (Olson et al., 2018). Therefore, KD is thought to offer a multifactorial anti-seizure effect - through metabolic, neurochemical, and microbiome-mediated pathways - providing a possible non-pharmacological option for adjunctive therapy for DRE. Despite its possible impact in better management of DRE, KD is associated with several potential adverse effects. Most common short-term issues include gastrointestinal disturbances such as constipation, vomiting, and diarrhea (Armeno et al., 2021). The Longer-term adverse effects consist of dyslipidemia, kidney stones, decreased bone mineral density, and growth retardation in children (Armeno et al., 2021; Martin-McGill et al., 2020). Most adverse events are shown to be reversible with appropriate supplementation, hydration, and adjustment of the diet, but have to be taken into consideration (Martin-McGill et al., 2020).

5. Experimental therapies and future directions

Gene-based and precision approaches are currently among the most promising possible therapies, particularly in monogenic epilepsies such as Dravet syndrome. Antisense oligonucleotides and gene replacement therapies aimed at the mutated SCN1A gene are currently being actively developed and have shown encouraging results in both preclinical studies and early-phase clinical trials (Knupp et al., 2022). Cellular and immunomodulatory therapies are also receiving growing attention: transplantation of GABAergic interneuron precursors has been shown in experimental models to restore inhibitory network function and reduce seizure frequency. Another possible opportunity of treatment is targeting modulation of neuroinflammation by using cytokine inhibitors or regulatory T-cell based therapy (Shetty & Upadhya, 2021). In parallel, advances in biomarker discovery are driving the move toward individualized care.

Novel candidates include digital electrophysiological signatures, protein markers in serum and cerebrospinal fluid, and metabolites derived from the gut microbiome, all of which may help predict treatment response and guide therapeutic decisions (Dossi et al., 2023; Kanner et al., 2021). Collectively, these experimental approaches reflect a broader shift toward precision medicine in epilepsy, integrating molecular, cellular, and systems-level insights to expand therapeutic options beyond conventional pharmacotherapy and surgery.

6. Discussion

Drug resistant Epilepsy remains one of the most paramount challenges in contemporary neurology, with many patients suffering from recurring seizures, despite adherence to medication regimen. This review provides analysis of many possible treatment strategies which are currently being developed or clinically tested, including latest pharmacological innovations, surgical and neuromodulatory techniques and emerging gene therapies.

Novel drugs such as Cenobamate (CNB), which features a distinct dual mechanism (blocking Na+ channels and enhancing GABA-A receptors' activity), have shown remarkable rates of seizure freedom in clinical studies, indicating a greater potential for effectiveness compared to older drugs (Błaszczyk et al., 2024; Badr et al., 2025). Likewise, the specific selectivity of Brivaracetam (BRV) and the unique AMPA receptor antagonistic properties of Perampanel (PMP) provide customized supplementary alternatives (Hwang & Kim, 2025; Yamamoto et al., 2022). Nonetheless, the data consistently support that no single medication is a cure for all DRE cases, highlighting the need for combination therapy and personalized selection, especially given the different adverse effect profiles, including the behavioral problems associated with PMP (Steinhoff et al., 2021; Bresnahan et al., 2023). The strong pipeline of medications in clinical trials, including XEN110 and Ganaxolone, indicates an ongoing shift towards addressing various pathways beyond the traditional sodium and calcium channels.

For patients whose seizures remain refractory to optimized pharmacotherapy, non-pharmacological interventions remain crucial. Resective surgery, particularly anterior temporal lobectomy, is reaffirmed to be gold standard for appropriately selected patients, and offers the highest long-term seizure freedom rates (up to 65% in some series) (Lagae et al., 2022). The growing adoption of Laser Interstitial Thermal Therapy (LITT) represents a significant technological advancement, allowing for minimally invasive ablation of deep-seated foci, earlier impossible to access. While LITT may offer a slightly lower seizure freedom rate than conventional resection, its reduced morbidity and potential for better preservation of cognitive function make it an almost ideal tool for complex cases and high-risk patients (Ali et al., 2025; Trimmel et al., 2023).

Furthermore, neuromodulatory devices (VNS, DBS, RNS) have cemented their role, particularly for non-localizable or multifocal epilepsy. The sustained, long-term efficacy reported for Responsive Neurostimulation (RNS), which offers a closed-loop, personalized therapy that improves over time, represents a paradigm shift from traditional open-loop stimulation (Nair et al., 2020). The effectiveness of all three device modalities confirms that DRE management is moving away from purely ablative or resective approaches toward functional network modulation.

The consistent efficacy of the Ketogenic Diet (KD), and its variants, across both pediatric and adult populations emphasizes that DRE is not solely a disorder of electrical hyperexcitability, but also a metabolic disorder (El-Shafie, A. M., 2023). The emerging understanding of KD's action, links metabolic changes with neurotransmitter balance and even gut microbiome modulation and opens new research possibilities for non-pharmacological targets (Rudy et al., 2020; Ruskin et al., 2021).

Looking forward, the integration of all these modalities into a precision medicine framework is paramount. As outlined in the advanced therapies section, the development of gene replacement and antisense oligonucleotide (ASO) therapies for monogenic epilepsies (like Dravet syndrome) offers the potential for etiology-specific, and potentially curative, treatment (Knupp et al., 2022). The ultimate success of individualized care hinges on reliable biomarkers - electrophysiological signatures, protein markers, and metabolomic profiles - that can reliably predict response to a specific drug (e.g., CNB, KD) or intervention (e.g., LITT, RNS), reducing the current trial-and-error approach (Dossi et al., 2023; Kanner et al., 2021).

Conclusions

A key limitation in evaluating DRE treatments is the heterogeneity of the epilepsy itself, including diverse etiologies (structural, genetic, infectious) and many seizure types. Much of the efficacy data from clinical trials is based on add-on therapy, which as a result makes it difficult to ascertain drugs' isolated effects. Long-term cognitive and psychiatric impacts of many DRE therapies must be closely monitored and researched further to ensure best possible treatment outcome.

Future research must focus on:

1. Head-to-head comparisons of new-generation ASMs, especially against gold-standard treatments.
2. Standardization of surgical and neuromodulatory indications to optimize patient selection.
3. Translating basic science findings on cellular, inflammatory, and genetic pathways into accessible and effective clinical therapies for all patients with DRE for better individualized seizure control.

Collectively, the therapeutic innovations reviewed demonstrate that while DRE remains a major clinical challenge, the field is rapidly progressing, offering a broader and more complex treatment options than ever before.

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