# Drug-Resistant Epilepsy: Molecular Mechanisms, Emerging Therapeutic Strategies, and Future Perspectives

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**Abstract**
Drug-resistant epilepsy (DRE), the condition where an individual fail to achieve sustained seizure freedom despite appropriate trials of two tolerated antiseizure medications (ASMs) individually or in combination, is one of the most challenging neurological disorders encountered, affecting nearly one-third of individuals with epilepsy. Uncontrolled seizures remain a primary contributor to global morbidity, mortality, psychosocial dysfunction, cognitive decline and healthcare costs.
The pathogenesis of DRE is multifactorial and includes a combination of genetic predisposition, abnormalities of drug targets, up-regulation of multi-drug efflux transporters, inflammation, oxidative stress, breakdown of blood-brain barrier and aberrant network plasticity. Progress in molecular neuroscience and neuroimaging has expanded our understanding of mechanisms of pharmacoresistance and has facilitated the development of newer therapeutic strategies such as neuromodulation, surgery, precision medicine, gene therapy and stem cell therapy.
In this review, we will provide an overview of the burden and epidemiology, classification and underlying pathophysiology and consequences of DRE and examine the emerging molecular targets and novel therapeutic modalities for the improvement of clinical outcomes in patients with pharmacoresistant epilepsy, as well as outline the future directions concerning personalized medicine and disease-modifying therapies.

**Keywords:** Drug-resistant epilepsy, antiseizure medications, neuro inflammation, epilepsy surgery, precision medicine, neuromodulation.

## 1. Introduction

Epilepsy is a neurological disorder characterised by recurrent unprovoked seizures due to sudden abnormal electrical discharge in neurons of the brain, affecting about 50 million people worldwide and it constitutes one of the leading causes of neurological disease on a global scale. [1, 3]. Drug-resistant epilepsy (DRE) has become a public health challenge as uncontrolled seizures are responsible for major increase in morbidity (e.g., injury, cognitive impairment, mental health disorders, SUDEP) and decrease in quality of life and increased societal costs [4,5]. Recent advances in technology, such as high-resolution neuroimaging techniques, sequencing technologies (genome sequencing), transcriptomics, proteomics, etc, and the use of artificial intelligence in interpreting these data have greatly facilitated the identification of new therapeutic approaches to improve seizure control in patients with DRE [6, 11,12].

### 2. Global Burden and Epidemiology of Drug-Resistant Epilepsy

Worldwide, an estimated 0.5%–1% of population suffer from epilepsy, with annual incidence of 40–70 per 100,000 individuals. The global burden is however greater in low- and middle- income countries where lack of adequate healthcare facilities result in delayed diagnoses and treatment [13, 14]. Epidemiologic studies over the past three decades demonstrate that the rates of complete seizure freedom with the introduction of newer ASMs have not significantly improved, suggesting that alternative strategies are critically needed [15, 16]. Drug-resistance occurs across all age groups but is more prevalent in those with early-onset epilepsy, developmental brain abnormalities, epileptic syndromes with specific genetic basis and structural brain lesions such as hippocampal sclerosis. [17, 18].
The health economic burden of DRE is immense as hospital admissions, diagnostic tests, cost of treatment and surgical among DRE patients are multiple times greater than among those without drug resistance [19, 20]. Similarly, mortality rates are significantly higher among DRE patients due to SUDEP, status epilepticus, accidents and coexisting psychiatric disorders. Recurrent seizures are the strongest predictor of outcomes in the context of DRE [21, 22].

### 3. Definition and Diagnostic Criteria

The International League Against Epilepsy definition of DRE was adopted in 2010 and is defined as the failure of an adequately tolerated trial of 2 appropriate ASMs individually or in combination to achieve sustained seizure freedom [22, 23]. Diagnostic investigations that can help identify the type and source of the seizures and assist with therapeutic choices include EEG, MRI, video-EEG monitoring, neuropsychological evaluation and now, genetics [24,25,26]. Correct classification and diagnosis of DRE can lead to prompt referral for treatment by an epilepsy center and consideration for surgical management or neuromodulation and adjunctive therapies; delayed referral is unfortunately common worldwide [27,28].

### 4. Classification of Drug-Resistant Epilepsy

Genetic epilepsy types have recently become a focus with advances in high-throughput sequencing technology

[29,30]. Immune mediated epilepsies are another category of refractory epilepsy that can benefit from treatment of the underlying autoimmune condition using immune modulating therapies as opposed to ASMs [31,32]. Early onset neurological developmental and epileptic encephalopathies are often accompanied by severe, multi-drug resistance and requires multimodality treatment [33,34].

## 5. Molecular mechanisms of drug resistance in epilepsy

Drug resistant epilepsy is a complex, multi-factorial process, occurring through alterations at molecular, cellular, and network levels. [35,36]. Neurobiological investigation has revealed that the occurrence of seizures leads to chronic changes in neuronal connectivity, receptor expression, inflammatory mediators, and blood-brain barrier function, resulting in the reduced entry of antiseizure drugs into epileptogenic tissues and reduced responsiveness to pharmacological treatments [37,38].

### 5.1 Transporter hypothesis

One of the most intensely studied mechanisms that contribute to the development of drug resistance in epilepsy is the transporter hypothesis, which postulates that an overexpression of efflux transporters at the blood-brain barrier limit the entry of antiseizure drugs into the diseased tissue, reducing their therapeutic concentration at target sites [39,40]. of the various transporter proteins, P-glycoprotein (P-gp), coded by the gene ABCB1, has received the most interest. Neuroinflammation plays a large role in the up regulation of these transporters. Increased levels of cytokines such as interleukin-1, tumor necrosis factor-alpha and interleukin-6 produced from the activation of glial cells following seizures can induce the increased expression of transporter genes in endothelial cells and astrocytes [41,42,43].

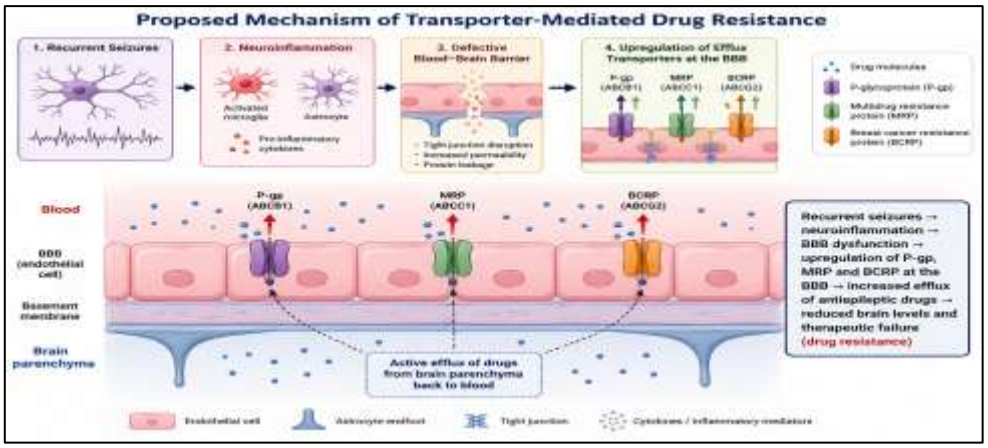


**Figure 1. Proposed mechanism of transporter-mediated drug resistance**

### 5.2 Target hypothesis

The target hypothesis is an explanation where there is a modification of the drug's molecular targets to reduce drug sensitivity and efficacy. These modifications can be brought about by an accumulation of changes at ion channels, receptors and signalling pathways caused by the ongoing seizure activity, which leads to a reduced responsiveness of the system to Pharmacological intervention [44,45,46].

### 5.3 Neural network hypothesis

The neural network hypothesis states that as epileptiform activity occurs more frequently, the structural and functional reorganization of neuronal circuits may cause networks to generate persistent seizures that are refractory to drugs [47,48,49]. This theory may also explain why removal of epileptogenic networks surgically provides an effective treatment option for a majority of patients who failed to respond to several antiepileptic drugs [50,51].

### 5.4 Intrinsic severity hypothesis

The intrinsic severity hypothesis is based on the theory that resistant epilepsy indicates a severe form of epilepsy, characterized by intense epileptogenic activity that is not responsive to any treatment [52,53]. Evidence for this hypothesis includes the fact that patients presenting with higher seizure frequencies before the start of treatment are more likely to become resistant to drug therapy; therefore, the number of seizures experienced before treatment is a marker for severity rather than an outcome of failed therapy [54,55]. Identifying severe epilepsy as being resistant to treatment may help to treat patients more effectively using either surgical or medical intervention sooner [56,57].

**Table 1. Major Hypotheses of Drug-Resistant Epilepsy**

| Hypothesis | Primary Mechanism | Clinical Significance |
|---|---|---|
| Transporter Hypothesis | Increased drug efflux by P-gp, MRP, BCRP | Reduced drug penetration into brain |
| Target Hypothesis | Altered drug targets and receptor sensitivity | Reduced drug efficacy |
| Neural Network Hypothesis | Structural and functional network remodeling | Persistent seizure generation |

| | | |
|---|---|---|
| Intrinsic Severity Hypothesis | Severe underlying epileptogenic process | Poor response to therapy |
| Gene Variant Hypothesis | Genetic alterations affecting pharmacokinetics and pharmacodynamics | Personalized treatment implications |

**5.5 Gene variant hypothesis**

It has also been proposed that variations in genes that encode proteins involved in seizure generation and control contribute to resistant epilepsy [80, 81]. Genes responsible for ion channels have also been looked at and variants that code for certain ion channels have been linked to particular seizure syndromes and treatments; sodium channel variants,[58,59] such as the SCN1A, SCN2A and SCN8A gene variants are common in certain childhood epilepsy syndromes and have also been shown to affect the way that individual patients respond to treatment [60,61].With the advancement in sequencing technology such as next-generation sequencing, further genes have been identified to be responsible for some epilepsy syndromes and drug resistance. This research is helping to bring about personalized medicine and the testing of drugs for individual patient profiles [62,63].

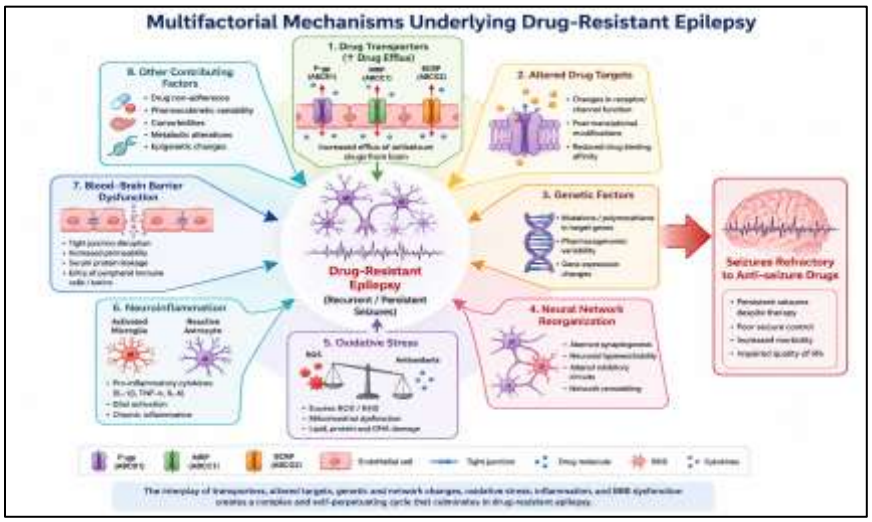


**Figure 2. Multifactorial mechanisms underlying drug-resistant epilepsy**

**6. Neuroinflammation and drug resistant epilepsy**

Neuroinflammation has become one of the more significant theories contributing to drug resistance in epilepsy. When seizures recur, the activation of both microglia and astrocytes leads to an accumulation of pro-inflammatory mediators, such as interleukins and cytokines, [64,65]. In patients suffering from drug-resistant epilepsy, high levels of interleukin-1, tumor necrosis factor-alpha and interleukin-6 are evident in their brain tissue, possibly continuing the pro-inflammatory cascade that can increase the excitability of neurons and thus resist the effect of antiseizure drugs [66,67,68].

**7. Oxidative Stress and Mitochondrial Dysfunction**

Oxidative stress is more recently found to be an important factor in epileptogenesis and drug resistance. Repeated seizure increases the production of ROS and reactive nitrogen species (RNS) causing cell injury, lipid peroxidation, protein oxidation and DNA damage [69,70]. The brain is highly vulnerable to oxidative stress due to its high oxygen consumption, abundant lipid composition and relatively poor antioxidant defense systems, the chronic oxidative stress might play a critical role in neuronal survival and progressive neuronal dysfunction in refractory epileptic individuals [71,72,73]. Several studies have revealed decreases in antioxidant enzyme activities (superoxide dismutase, catalase and glutathione peroxidase) in patients with drug-resistant epilepsy, and such deficit can further accelerate oxidative damage and contribute to poor therapeutic response [74,75,76]. Identification of oxidative stress as a pathogenic mechanism has led to the development of potential therapeutic strategies by using antioxidant compounds, as they have shown to provide neuronal protection, increase mitochondrial function and potentiate the action of conventional antiseizure drugs [77,78].

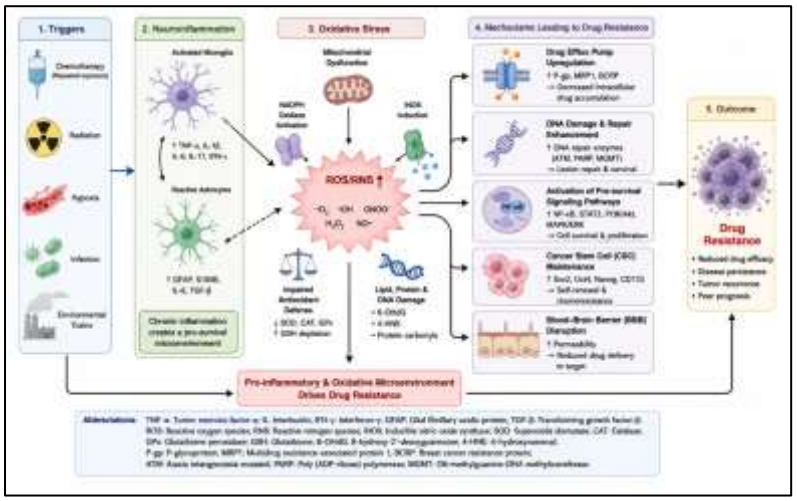


**Figure 3. Role of Neuroinflammation and Oxidative Stress in Drug Resistance**

**8. Blood-Brain Barrier Dysfunction**

The blood-brain barrier (BBB) is a specialized barrier system regulating passage of substances between the blood and brain and it has been considered to play an important role in epileptogenesis and drug resistance [79,80,81]. Albumin leakage caused by BBB dysfunction can trigger TGF-beta signaling in astrocytes which leads to changes in synaptic plasticity, rewiring and neuronal hyperexcitability and persistent seizures [82,83,84].

**9. Epigenetic Regulation in Drug Resistant Epilepsy**

Epigenetic regulation refers to heritable alterations in gene expression without a change in underlying DNA sequence, and this process has been proposed to have a role in epilepsy and its associated pharmaco-resistance [85,86]. DNA methylation is one of the most widely studied epigenetic mechanisms, abnormal methylation of genes involved in neuronal signalling, inflammation and regulation of neurotransmitter function has been observed to contribute to epilepsy susceptibility and therapeutic response [87,88].

**10. Biomarkers of drug-resistant epilepsy**

Developing reliable biomarkers of DRE is a research priority that will hopefully allow for early diagnosis of pharmacoresistance, predict treatment outcome and enable personalized treatment selection [89.90]. Neuroimaging biomarkers have shown a great deal of promise for clinical application; modern magnetic resonance imaging modalities (i.e., MRI, fMRI, DTI, MRS) can identify structural and functional anomalies present in refractory epilepsy [91,92,93]. It is likely that the integration of imaging, electrophysiological and molecular biomarkers will provide superior decision making capacity and treatment outcome [94,95].

**Table 2. Novel biomarkers of drug-resistant epilepsy**

| Biomarker Category | Examples | Potential Clinical Application |
|---|---|---|
| Neuroimaging Biomarkers | MRI, fMRI, DTI, MRS | Localization of epileptogenic zones |
| EEG Biomarkers | High-frequency oscillations, connectivity analysis | Prediction of seizure recurrence |
| Inflammatory Biomarkers | IL-1β, TNF-α, IL-6 | Assessment of neuro inflammation |

**11. Clinical significance of mechanisms**

The understanding of molecular mechanisms underlying drug resistant epilepsy carries substantial clinical implications. The role of transporter overexpression, neuroinflammation, oxidative stress and genetic susceptibility has significantly broadened therapeutic targets beyond mere seizure suppression [96.97]. Mechanisms based therapies have opened new frontiers for individualized treatment selection, where specific treatments could be applied to particular patients according to their underlying mechanisms [98.99].

**12. Current treatments of drug-resistant epilepsy**

Despite the availability of over 30 anti-seizure drugs (ASMs), drug-resistant epilepsy (DRE) remains a significant clinical challenge. [100.101]. Beyond seizure control and improvement of life quality, psychosocial well-being, reduction of mortality and cognitive benefits are also key elements in the management of DRE. A comprehensive multidisciplinary approach involving neurologists, neurosurgeons, neuropsychologists, neuroradiologists and epilepsy specialists is essential for the best outcome in patients with DRE [102,103].

**12.1. ASMs in drug resistant epilepsy**

While the defining criteria for DRE include failed at least two appropriately chosen ASMs, judicious poly therapy with ASMs with complementary mechanisms may still lead to benefit in seizure control and minimization of side effects in selected individuals [104,105,106]. Therefore, it is advised that patients with suspected DRE be referred to

specialized epilepsy centres where they may be candidates for non-pharmacological treatment modalities [107,108,109].

**13. Epilepsy Surgery**

Epilepsy surgery is the most effective treatment for selected patients with focal DRE and its aims are to resect or disconnect the epileptogenic zone while preserving critical neural functions [110,111]. Anterior temporal lobectomy for mesial temporal lobe epilepsy and medial temporal sclerosis remain the most successful form of epilepsy surgery where up to 60–80% of patients have complete seizure freedom compared to merely continuing medical therapy [112,113]. Despite the solid evidence in support of surgery, the rate at which patients are identified and referred to an epilepsy center remains very low [114,115].

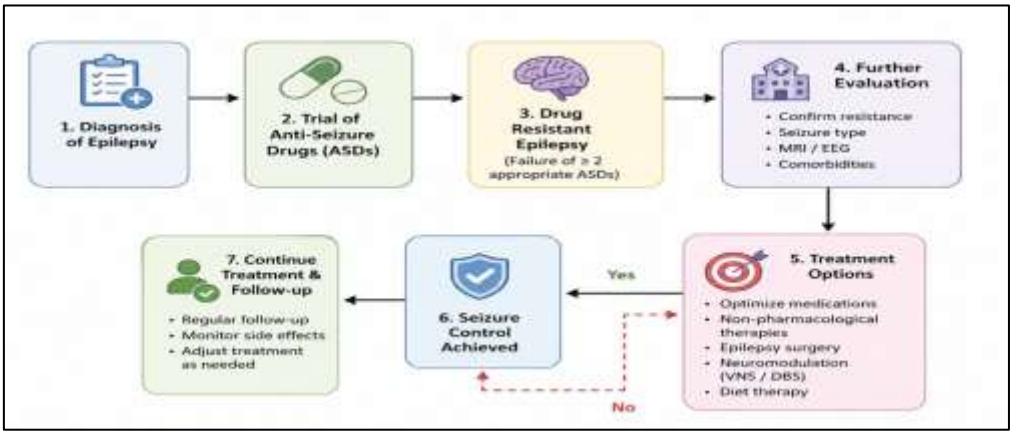


**Figure 4. Treatment pathway of drug-resistant epilepsy**

This proposed management strategy in DRE starts with the confirmed diagnosis of DRE, proceeds through appropriate investigations and consultation with an epilepsy center, to consider the utility of surgical interventions, then neuromodulation or dietary therapy, followed by precision medicine application if appropriate.

**14. Neurostimulation Therapies**

Neurostimulation has developed into a key treatment for patients ineligible for curative epilepsy surgery, as techniques aim to diminish seizure frequency through modification of aberrant neuronal network activity [116,117].

**14.1 Vagus Nerve Stimulation (VNS)**

The Vagus Nerve Stimulation system consists of an implanted pulse generator connected to the left vagal nerve. This system delivers intermittent electrical pulses, modulating broad neural networks involved in seizures [118,119]. Many patients benefit from reduced seizure frequency with VNS, with some studies demonstrating ongoing treatment efficacy, with over half the patients having a 50% seizure reduction [120,121]. As well as treating seizures, VNS has been shown to alleviate symptoms of depression, improve quality of life, and enhance cognition, in certain patients [122,123]. 14.2 Responsive Neurostimulation (RNS). Stimulation of the anterior nucleus of the thalamus via DBS has proven to be a successful treatment for some individuals with refractory focal epilepsy. The delivered stimulation may interrupt seizure propagation networks [124,125]. DBS of the anterior nucleus of the thalamus resulted in a 43% reduction in seizure frequency in a long-term study [126,127].

**15. Dietary Therapies**

Increasing attention is being given to dietary therapy as an add-on treatment for drug-resistant epilepsy patients. These therapies influence neuronal excitability by altering the brain's metabolism and neurotransmitters [128,129]. The Ketogenic Diet, is the most widely used and best researched dietary therapy for epilepsy. The Low Glycemic Index treatment and Modified Atkins Diet are less restrictive variations of the ketogenic diet that may provide an improved patient compliance profile while still being efficacious [130,131].

**16. Emerging Therapeutic Strategies**

Advances in molecular neuroscience are now making novel therapies available that do not focus on seizing itself but rather on underlying factors contributing to pharmaco-resistance [132,133,134]. Gene therapy offers an avenue towards correcting underlying genetic problems, with potential to fix disease-causing molecular processes [135,136,137]. Experimental stem cell therapies that may be able to reverse the damage causing epileptic networks, offer another exciting prospect in the therapy for drug-resistant epilepsy [138,139].

**17. Future Perspectives**

The treatment of drug-resistant epilepsy is entering a new phase. As research advances across multiple disciplines including molecular biology, neuroimaging, genomics, artificial intelligence, and precision medicine, conventional therapies that primarily aimed at seizure suppression are shifting towards identification and modification of the fundamental mechanisms underlying epileptogenesis and pharmacoresistance [140,141]. Precision medicine has emerged as one of the most promising avenues. Combining genomic data, biomarkers, and individual patient

characteristics promises more efficacious therapies with reduced adverse events. Characterizing disease-causing gene mutations could lead to development of target-specific therapeutics [142,143]. Gene therapy is another innovative field, with gene editing, viral vectors and targeted delivery offering the potential for disease modification in specific epilepsies, albeit in early stages of investigation [44,145,46]. Stem cell therapy is also being actively explored to repair damaged neuronal circuits and restore the function of inhibitory neurotransmission. While still predominantly experimental, early findings are encouraging for its long-term use [147,148]. The roles of artificial intelligence and machine learning in diagnosis, predicting seizures, determining optimal treatments, and personalizing care are all anticipated to grow in the future [149,150].

## 18. Conclusion

Approximately one third of people with epilepsy worldwide are not adequately controlled by standard antiseizure drugs, and remain suffering from drug-resistant epilepsy. This is one of the most challenging neurological disorders with high morbidity, mortality, psychosocial effects, cognitive deficits, impaired quality of life and high costs of care. The complex and multifactorial mechanism of pharmacoresistance of epilepsy includes over-expression of transporters, modification of drug targets, and network reorganization of neural tissue, genetic predispositions, neuroinflammation, oxidative stress, impaired blood - brain barrier, and epigenetic changes. These factors are all linked together and contribute to the condition of pharmacoresistance. All these mechanisms reflect the limitations of currently conventional treatments that solely aim at suppression of seizures.

Recent advances in neuroimaging, molecular diagnostics, genetics and the discovery of biomarkers have increased our understanding of the underlying mechanisms and facilitated the development of personalized therapies. Identification of those patients who are at risk of drug-resistant epilepsy in early stage seems more important in the optimal treatment of epilepsy.

In selected surgical patients, epilepsy surgery has been confirmed to be the most effective therapy leading to the highest chance of long-term seizure freedom. For patients who are not eligible for surgery, neuromodulation therapy such as VNS, RNS, DBS may effectively reduce seizure frequency and improve the quality of life.

The role of dietary therapy, such as the ketogenic and modified Atkins diets, is established for the treatment of refractory epilepsy in selected groups of patients. In addition, new therapeutic strategies, such as gene therapy, stem cell therapy, immunomodulation and precision medicine offer new promising ways of disease modification, not only symptomatic treatments, in future.

In conclusion, combining of basic scientific discoveries with the utilization of novel neurotechnology and personalized therapies is believed to be the direction to resolve the challenge of drug-resistant epilepsy. The efforts of all scientific communities with the translational aspect are of vital importance in alleviating the burden of drug-resistant epilepsy.

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