

## REVIEW ARTICLE

## A comprehensive review of drug-resistant epilepsy and animal models: Existing and emerging therapies and future research directions

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**Abstract**

Epilepsy is a long-term neurological disorder that results in recurring, uncontrolled seizures. These kinds of seizures are caused by excessively high and irregular electrical discharge in the central nervous system. Epilepsy is among the most common neurological disorders, with approximately 50–70 new cases/100,000 people every year. This review critically examines the current landscape of pharmacological experimental animal models employed in the study of drug-resistant and refractory epilepsy, shedding light on the complexities of this multifaceted disorder. Through an extensive analysis of preclinical models, the review explores the diverse mechanisms underlying resistance to antiepileptic drugs, emphasizing the need for innovative therapeutic strategies. This review was conducted using a comprehensive search of databases, including PubMed, Scopus, and Web of Science, focusing on studies published from 2000 to 2024. Articles were selected based on relevance to drug-resistant epilepsy (DRE) models, emerging technologies, and translational potential, using keywords such as DRE, animal models, and epileptogenesis. In addition, emerging experimental approaches, such as optogenetics, chemogenetics, and advanced imaging techniques, were scrutinized. Furthermore, this review outlines innovative approaches, including novel pharmacotherapies, gene therapies, and precision medicine interventions, that hold promise for overcoming drug resistance. By synthesizing current knowledge and identifying gaps, this article aims to guide

future research directions and stimulate innovative strategies for developing effective interventions for drug-resistant and refractory epilepsy. Ultimately, a comprehensive grasp of experimental models and innovative approaches is crucial for advancing our understanding of epilepsy pathophysiology and paving the way for more efficacious and personalized therapeutic interventions.

**Keywords:** Epilepsy; Clinical implication; Pharmacological mechanism; Experimental therapeutic strategies; Pharmacotherapy; Drug-resistant epilepsy

## 1. Introduction

Epilepsy is the most common long-term neurological condition in which frequent, spontaneous seizures develop. A seizure can be defined as an abrupt increase in brain activity. It is a sudden surge in brain activity that can manifest in various ways, ranging from mild attention lapses or muscle twitches to intense and prolonged convulsions. All ages are susceptible to epilepsy, although those over 60 or those in childhood are more likely to develop it.<sup>1</sup> Numerous variables, including genetics, traumatic brain damage, brain tumors, infections, and specific developmental problems, can cause epilepsy. It is common for the precise cause to remain unknown.

A comprehensive medical history, a neurological examination, and specific diagnostic tests, including blood tests, magnetic resonance imaging (MRI), and electroencephalograms, are frequently used in the diagnostic process. People are usually diagnosed with epilepsy if they have experienced two or more spontaneous seizures. Antiepileptic drugs (AEDs) are the most common pharmaceuticals used to treat epilepsy. These medications function to reduce or stop seizures. For patients who do not respond to conventional treatments, options such as surgical intervention, dietary therapies including the ketogenic diet, or the use of nerve stimulation devices may be considered. To effectively manage their illness, people with epilepsy frequently need to make specific lifestyle alterations. This could entail taking prescribed drugs as directed, controlling stress, avoiding recognized triggers, and getting enough sleep.<sup>2</sup>

In recent years, genetically modified animal models have played a significant role in advancing epilepsy research. Transgenic mice harboring mutations in ion channel genes, such as *Scn1a*, *Scn2a*, and *Kcnq2*, are now extensively used to mimic specific human epilepsy syndromes, including Dravet syndrome and benign familial neonatal seizures. These models are instrumental in understanding genotype–phenotype relationships and in evaluating targeted therapeutic approaches.<sup>3</sup>

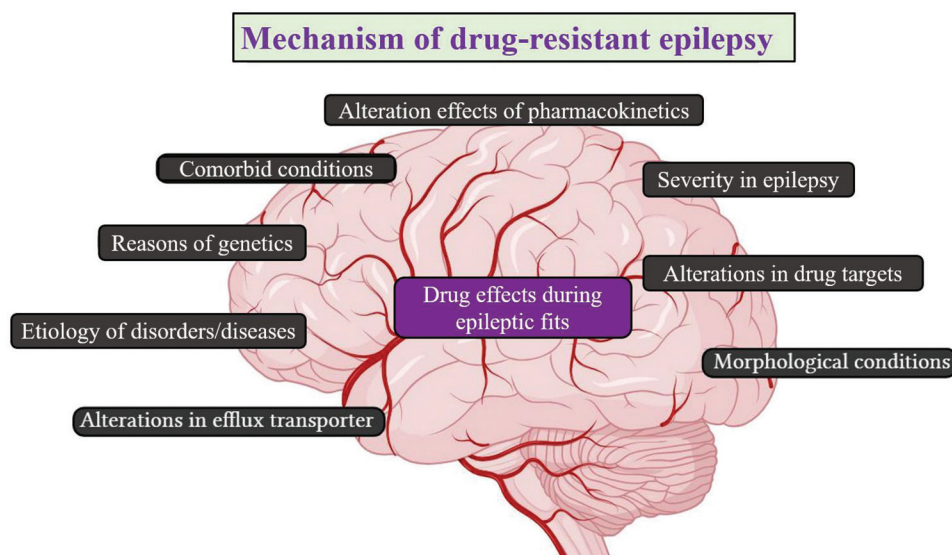
Since epilepsy is a varied condition, no two people's experiences are ever the same. The inability to attain prolonged seizure independence after two acceptable, well-chosen, and well-administered AED regimens has been referred to as drug-resistant epilepsy (DRE). Researchers frequently use experimental animal models to elucidate the mechanisms underlying DRE and to create new therapeutic approaches.<sup>4</sup> For example, excitatory amino acids, such as kainate, induce both localized and generalized seizures by opening up glutamate receptors. Kainate is used to investigate the mechanisms behind drug resistance. Excitatory amino acids entail repeatedly stimulating certain brain regions with chemicals or electricity, causing seizures to get more severe over time.<sup>5</sup> In addition, they help research medications that target the frequently drug-resistant complex partial seizures. To evaluate a medication's ability to prevent seizures, animals are administered pentylenetetrazole (PTZ) a gamma-aminobutyric acid (GABA)<sub>A</sub> receptor antagonist, which induces seizures over time. This approach is pertinent to research on DRE involves repeatedly stimulating certain brain areas with electricity to worsen seizures over time.

Animal models serve as indispensable tools for dissecting the underlying mechanisms of DRE and for evaluating novel therapies. Emerging technologies such as optogenetics, chemogenetics, and precision imaging have further enhanced the ability to study DRE in preclinical settings. Therefore, this review aims to consolidate current knowledge on animal models and emerging methodologies to guide the future direction of DRE research. Using these models, scientists may assess new chemicals, identify potential pharmacological targets and mechanisms, and investigate the intricate processes that underlie the emergence and maintenance of DRE (Figure 1).<sup>6</sup>

## 2. Epidemiology

### 2.1. Prevalence

Epilepsy, typically defined as the occurrence of two or more unprovoked seizures separated by at least 24 h, has a global prevalence estimated between 4 and 10/1,000



**Figure 1.** Mechanisms of drugs in the brain during epileptic seizures in drug-resistant epilepsy. Image created using BioRender.

individuals, depending on population and study design.<sup>7</sup> Unlike lifetime prevalence, which encompasses people with a history of epilepsy regardless of how frequently they have seizures or whether they take medicine to prevent them, active prevalence is different.<sup>8</sup> The prevalence of epilepsy varies significantly across countries, depending on factors such as the local distribution of risk and etiological factors, the number of seizures present at diagnosis, and whether lifetime prevalence includes cases in remission or only active epilepsy. The estimates of prevalence in certain communities also vary and are generally higher among those belonging to particular ethnic groups, those who are ill, and subjects from socially disadvantaged backgrounds. While general epilepsy affects approximately 50 million people worldwide, DRE accounts for nearly 30–40% of these cases, representing a significant therapeutic challenge. Studies indicate a DRE prevalence of 10–15/100,000 annually, with higher rates in low- and middle-income countries (LMICs) due to limited access to adequate healthcare and delayed diagnosis. Besides, study design challenges include the demographic composition of the population, the frequency of environmental risk factors, and the quality of health treatment.<sup>9</sup>

## 2.2. Incidence

The number of new epilepsy cases during a given period is known as the incidence of epilepsy. The incidence in this review is defined as the number of new cases per 100,000 people annually and is calculated by dividing the annual number of new cases by the average susceptible population under study during a specific period.<sup>10</sup> A systematic review and meta-analysis of incidence studies estimated the pooled

incidence rate of epilepsy at 61.4/100,000 person/year (95% confidence interval [CI]: 50.7–74.7). Notably, the incidence was significantly lower in high-income countries at 48.9/100,000 person/year (95% CI: 39.0–61.1) compared to 139.0/100,000 person/year (95% CI: 69.4–278.2) in LMICs. This disparity may be attributed to differences in the populations at risk, greater exposure to perinatal complications, and a higher prevalence of traumatic brain injury and central nervous system infections in LMICs. In addition, among the same population, those with varying ethnic backgrounds and those from the lowest socioeconomic groups in high-income countries have greater incidences of epilepsy.<sup>11</sup>

Methodological challenges, such as stricter case verification and the removal of isolated and acute symptomatic seizures in some studies, can potentially account for differences. In terms of the notion of “active epilepsy,” at least, variations in the prevalence and incidence of epilepsy are mostly caused by remission and less so by death. Nonetheless, 25% of epileptic patients who first experienced epilepsy as children still have a cumulative mortality rate at age 45.<sup>12</sup> One of the few population-based studies on epilepsy epidemiology in France investigated the incidence of epileptic seizures among individuals over the age of 60 in southwest France. The study reported an annual seizure incidence rate of 127.2/100,000 people. Of these, 34.1/100,000 had lesion-related or unknown epilepsies, 16.1/100,000 experienced isolated seizures, and 77/100,000 had contextual seizures. As for the gender effect, a higher frequency of head trauma in men than in women may be the cause of a higher frequency of seizures in men. In an Icelandic population, for example,

the cumulative incidence following the summation of age-specific incidence was 1.5% after age 55, 3.6% in those over 75, and 4.5% in those 85 years of age or more.<sup>13</sup>

### 3. Pathogenesis of seizures

Stroke is a major cause of new-onset epilepsy in the elderly population, particularly ischemic stroke, which has been extensively studied due to its high incidence. However, hemorrhagic stroke—including subarachnoid and intracerebral hemorrhages—also contributes significantly to post-stroke seizures and epileptogenesis, particularly through mechanisms involving iron toxicity, hemoglobin breakdown, and inflammation. The likelihood of a brain stroke and the frequency of post-stroke epilepsy (PSE) both rise with life expectancy. Following a stroke, there are many types of seizures, and the type and location of a stroke have a direct impact on the development of epilepsy. Furthermore, the complex therapeutic management of PSE adversely affects patients' prognosis and quality of life, increasing the risk of disability and mortality.<sup>14</sup>

Currently, the medical community is paying more attention to seizures and epilepsy following strokes. A growing number of researchers are focusing on PSE and seizures following strokes in clinical and basic settings to provide a unified, scientific guideline that allows for prompt and efficient treatment; however, a consensus on the precise pathophysiologic mechanism has not yet been reached. Numerous factors, including ion channels, neurotransmitters, glial cell proliferation, and genetics, are involved in the occurrence and development of PSE. Findings from these factors should facilitate clinicians' understanding of the disease and potentially inspire further research (Figure 2).<sup>15</sup>

### 3.1. Pathogenic mechanisms of seizure generation

#### 3.1.1. Ion channel dysfunction

Acute ischemia and hypoxia resulting from stroke can compromise the structural integrity of neuronal cell membranes and disrupt normal cellular metabolism. Such acute brain injury may lead to membrane depolarization, excessive sodium ion influx, and eventual failure of the sodium–potassium pump. A specific amount of membrane potential depolarization will cause calcium channels to open, allowing calcium ions ( $\text{Ca}^{2+}$ ) to enter the cell rapidly and raise intracellular  $\text{Ca}^{2+}$  concentrations. As a consequence, neurons become excessively stimulated, resulting in excitotoxicity and a gradual decline in the function of local inhibitory cells.<sup>16</sup>

#### 3.1.2. Neurotransmitter imbalance

Neurotransmitter imbalance causes neurons to be more irritable and excitable, increasing the risk of epileptic seizures in patients' brains. In addition, following a stroke, there is a reduction in the messenger RNA and protein levels of the GABA receptor  $\alpha 1$  subunit and in the trafficking of the GABA receptor to the cell membrane, both of which reduce seizure thresholds and the GABA receptor-dependent inhibitory postsynaptic potential, favoring the induction of seizures. Other research has demonstrated that during the early stages of ischemic stroke, nitric oxide levels are increased through the ionotropic glutamate N-methyl-D-aspartate receptor (NMDAR) as a result of a drop in GABA levels and GABAergic neuronal activity.<sup>17</sup> Moreover, an essential modulator of neuronal excitability, the M-type  $\text{K}^+$  channel, can influence inhibitory neuronal subthreshold

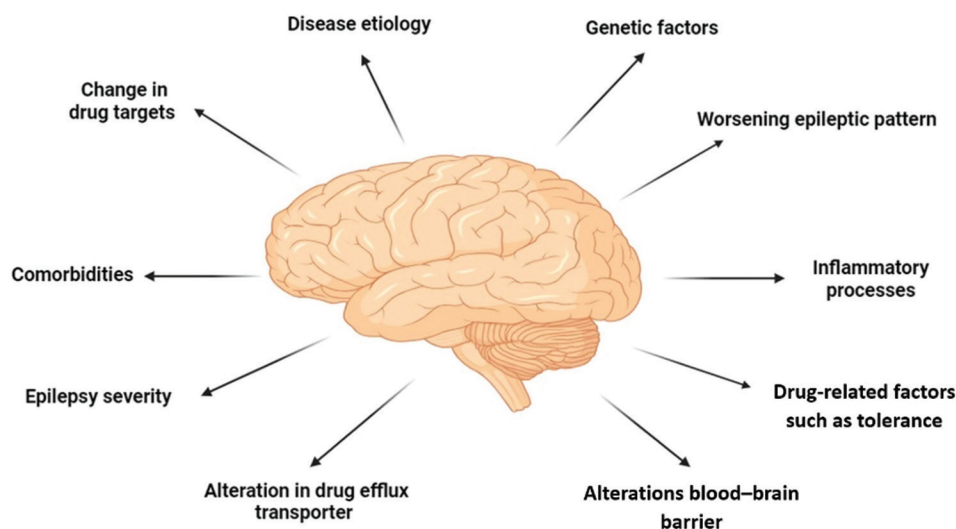


Figure 2. Conditions of drug resistance in epilepsy. Image created using BioRender.



excitability and stabilize the resting membrane potential. By inhibiting M-type  $K^+$  channels, the elevated nitric oxide can excite the central nervous system, potentially inducing epileptic seizures.<sup>18</sup>

### 3.1.3. Increased amount of cortisol in the serum

In the initial phases of ischemic stroke, stress activates the hypothalamus–pituitary–adrenal axis, sharply increasing blood cortisol levels. As excessive cortisol is neurotoxic, it can worsen hypoxia in neurons and astrocytes, as well as alter how glucose is absorbed and metabolized in the brain, ultimately leading to epileptic seizures. Moreover, glutamate receptors in the postsynaptic membrane of neurons are predictive of irritability in acute sickness, greatly increasing the excitability of neurons.<sup>19</sup> Additional research indicates that, following an acute stroke, elevated serum cortisol levels lead to a reduction in the number of neurons in the *Cornu Ammonis* 3 region of the hippocampus and impair the neurogenesis of granule cells in adult rats. These effects alter the structure and physiological function of the temporal lobe, causing periodic episodes of epilepsy in the lobe. Lastly, a high blood cortisol level plays a significant role in the onset of convulsions in the early stages of acute stroke.<sup>20</sup>

### 3.2. Pathological processes driving astrocyte proliferation in chronic epileptic seizures

The central nervous system is harmed in the latter stages of stroke because reactive astrocytes can create glial scars that lead to acquired epilepsies. The physiological activity of astrocytes is altered by astrocytic creation of scar, which impacts neuronal network function and causes late epilepsy. According to some studies, astrocytes located far from the site of the acute brain injury developed lengthy, hypertrophic projections that extended in the direction of the injury site following a stroke.<sup>21</sup> In contrast, the astrocyte-formed protrusions at the injury's core were evenly spaced out radially, overlapped one another, and combined to produce glial scars. While hypertrophic astrocytes can revert to their normal phenotype, scar-forming astrocytes exhibited lasting morphological alterations due to their ongoing expression of elevated glial fibrin, even after the acute damage triggers had subsided.

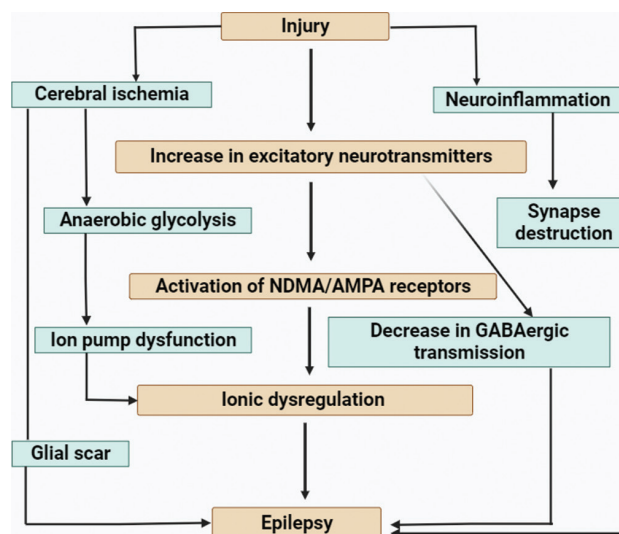
According to other research, astrocytes' Swell1 channels allow them to release glutamate.<sup>22</sup> Neuroinflammation, particularly that involving interleukin 1-beta and tumor necrosis factor-alpha, exacerbates hyperexcitability and contributes to seizure recurrence. In addition, seizures and neuronal hyperexcitability may be induced by reactive astrocytes. Following a stroke, reactive astrocytes undergo morphological and protein expression changes, along with a physiological function deficit, resulting in

a disruption of glutamate homeostasis and an increase in the excitatory neurotransmitter glutamate synthesis. Furthermore, astrocytes affect the integrity and contribute to the neuroinflammation of blood–brain barrier (BBB). Their activation post-injury leads to cytokine release and matrix remodeling, disrupting BBB function and increasing seizure susceptibility. Genetic factors such as acetaldehyde dehydrogenase 2 (*ALDH2*) polymorphisms further influence astrocyte behavior under oxidative stress. In addition, reactive astrocytes can alter the extracellular matrix's composition, indirectly affecting neuronal homeostasis and synaptic function, ultimately increasing the likelihood of epileptic convulsions (Figure 3).<sup>23</sup>

### 3.1.4. Damage to the BBB

The term BBB describes the barriers that the choroid plexus forms between plasma and cerebrospinal fluid, and the cerebral capillary wall and glial cells form between plasma and brain cells. Certain chemicals from the blood cannot pass through these barriers to enter the brain. However, during an ischemic stroke, these components leak into the brain tissue, damaging the BBB and impairing neuronal activity. Due to the disruption of the BBB, cerebral ischemia injury can result in late-onset vasogenic brain edema.<sup>24</sup>

Damage to the BBB allows large amounts of blood-derived fluid to seep into the extravascular region.<sup>25</sup> Consequently, blood-borne serine proteases, including plasmin and thrombin, penetrate brain tissue and activate protease-activated receptors (PAR). Activation of NMDARs further increases NMDAR numbers, leading



**Figure 3.** Illustration of epilepsy induced by traumatic brain injury. Image created using BioRender.

Abbreviations: AMPA:  $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA: Gamma-aminobutyric acid; NMDA: N-methyl-D-aspartate.

to glutamate-mediated excitotoxicity.<sup>26</sup> It has been shown that the concentration of thrombin in the CA1 area of the hippocampus rose dramatically in mice administered with pilocarpine, inducing seizures. Therefore, seizures can result from excitatory neurotoxicity, a substantial increase in NMDARs, and even a small rise in thrombin. It has been shown that a high NMDAR expression encourages the growth of new synapses and axons. However, following a stroke, overexpression of NMDAR, along with a high level of PAR1 activation and faulty synaptic reconstruction, leads to the reconstruction of neural networks, resulting in the loss of brain function and inducing seizures.<sup>27</sup> According to recent research, BBB disruption has been linked to seizure induction, indicating it as the root cause of seizures.<sup>28</sup>

### 3.1.5. Genetics

Over 500 genetic loci have been associated with epilepsy in both humans and rodents, with approximately 30% of all epileptic disorders believed to be inherited. According to some studies on the connection between genetics and PSE, late post-stroke seizures are linked to a polymorphism in the *rs671* allele, which encodes mitochondrial ALDH2. The specific indicator of oxidative stress, 4-hydroxy-2-nonalal (4-HNE), was found in higher concentrations in patients who carry the *rs671* allele polymorphism.<sup>29</sup> In rats that were genetically predisposed to stroke, rats affected by middle cerebral artery occlusion, and stroke patients experiencing epilepsy, the levels of 4-HNE were markedly elevated. Furthermore, in the latter stages of an ischemic stroke, epilepsy was linked to an increase in 4-HNE.<sup>30</sup> To lessen neuronal death, ALDH2 detoxifies aldehydes generated by reactive oxygen species and metabolizes 4-HNE into acetic acid. Growing research has demonstrated a connection between the onset and progression of epilepsy and oxidative stress brought on by an increase in reactive oxygen species or nitrogen. The low level of serum magnesium ion and the polymorphism of *TRPM6 rs2274924* are suggested to be potential predictors of epilepsy following stroke.<sup>31</sup>

### 3.1.6. Structural changes in the brain network

Epilepsy is now more often seen as a complete functional illness of the brain due to advancements in electrophysiological and neuroimaging research on the anatomy and physiology of the brain. Recent years have seen a progressive explanation of epileptic processes from a neural network approach. The epileptic network that links the subcutaneous structures with the cerebral cortical morphology and function was identified by Guevara.<sup>32</sup> In the network, any abnormal behavior in one part of the

network will also impact the other portions' activities. In addition, neural network alterations are linked to both typical focal seizures and late epilepsy following a stroke. These suggest that joint input from the cerebral hemisphere activates functional hippocampal circuits. Furthermore, PSE may promote neurogenesis on the contralateral side, making the neural network more vulnerable to seizures.<sup>33,34</sup> At the location of acquired epilepsy, mossy fiber sprouting in the hippocampus can be seen in both the affected and unaffected hemispheres. Studies on the alterations in the epileptic functional network following a stroke are, nevertheless, comparatively scarce. To fully understand the connection between neural networks and PSE, more investigation is required.<sup>35</sup>

## 3.3. Exploration of emerging technologies and methodologies

Advancements in scientific research are being driven by technologies that also uphold ethical standards. Techniques such as optogenetics, chemogenetics, and advanced imaging have revolutionized the understanding of complex biological processes. This section presents a closer look at these technologies and their implications.<sup>36</sup>

### 3.3.1. Optogenetics

Optogenetics uses both genetic and optical techniques to regulate and track the actions of individual neurons in living tissue. An exciting recent development is the optogenetic kindling (opto-kindling) model, where repeated light stimulation of specific cortical neuronal populations leads to progressive seizure susceptibility. This model offers high spatial and temporal resolution and allows identification of molecular pathways driving hyperexcitability.<sup>37,38</sup> Using this technique, researchers can examine the brain's complex networks with high precision through light to activate or inhibit specific neurons that have been genetically altered to express light-sensitive ion channels.<sup>39</sup>

- Precision control: Allows for the manipulation of specific neurons without affecting surrounding cells
- Temporal resolution: Enables real-time control of neuronal activity, crucial for studying dynamic processes in the brain
- Versatility: It can be applied to various types of cells and organisms, providing broad research applications
- Challenges on technical complexity and ethical considerations: Requires sophisticated equipment and expertise in genetics, optics, and neuroscience. The potential for misuse in controlling behavior necessitates stringent ethical oversight. The long-term impacts of inserting foreign genes into organisms remain uncertain and need thorough investigation.

### 3.3.2. Chemogenetics

Chemogenetics involves the use of engineered proteins that interact with specific drugs to control cellular activity. This method offers a pharmacological approach to modulating neuronal functions and can be tailored to achieve precise outcomes.

- **Specificity:** Targets particular cell types without affecting others, minimizing off-target effects
- **Non-invasiveness:** Unlike optogenetics, it does not require invasive procedures once the genetic modifications are in place
- **Flexible applications:** It can be used to study a wide range of biological processes beyond neuroscience, including cancer and metabolic diseases
- **Drug development:** It requires the development of specific drugs that interact with the engineered proteins, a process that can be time-consuming and expensive
- **Ethical and regulatory issues:** The introduction of synthetic genes and drugs into organisms raises ethical and regulatory concerns that must be addressed.

### 3.3.3. Advanced imaging techniques

Modern imaging methods, including two-photon microscopy, functional MRI (fMRI), and super-resolution microscopy, have greatly enhanced the ability to observe and comprehend biological processes at the cellular and molecular levels. They provide detailed images of cellular structures and dynamics that were previously unattainable.<sup>40</sup> Specifically, advanced imaging techniques such as fMRI, two-photon laser scanning microscopy, and near-infrared optical imaging have significantly enhanced the ability to visualize seizure networks in real time. For example, voltage-sensitive dye imaging and optical intrinsic signal imaging enable researchers to monitor cortical excitability and seizure propagation with high spatiotemporal resolution. These techniques complement electrophysiological recordings and are increasingly used in translational research.<sup>41</sup>

Many advanced imaging techniques are non-invasive, allowing for the study of live organisms without causing harm. This enables real-time monitoring of biological processes, crucial for studying dynamic changes in living systems. However, advanced imaging equipment and techniques can be prohibitively expensive, limiting accessibility for some researchers. Moreover, the high volume of data generated requires sophisticated data management and analysis tools. For example, specialized training is required to operate advanced imaging systems and accurately interpret the resulting data.

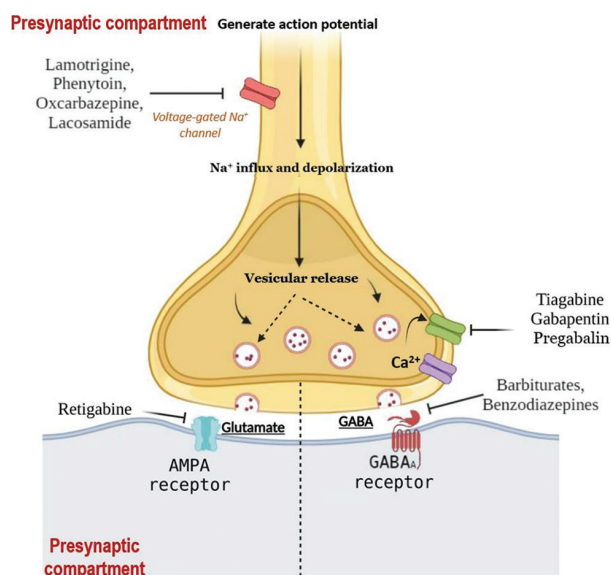
The scrutiny of emerging technologies such as optogenetics, chemogenetics, and advanced imaging is

vital for harnessing their full potential while addressing the associated challenges. These methodologies offer unprecedented opportunities for scientific discovery but come with significant technical, ethical, and regulatory hurdles.

## 4. Mechanisms of DRE

DRE, sometimes referred to as refractory or intractable epilepsy, is a disease in which the administration of the proper AEDs is ineffective in controlling seizures (Figure 4). While many epileptic patients can effectively manage their disease with medication, other patients with epilepsy still experience seizures even after taking several medications. DRE can result from a variety of causes, including structural brain abnormalities, hereditary variables, the underlying causes of these conditions, and other unknown factors. Sometimes, it is unclear what causes drug resistance.<sup>42</sup> Moreover, the results of epileptic treatments appear to be influenced by age; older patients have a higher seizure-free rate than younger patients.

Major cellular mechanism hypotheses that are now being investigated can be divided into several categories. AEDs target these mechanisms within the brain to control and prevent seizures, addressing the complex pathophysiology of epilepsy. Key mechanisms include modulation of ion channels, such as sodium, calcium, and potassium channels, which stabilize neuronal membranes and reduce hyperexcitability. AEDs such as phenytoin and



**Figure 4.** Graphical representation shows multiple target mechanisms of significant antiepileptic drugs at the cellular level. Image created using BioRender.

Abbreviations: AMPA:  $\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA: Gamma-aminobutyric acid.

carbamazepine act primarily on sodium channels, whereas ethosuximide targets T-type calcium channels. In addition, some AEDs target the inhibitory neurotransmitter GABA through various means, such as increasing GABA synthesis, inhibiting GABA degradation, or enhancing GABA receptor activity, leading to reduced neuronal excitability. Examples of such drugs include benzodiazepines and barbiturates. Other AEDs, including levetiracetam, bind to synaptic vesicle protein 2A to modulate neurotransmitter release. By targeting these diverse mechanisms, AEDs can effectively manage different types of seizures and provide personalized treatment options for patients with epilepsy.<sup>43</sup>

#### 4.1. Alteration of drug targets

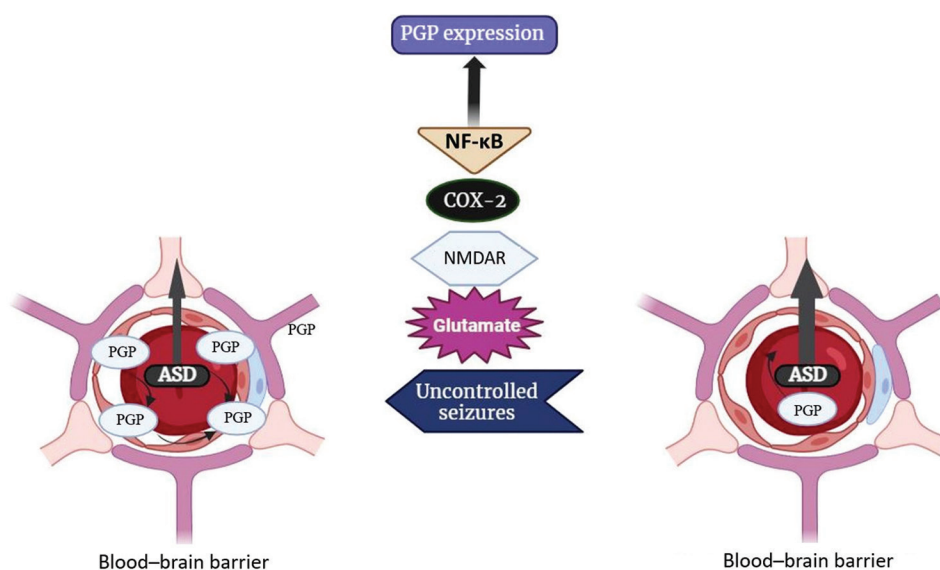
The main challenge with the target hypothesis is that it assumes a working knowledge of the still-uncertain mechanisms of action of AEDs. The AEDs whose cellular targets are altered exhibit decreased sensitivity to treatment. Researchers removed the hippocampi from temporal lobe epileptic patients who were resistant to carbamazepine and found that the medication was no longer able to inhibit the fast sodium current in dentate granule cells in a use-dependent manner. This result did not hold for lamotrigine, though it functions pharmacologically similarly to carbamazepine. Moreover, mutations in the *SCN2A* gene, which encodes the  $\alpha$ -2 subunit of neuronal sodium channels, as well as those that impact sodium channels, are associated with resistance to AEDs. For example, patients suffering from drug-resistant temporal lobe epilepsy have also been found to exhibit altered expressions of GABA

receptor subtypes.<sup>44</sup> However, it is still unknown if these modifications lead to a decrease in receptor sensitivity toward AEDs. Therefore, alteration in medication targets may be a contributing factor; however, the concept is unable to explain the observation that epileptic patients frequently resisted multiple drugs with diverse modes of action (Figure 5).<sup>45</sup>

#### 4.2. Drugs missing the real targets

The primary goal of currently available AEDs is to inhibit seizures; in certain patients, they might not address the underlying pathological mechanisms. For example, autoantibodies that selectively target ion channels involved in neuronal excitation and inhibition, such as voltage-gated potassium and calcium channels, NMDARs, and GABA<sub>B</sub> receptors, have been identified in patients experiencing seizures of unknown origin. These autoantibodies are often associated with clinical presentations of encephalitis and, in some cases, are linked to underlying occult cancers. Conventional AEDs do not usually work for these patients, and there is inconsistent evidence from uncontrolled research regarding the potential benefits of immunotherapy.<sup>46</sup>

Other proposed biological mechanisms contributing to seizures and epileptogenesis include electrical coupling through neuronal or glial gap junctions, as well as mitochondrial oxidative stress and dysfunction. These mechanisms may serve as potential targets for the development of pharmaceuticals in the future.<sup>47</sup>



**Figure 5.** Graphical representation of transporter mechanisms during epileptic seizure in drug-resistant epilepsy. Image created using BioRender.

Abbreviations: ASD: Antiseizure drug; COX-2: Cyclooxygenase-2; NF- $\kappa$ B: Nuclear factor kappa B; NMDAR: N-methyl-D-aspartate receptor; PGP: P-glycoprotein.



### 4.3. Role of epileptogenic drugs

Some tricyclic antidepressant, antibacterial, and antineoplastic drugs demonstrate high epileptogenic potential and contribute to increased epileptic seizure risks. Several epileptogenic medications are used to treat other diseases or disorders. Among established epileptogenic agents, 4-aminopyridine (4-AP) is a widely used potassium channel blocker that induces focal epileptic activity by enhancing neuronal excitability. It has been extensively utilized in both *in vitro* brain slice preparations and *in vivo* rodent models, particularly in studies involving optical imaging and seizure network mapping. The analgesic agents (e.g., meperidine), antipsychotic agents (e.g., clozapine and phenothiazine), antineoplastic agents (e.g., chlorambucil), antibacterial agents (e.g., carbapenems and fluoroquinolones), antidepressant drugs (e.g., bupropion and maprotiline), anesthetic agents (e.g., propofol and sevoflurane), and immunosuppressants and immunomodulators (e.g., cyclosporine, interferon, and tricyclic antidepressants)<sup>48</sup> are examples of epileptogenic drugs (Table 1).

## 5. Pharmacological experimental animal models of DRE

It is unknown why and how 20–30% of patients with epilepsy develop drug resistance, while other patients with seemingly similar seizure patterns can control their seizures with medicine. To qualify as a model of DRE, an animal model must exhibit spontaneous, unprovoked seizures that persist despite administration of at least two AEDs at therapeutic concentrations—a criterion fulfilled

by certain genetically and chemically induced models. For example, the amygdala-kindling model—featuring responder and non-responder phenotypes—and genetic models such as *Scn1a* knockout mice for Dravet syndrome have been established as valid DRE models. In addition, the baboon (*Papio*) model has been instrumental in studying photosensitive and spontaneous generalized seizures, while the zebrafish (*Danio rerio*) model serves as a cost-effective, genetically tractable system increasingly used for high-throughput screening of drug resistance and seizure phenotypes.

In general, an animal epilepsy model that enables the identification of pharmacoresistant and pharmacosensitive subgroups is a useful resource for researching pharmacoresistant mechanisms and developing more potent treatment plans. There are very few models that replicate the patterns of medication resistance seen in epileptic patients.<sup>57</sup> One such model involves Wistar rats with activated amygdalae, which enables differentiation between responders and non-responders to prolonged AED treatment. This model allows direct comparison between pharmacoresistant and pharmacosensitive animals, providing a unique tool to explore the mechanisms underlying intractable seizures. Using this paradigm, it has recently been demonstrated that a rat's ability to respond to anticonvulsant medication following kindling depends on both its genetic background and mechanisms generated by kindling.<sup>58</sup>

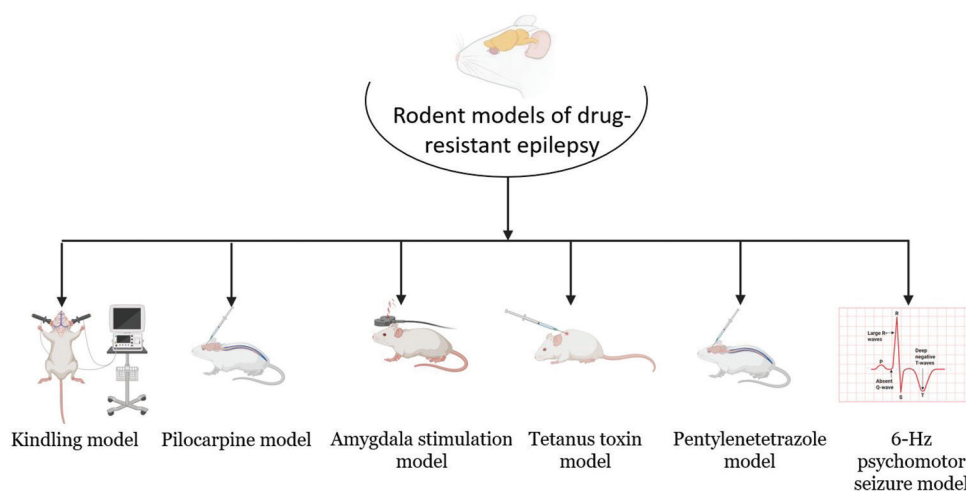
Genetically modified animal models, such as *Scn1a* knockout mice (Dravet syndrome) or genetic absence epilepsy rats from Strasbourg (GAERS), mimic human monogenic epilepsies and often exhibit drug resistance. These models have facilitated the validation of novel agents such as stiripentol and the exploration of precision medicine strategies. Translation of findings from such models has led to improved genotype-based therapeutic approaches in clinical settings. Different animal models of DRE are illustrated in Table 2 and Figure 6.

### 5.1. Chemical kindling models

Numerous animal models have been developed to investigate the effects of AEDs by inducing epileptogenesis through altered brain activity. Kindling is a long-lasting alteration in the brain triggered by repetitive stimulation, leading to prolonged and intensified seizures. It is frequently employed to investigate the mechanisms underlying epileptogenesis. In many animal species, both pharmacological convulsants and electrical brain stimulation can induce evoked seizures.<sup>67</sup> Chemical kindling involves repeated administration of sub-threshold doses of convulsant agents, such as GABAergic antagonists, neurotoxicants, and local anesthetics. This

**Table 1. List of different classes of epileptogenic drugs**

Drug class	Examples	Uses	References
Antidepressants	Bupropion, amitriptyline	Treatment of depression	49
Antipsychotics	Clozapine, olanzapine	Treatment of schizophrenia and bipolar disorder	50
Antibiotics	Ciprofloxacin, imipenem	Broad-spectrum antibiotics	51
Antimalarials	Chloroquine, quinine	Treatment and prevention of malaria	52
Analgesic	Tramadol	Pain relief	53
Bronchodilator	Theophylline	Treatment of respiratory conditions	54
Mood stabilizer	Lithium	Treatment of bipolar disorder	55
Stimulants	Methylphenidate, amphetamine	Treatment of attention-deficit/hyperactivity disorder	56



**Figure 6.** Graphical representation of experimental rodent models of drug-resistant epilepsy. Image created using BioRender.

**Table 2.** List of pharmacologically induced animal models

Models	Method of induction	Animals used	Drugs tested	Description	References
Kindling model	Repeated electrical stimulation	Wistar rats	Carbamazepine, phenytoin	Gradual development of chronic seizures; mimics epileptogenesis	59
Pilocarpine model	Systemic administration of pilocarpine	Wistar rats, mice	Valproate, topiramate, levetiracetam	Induces status epilepticus; leads to spontaneous recurrent seizures	60
Amygdala stimulation model	Electrical stimulation of the amygdala	Wistar rats	Lamotrigine, felbamate	Induction of focal seizures; often results in DRE	61
Tetanus toxin model	Microinjection of tetanus toxin	Mice	Gabapentin, tiagabine	Causes localized epileptiform activity; may progress to chronic seizures	62
PTZ model	Systemic administration of PTZ	Wistar rats, mice	Diazepam, phenobarbital	Induces generalized seizures; used for screening AEDs	63
6-Hz Psychomotor seizure model	Electrical stimulation	Wistar rats, mice	Lamotrigine, perampamel, carisbamate	Provokes psychomotor seizures; often resistant to traditional AEDs	64
Genetically modified epilepsy models	Genetic manipulations	Wistar rats, mice	Zonisamide, rufinamide, stiripentol	Mimics genetic aspects of epilepsy; may exhibit drug-resistant phenotypes	65
Electrical kindling model	Repeated electrical stimulation	Rats	Carbamazepine, phenytoin, valproate	Similar to the kindling model, it involves repeated stimulation to induce chronic seizures	66

Abbreviations: AEDs: Antiepileptic drugs; PTZ: Pentylenetetrazole; DRE: Drug-resistant epilepsy.

approach is commonly used to examine the effects of numerous seizures. The following sections compare different chemical kindling models.<sup>68</sup>

## 5.2. Kindling induced by GABAergic antagonists

The key inhibitory neurotransmitter that balances neuronal excitability by maintaining the inhibitory tone is GABA. A disruption in this balance could result in seizures. Thus, one of the modes of action to induce seizures is GABAergic antagonism. Strong GABA antagonists, including PTZ, bicuculline, picrotoxin, and  $\beta$ -carbolines, are often used to induce kindling models of epilepsy. The drug PTZ has

been extensively utilized in epilepsy experimental models to induce absence, myoclonic, and generalized tonic-clonic seizures. This method is frequently chosen when studying brain excitability with chemical kindling.<sup>69</sup> PTZ causes convulsions in mice and rats and has a pro-conflict effect when administered acutely. There is an increased risk of seizures following several doses. Following each PTZ administration, a seizure score is determined. Specifically, 5 min after an animal received a single high dosage of PTZ (50 mg/kg), rapid and severe convulsions began, lasting approximately half an hour.<sup>70</sup> On the other hand, during the first one to two weeks following repeated daily treatment

with a subconvulsive dose of PTZ (30 mg/kg), the animals exhibited very mild behavioral hyperactivity. However, in the ensuing three to four weeks, there was a stronger onset of epileptic activity, which culminated in full kindling in the next four to six weeks. PTZ-induced kindling results in a variety of behavioral, neurophysiological, and neurochemical alterations. In animal models, PTZ induces atrophy, selective neuronal death, and astrogliosis in the hippocampal regions.<sup>34</sup>

### 5.3. Kindling induced by picrotoxin

A deadly crystalline substance, picrotoxin, is present in the fruit of the *Anamirta cocculus* plant, which belongs to the moonseed family. Picrotoxin inhibits GABA-mediated chloride conductance to produce epileptogenic effects. According to several studies, picrotoxin induces seizures by lessening the inhibitory action of GABA,<sup>71</sup> resulting in repeated excitatory events that lead to paroxysmal depolarizing changes. Picrotoxin inhibition of GABA receptors is a complicated process. It was initially considered a straightforward open-channel blocker, where an allosteric site is bound by a mixed/non-competitive inhibitor or a non-competitive inhibitor to stabilize a closed or desensitized state of ligand-gated ion channels.<sup>72</sup> However, detailed single-channel current recordings indicate a more intricate mechanism: picrotoxin and its more potent derivative, picrotoxinin, did not alter the conductance of GABA<sub>A</sub> receptor-mediated single-channel events.<sup>73</sup> Instead, picrotoxin decreased the channel-opening frequency in a manner compatible with the stabilization of an agonist-bound closed state, suggesting a desensitized receptor conformation.<sup>74</sup>

### 5.4. Kindling induced by neurotoxicants

Neurotoxicants target the nervous system and change the quantities of neurotransmitters in nerve cells, altering those cells' functions.<sup>75</sup> These substances affect the binding and release of neurotransmitters, impacting ion channel receptors. Seizures may result from exposure to certain hazardous substances. Consequently, kindling models have utilized a few of these chemicals.<sup>76</sup>

### 5.5. Kindling induced by endosulfan

Endosulfan is a pesticide that is a member of the chlorinated cyclodienes subclass, which is a subclass of the chemical family of organochlorines. It has a double bond. Previous studies have demonstrated that organochlorine insecticides exhibit a strong proconvulsant component in addition to other detrimental effects on the central nervous system.<sup>77</sup> In kindling models, chemical kindling is induced through repeated subconvulsive dosages of endosulfan. The spontaneous electrographic and behavioral seizures are

also induced using this proconvulsant kindling paradigm. In addition, electrical stimulation of the amygdala has also been used to study the proconvulsant effects of endosulfan. The number of stimulations needed to cause stage 5 generalized seizures is dramatically decreased by endosulfan. Moreover, amygdala kindling was also facilitated by endosulfan.<sup>78,79</sup> Endosulfan works by binding to the GABA receptor ionophore complex and blocking the GABA-gated chloride channel, preventing chloride flow across membranes. Endosulfan has been shown to lower seizure thresholds, increasing seizure incidents.<sup>80</sup>

### 5.6. Kindling induced by PTZ

A single high-dose intraperitoneal injection of PTZ results in a sudden, severe seizure in animals, while repeated injections of subconvulsive dosages form the basis of a chemical kindling model of epilepsy.<sup>81,82</sup> PTZ acts as a GABA<sub>A</sub> receptor antagonist. A single low-dose PTZ injection may cause mild seizures without convulsion,<sup>83</sup> but repeated low-dose PTZ injections over time lower the threshold for inducing convulsions,<sup>84</sup> eventually leading to severe tonic-clonic seizures. This chronic model mimics the recurring nature of epilepsy, allowing the study of its pathophysiology. Animals subjected to this chemical kindling technique develop recurrent seizures,<sup>85</sup> making it a valuable tool for assessing seizure susceptibility, identifying epilepsy-related genes, and screening AEDs.<sup>86</sup> Furthermore, as chemically induced animals' brains exhibit the same histological alterations as those of epileptic patients, this technique has been utilized to study neuronal damage following epileptic convulsions. Overall, this procedure offers a simple approach for generating animal epilepsy models.<sup>87,88</sup>

### 5.7. Kindling induced by devices

#### 5.7.1. Amygdala kindling models

Carbamazepine's anticonvulsant potential was assessed in the kindling amygdaloid seizure model in rats following both single and multiple doses.<sup>89</sup> Following a 30 mg/kg dosage, carbamazepine significantly decreased the duration and severity of motor seizures as well as the length of after-discharges recorded from the stimulated amygdala. However, tolerance developed during the chronic treatment of rats receiving 30 mg/kg intraperitoneal injections, three times a day for two weeks. In addition, tolerance was also observed concerning the main side effects of the medication (muscular relaxation and ataxia).<sup>90,91</sup> The primary active metabolite of carbamazepine, carbamazepine-10,11-epoxide, increased throughout long-term treatment but was not quantifiable in plasma following the initial dose, suggesting that the parent medication was being metabolically processed more

efficiently.<sup>92</sup> Following one or two weeks of treatment, the total concentrations of both compounds did not deviate from the initial concentration of unaltered carbamazepine due to declining carbamazepine concentrations but rising epoxide levels.<sup>93,94</sup> Notably, in kindling rats, the acute anticonvulsant potency of carbamazepine-10,11-epoxide was found to be approximately half that of the parent medication.<sup>95,96</sup>

### 5.7.2. Vagus nerve stimulation (VNS) in the kindling model

The electrographic seizure threshold (EST) was calculated by measuring the amygdala electrode current necessary to trigger a seizure after kindling was induced. VNS devices were set up to deliver electrical stimulation after stable ESTs were obtained.<sup>97,98</sup> VNS is a United States Food and Drug Administration-approved method that can be employed either clinically (standard) or experimentally (microburst) with varying intensities.<sup>99</sup> The control animals' VNS devices were programmed in the same way without a current supply. EST was measured in the control and VNS groups after 60 min and a week, showing significant drops in EST levels in the control animals.<sup>100,101</sup> In contrast, both clinically utilized and experimental patterns of VNS prevented the reduction of EST observed in control animals.<sup>102,103</sup> These results provide an experimental framework for clarifying the mechanisms underlying VNS's antiseizure effects and identifying optimal VNS patterns in raising seizure thresholds.<sup>104,105</sup>

## 6. Future use of DRE animal models in the development of AEDs

One of the primary advantages of drug-resistant animal models lies in their ability to replicate the heterogeneity of human epilepsies.<sup>106</sup> By studying how seizures persist despite treatment attempts, researchers can uncover novel mechanisms underlying drug resistance. This deeper understanding can potentially unveil new drug targets or therapeutic strategies that could benefit patients resistant to current treatments.<sup>107</sup> Moreover, these models allow researchers to test the efficacy of experimental drugs specifically designed to target DRE. This targeted approach accelerates the development of medications that could significantly improve outcomes for patients whose seizures are refractory to existing therapies.<sup>108</sup>

### 6.1. Current challenges and limitations

Drug-resistant animal models are facing several challenges. One major hurdle is the variability in how drug resistance manifests in different species and strains of animals, complicating the interpretation of results and limiting the generalizability of findings to human patients.<sup>109</sup> In addition, ethical considerations surrounding the induction

of seizures and the testing of potentially harmful drugs in animals necessitate stringent adherence to ethical guidelines and the use of humane practices. These factors can influence study outcomes and the applicability of findings to clinical settings.<sup>110</sup>

### 6.2. Future directions and implications

The future use of drug-resistant animal models holds significant promise. Advances in genetic engineering techniques, such as the development of animal models with specific mutations associated with drug resistance, could enhance the relevance and reliability of these models in predicting human responses to AEDs.<sup>111,112</sup> Furthermore, integrating data from drug-resistant animal models with clinical studies and patient data through translational research efforts could lead to more personalized treatment approaches for epilepsy.<sup>113</sup> By bridging the gap between preclinical research and clinical practice, researchers can optimize therapeutic strategies and improve outcomes for patients with DRE.<sup>114</sup> Overall, while challenges persist, drug-resistant animal models represent a crucial tool in advancing the understanding of epilepsy and developing effective AEDs.<sup>115</sup> Continued research efforts and collaborations across disciplines are essential to harnessing the full potential of these models and translating findings into meaningful clinical benefits for individuals living with DRE.<sup>116</sup>

## 7. Discussion

Optogenetics has enabled the precise mapping of seizure circuits in hippocampal models of DRE. Similarly, chemogenetically designed receptors exclusively activated by designer drug systems have allowed selective silencing of hyperactive neuronal clusters in rodent models. Advanced imaging techniques, such as fMRI, have been used to monitor real-time seizure propagation and drug response. These tools are gradually finding clinical relevance through integration in surgical planning and biomarker identification. Recent studies suggest that the pro-convulsant effects of certain medications, such as fluoroquinolones or tricyclic antidepressants, may be potentiated in individuals carrying mutations in ion channel genes (e.g., *SCN1A* and *SCN2A*). This gene-drug interaction could explain variability in seizure thresholds and drug-induced epilepsy in genetically susceptible individuals.

## 8. Conclusion

This review synthesizes evidence from pre-clinical and clinical studies, underscoring the interconnectedness of astrocytic dysfunction, BBB breakdown, and neuroinflammation in DRE. A key future direction involves integrating omics data and humanized models to identify individualized drug targets. In addition, combining animal



model data with real-world patient data could bridge the translational gap and inform precision treatment strategies. The innovative approaches discussed in this review hold promise for advancing the comprehension of DRE. Innovative technologies, such as optogenetics and advanced imaging techniques, offer unprecedented opportunities to unravel the intricate neural circuits involved in seizure generation and propagation. These emerging tools not only provide a deeper understanding of the underlying pathophysiology but also pave the way for the development of targeted interventions.

Despite the strides made in experimental models, it is evident that bridging the translational gap between preclinical findings and clinical application remains a formidable challenge. The multifaceted nature of DRE demands collaborative efforts across disciplines and the integration of diverse expertise to design more representative models and rigorously validate potential therapeutic strategies. As we look toward the future, a holistic approach encompassing molecular, cellular, and network-level investigations will be essential to decipher the intricacies of drug resistance. Furthermore, fostering dialogue between basic researchers, clinicians, and industry stakeholders is imperative for the successful translation of experimental findings into tangible clinical outcomes. In essence, this review underscores the dynamic landscape of pharmacological experimental animal models for drug-resistant or refractory epilepsy and emphasizes the necessity of embracing innovative approaches for a comprehensive understanding of this challenging condition. By fostering collaboration and leveraging cutting-edge technologies, the scientific community can strive toward transformative breakthroughs in the management of DRE, ultimately improving the quality of life for individuals living with this debilitating disorder.

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## Author contributions

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