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Review

Seizure Control: Exploring new therapies and technologies

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Abstract

Epilepsy is a neurological disorder, marked by sudden episodes of seizures, disturbances, and abnormal electrical activity in the brain which results from the excessive release /discharge of cortical neurons. Even though there is a wide availability of anti-seizure/anti-epileptic or anticonvulsants therapy, 30% of patients with epilepsy experience retain of seizures and some with comorbidities, risk of premature death. This review will cover the points regarding new therapies (pharmacological and non pharmacological) and technologies for seizure control. This review explores emerging pharmacological therapies such as selective ion channel modulators, neurosteroids, anti-inflammatory agents, and genetic and epigenetic-targeted treatments that offer improved efficacy and fewer adverse effects. Additionally, non-pharmacological interventions including vagus nerve stimulation (VNS), deep brain stimulation (DBS), responsive neurostimulation (RNS), and transcranial magnetic stimulation (TMS) have shown promise in patients unresponsive to traditional medications. Dietary therapies such as the ketogenic diet, modified Atkins diet, and low glycemic index therapy have also demonstrated success in specific epilepsy syndromes. Recent advances in neurotechnology and computational tools, particularly machine learning algorithms, wearable seizure detection devices, and predictive brain mapping, have further enhanced our understanding of seizure patterns and patient-specific triggers. These innovations hold potential for real-time seizure prediction and individualized treatment planning.

Keywords: Seizure Control

INTRODUCTION

Epilepsy is the enduring predisposition of the brain to generate seizures, a condition that carries neurobiological, cognitive, psychological, and social consequences (1). Over 30% of individuals do not respond to common antiseizure therapy for epilepsy and they are termed as “drug resistant” (2). Therefore, a huge responsibility has been initiated on the research and development of informative and innovative pharmacological

and non-pharmacological approaches, regarding improvement in patient's symptoms and quality of life. Traditional anti-seizures medications are related with adverse effects and mood disturbance, systemic toxicity (3). Several investigations are currently in progress, this review will look into points regarding new therapies and technologies leading to improved quality of life of patients. This article also provides an overview of the latest advancements in seizure control, focusing on new pharmacological therapies, neuromodulation techniques, and wearable technology. The pathophysiology of epilepsy involves complex alterations in neuronal excitability and connectivity, often leading to hypersynchronous activity among cortical neurons. These disturbances may be the result of genetic mutations, structural brain abnormalities, infections, traumatic brain injuries, metabolic imbalances, or idiopathic causes. Diagnosis is typically based on clinical history, neurological examination, and confirmatory tools such as electroencephalography (EEG) and neuroimaging [1].

While anti-seizure medications (ASMs) serve as the cornerstone of epilepsy management, a major clinical challenge persists: approximately 30–35% of patients are diagnosed with drug-resistant epilepsy (DRE), defined as the failure to achieve sustained seizure freedom despite adequate trials of two or more appropriate ASMs [2]. In addition to persistent seizures, many patients experience adverse effects of long-term medication use, including sedation, cognitive impairment, mood disturbances, hepatotoxicity, and teratogenicity [3,5,6], which further complicate treatment adherence and patient outcomes.

Given the limitations of current pharmacotherapy, there is a growing emphasis on exploring new pharmacological compounds and non-pharmacological interventions that can either supplement or replace conventional treatment strategies. Advances in neurobiology, genetics, and computational neuroscience have led to the development of targeted therapies that act on specific molecular pathways involved in seizure generation and propagation [6]. Simultaneously, innovations in neuromodulation such as vagus nerve stimulation (VNS), deep brain stimulation (DBS), responsive neurostimulation (RNS), and transcranial magnetic stimulation (TMS) offer alternative treatment avenues for patients with refractory epilepsy [7,8].

Moreover, the integration of emerging technologies such as wearable seizure detection devices, mobile health applications, artificial intelligence (AI)-driven prediction models, and real-time monitoring systems is revolutionizing epilepsy care [9,10]. These tools not only aid in early detection and intervention but also empower patients through personalized and data-driven management plans.

In this context, the present review aims to provide a comprehensive overview of the latest advancements in the management of epilepsy, focusing on novel pharmacological treatments, non-invasive neuromodulation techniques, and cutting-edge technologies that collectively aim to improve seizure control, reduce side effects, and ultimately enhance the quality of life for individuals living with epilepsy.

New pharmacological therapies

Cannabidiol oil

It may reduce symptoms of epilepsy. It is administered orally. cannabidiol oil has gained attention for its anticonvulsant properties. EPIDIOLEXss, a pharmaceutical grade CBD product has been approved by FDA for the treatment of seizures related with Lennox-Gastaut syndrome and Dravet syndrome .in 2019 CBD was approved in Europe in combination with clobazam (CLB). Based on clinical trails data the combination of CBD and CLB showed greater efficacy outcome (11). In 2019, the European Medicines Agency (EMA) also approved CBD for use in combination with clobazam (CLB). Clinical trials demonstrated that the CBD-CLB combination significantly improved seizure control compared to standard therapy alone [11]. The precise mechanism of CBD's anticonvulsant action is not fully understood but is thought to involve modulation of calcium and sodium channels, GABAergic activity, and anti-inflammatory pathways. Administered orally, CBD has shown promise in reducing seizure frequency in treatment-resistant epilepsy. EPIDIOLEX®, a purified, pharmaceutical-grade CBD product, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, two severe forms of childhood-onset epilepsy [11].

Fenfluramine

Fenfluramine (FFA) was actually used as an appetite suppressant or as a weight loss drug. But it also showed its activity by reducing seizures in epileptic patients.FFA has then provided clinically meaningful reduction on convulsive seizures over a median of 445 days of treatment (11). The most side effects of FFA include loss of appetite, weight loss, diarrhoea, fatigue, lethargy (11). FFA is approved by FDA and is under evaluation of Europe Medicines Agency. It is particularly effective in reducing the frequency of generalized tonic-clonic seizures in patients with Dravet syndrome. Clinical trials have shown that FFA provides a clinically meaningful reduction in seizure frequency, sustained over a median treatment period of 445 days [11]. The FDA has approved fenfluramine for epilepsy treatment, and it is currently under review by the European Medicines Agency. Common adverse effects include loss of appetite, weight loss, fatigue, lethargy, and diarrhea [11]. Despite its effectiveness, careful monitoring is required due to its history of cardiovascular side effects at higher doses, especially when used for weight loss in the past.

Neuromodulation techniques

Responsive neurostimulation (RNS)

Responsive neurostimulation is cutting-edge technology designed for treatment for drug resistant epilepsy. In this system a neurostimulator, a device is implanted into the skull with help of two intracranial electrodes placed in or near the epileptogenic brain region responsible for seizure occurrence (12)(13). The mechanism of action of RNS include

a. monitoring brain activity
b. Detecting seizure onset
c. Responsive stimulation
d. Adaptation and learning

As RNS continuously monitors the brain activity it can detect the seizure initiation and stimulation parameters for each patient, improving treatment efficacy.

The mechanism of action of RNS includes

Continuous monitoring of brain activity through intracranial EEG, Real-time detection of abnormal electrical patterns indicating seizure onset, Immediate delivery of electrical stimulation to disrupt the seizure activity, Adaptive learning, where stimulation parameters are personalized over time to improve efficacy. By delivering targeted stimulation only when abnormal activity is detected, RNS minimizes unnecessary stimulation, preserves brain function, and helps reduce seizure frequency and severity. Clinical trials have demonstrated sustained efficacy and good safety profiles for RNS over long-term use [13].

Vagus Nerve Stimulation:(VNS)

Vagus nerve stimulation is a neuromodulation therapy that involves the implantation of device that stimulates the vagus nerve. In VNS, a small generator is placed under the skin, and a lead wire is connected around the neck left vagus nerve on the neck. Vagus nerve plays an important role in regulation of various body functions and maintenance of neuronal activities and promotes inhibitory pathways and reduce excessive excitary activity which leads to seizures (15) (16). This stimulation has been created to reduce seizure frequency and severity in patients with drug resistant epilepsy (17) (18).

Dietary therapies

Modified ketogenic diets

Ketogenic diet is a reliable intervention in the treatment of refractory epilepsies, especially for kids. The ketogenic diet is a low-carbohydrate, high-fat diet imitates the metabolic state of fasting it typically consists of 70-80% fat 10-20% protein and 5-10% carbohydrates. Including modifications such as the Modified Atkins Diet (MAD). Low gleyic index treatment (LGIT), allow more flexibility in diet style while still maintaining ketogenic efficacy. The therapeutic use of the ketogenic diet for epilepsy management brings back the early 1920s, when it was first introduced as the potential treatment for drug resistant epilepsy. (19) (20)

Dietary approaches have long been recognized as valuable alternatives in the treatment of epilepsy, especially in cases that are unresponsive to conventional anti-seizure medications. Among these, the ketogenic diet (KD) remains one of the most effective and widely studied interventions. First introduced in the 1920s, the ketogenic diet is a high-fat, low-carbohydrate, and moderate-protein dietary regimen that induces a metabolic state known as ketosis a condition where the body primarily utilizes ketone bodies, rather than glucose, as its energy source. This shift in metabolism is believed to exert an anticonvulsant effect by stabilizing neuronal activity and reducing excitability in the brain. The classical ketogenic diet typically consists of approximately 70–80% fat, 10–20% protein, and only 5–10% carbohydrates, making it highly restrictive but effective, particularly in children with drug-resistant epilepsy. Over the years, modified versions of the ketogenic diet have been developed to improve palatability and compliance while maintaining therapeutic benefits. These include the Modified Atkins Diet (MAD) and the Low Glycemic Index Treatment (LGIT). The Modified Atkins Diet is a less restrictive variant that permits greater protein intake and eliminates the need for meticulous food measurements, whereas LGIT focuses on the intake of carbohydrates with a low glycemic index to ensure stable blood glucose levels. Both modifications offer greater dietary flexibility, which is especially beneficial for long-term adherence in pediatric and adult populations. Clinical studies have demonstrated that these dietary therapies can significantly reduce seizure frequency and severity in various types of refractory epilepsy, including Lennox-Gastaut syndrome, Dravet syndrome, and other generalized and focal epilepsies. As a non-pharmacological approach with a favorable safety profile, the ketogenic and its modified diets continue to play a critical role in comprehensive epilepsy management, especially for patients who have limited response to medication or are not suitable candidates for surgical interventions.

Gene therapy

Gene replacement and editing

The data has emerged supporting the potential cures for genetic epilepsies using gene replacement techniques in emerging era of gene therapy. CRISPR-Cas9: An experiment gene-editing technology that holds promise for curing genetic epilepsies, allowing precise changes to the genome.

In recent years, advancements in molecular genetics and neuroscience have opened new avenues for the treatment of genetic epilepsies, many of which were previously considered untreatable. One of the most promising developments is gene therapy, particularly through gene replacement and gene-editing technologies. These approaches aim to address the root cause of epilepsy by correcting or replacing the faulty gene responsible for abnormal neuronal function, rather than merely controlling symptoms with medication [21].

Gene replacement therapy involves delivering a functional copy of a defective gene into a patient's brain cells using viral vectors, such as adeno-associated viruses (AAVs). This method holds potential for treating monogenic forms of epilepsy such as Dravet syndrome, caused by mutations in the SCN1A gene by restoring normal protein function and neuronal stability [22].

In parallel, gene-editing technologies like CRISPR-Cas9 have revolutionized the field by enabling scientists to make precise and targeted modifications to the genome. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) paired with the Cas9 enzyme acts like molecular scissors, allowing the removal, correction, or replacement of specific DNA sequences responsible for epileptic phenotypes [23]. While still experimental, preclinical studies using CRISPR-Cas9 have demonstrated significant promise in correcting genetic mutations associated with epilepsy in animal models [24]. These cutting-edge therapies not only represent a shift from symptom management to potential cures but also mark the beginning of precision medicine in epilepsy care, offering hope to patients with genetically determined epileptic syndromes. However, challenges such as delivery efficiency, long-term safety, immune responses, and ethical concerns must be addressed before these therapies can become routine clinical practice [25].

Viral Vectors for Gene Transfer

Viral vectors, in conjunction with other methods of in vivo gene transfer, are novel tools for studying the function of genes in the mammalian central nervous system (CNS). Moreover, such gene-transfer approaches can induce the expression of "therapeutic" molecules, providing potential opportunities for treating some CNS diseases. Neurotropic viral vectors can express single or multiple foreign genes as well as a wide variety of regulatory elements and can be engineered at either or both the capsid and promoter level to provide highly targeted, cell-specific gene transfer. Neurotropic viral vectors also permit short-term or long-term CNS transgene expression to be achieved in different regions of the brain through stereotaxic delivery.

Various viral vectors, including herpes simplex virus, adenoviruses, and retroviruses, have been developed for gene therapy (27,28). The adeno-associated virus (AAV) vector system appears to have several advantages for gene transfer over the other virus vectors, including a high efficiency of infection and minimal induction of host immune and inflammatory responses (29,30). The efficacy of the AAV system is based on its ability to package any DNA up to a size limit of ~4.5 kb (31). The AAV vectors are nonpathogenic in that they lack the machinery for virus replication, and consequently, infection will be limited to the site of injection. AAVs are very promiscuous and infect virtually all cell types in a variety of host organisms; therefore to restrict gene expression to specific cell types, the use of a tissue-specific (i.e., cell-specific) promoter is needed.

Harmful recombination events, such as insertional mutagenesis or reversion to wild type, are a general problem that may occur with viral vectors, particularly when pathogenic viruses are modified for gene transfer. Because of replication initiator protein (Rep) deletion, recombinant AAV (rAAV) is believed to exist mainly in episomal form, with variable levels of integration in nondividing cells. Nonspecific host effects on the virus activity, such as promoter silencing or immunologic reactions, are another issue of concern with the use of viral vectors. Integrated rAAVs have not been reported to have any mutagenic or deleterious effects; however, high-dose vascular delivery could be tumorigenic (32), thus warranting further long-term studies.

Gene Transfer in Seizure Disorders: The Choice of "Therapeutic" Genes

An imbalance in excitatory and inhibitory neurotransmission is a widely recognized hypothesis for CNS hyperexcitability underlying the epileptic state. Because viral-mediated gene delivery can result in stable transduction of neurons with agents that have the potential to affect this imbalance, seizure disorders represent an attractive target for gene therapy. Thus far, therapeutic strategies have focused on the modulation of signaling, mediated by the main classic excitatory and inhibitory neurotransmitters, glutamate and γ-aminobutyric acid (GABA). However, over the past 20-year period, increasing attention has been focused on a group of bioactive peptides, including galanin and neuropeptide Y, which are abundantly expressed in the brain (33). As increased information has accumulated on the involvement of these peptides in fundamental physiologic and behavioral functions, such as feeding, anxiety, learning, memory, and attention, it has become clear that the peptides also can modulate neuronal excitability in a beneficial way to protect against seizures.

The preferential release of neuropeptides under conditions of increased neuronal activity, and in particular during seizures, has encouraged investigation of their role in seizure modulation (33). Both galanin (a 29- to 30-amino acid peptide) and neuropeptide Y (a 36-amino acid polypeptide) have been shown to antagonize excitatory glutamatergic neurotransmission in the hippocampus (34–36). Compelling evidence supports an anticonvulsant role for these peptides in various experimental models of seizures, either when exogenously applied or when endogenously released (37-41). Neuroprotection against excitotoxic cell death (43) and seizure-induced neurogenesis (44) are two novel aspects of peptide action in the CNS that are relevant to epilepsy research. These findings led to the hypothesis that augmentation of local inhibitory tone, resulting from overexpression of these two neuroactive peptides in specific brain areas, may be an effective strategy for inhibition of seizures and epileptogenesis. Attenuation of seizure and neuronal death by AAV vectors that mediate galanin expression and secretion recently has been reported (43,45).

AAV vectors with different characteristics were designed to overexpress galanin constitutively in neurons. In one study, an AAV vector was engineered to carry a fibronectin sequence together with the galanin gene (43). AAV-mediated delivery of this secretory signal, along with the coding sequence for the active galanin peptide, significantly attenuated in vivo focal seizure sensitivity in rat inferior collicular cortex and prevented hippocampal hilar cell loss consequent to kainate-induced seizures. By adopting a doxycycline-sensitive rAAV vector, this elegant study showed that when doxycycline was added to drinking water, the threshold for seizure generation returned to baseline within 1 week. This study demonstrates the feasibility of both controllable and long-term (≤4 weeks) seizure attenuation with a gene-therapy vector. In another study, Lin et al. (45) adopted an rAAV vector in which the galanin gene was driven by a neuron-specific promoter. The study showed long-lasting (≤2.5 months) functional overexpression of galanin, specifically in hilar interneurons and their terminal projection fields, thus demonstrating that the peptide can be produced and transported along axons even a long distance from its site of synthesis. Lin and colleagues (45) reported that restricted galanin overexpression results in powerful inhibition of seizures induced by intrahippocampal injection of kainic acid, as detected on electroencephalogram (EEG).

Richichi et al. (46) studied the effect on acute kainate-induced seizures and kindling epileptogenesis of long-lasting neuropeptide Y overexpression by local application of recombinant AAV vectors in the rat hippocampus (46). The authors used vectors with different serotypes and clearly showed that tissue can be more efficiently targeted by varying capsid genes (47). rAAV serotype 2 (rAAV2) vector increased neuropeptide Y expression in hilar interneurons only, whereas the chimeric serotypes 1 and 2 vector caused far more widespread expression including mossy fibers, pyramidal cells, and subiculum. Seizures detected by EEG, induced by intrahippocampal injection of kainate, were reduced by 50% to 75%, depending on the spread of neuropeptide Y expression, and seizure onset was markedly delayed. In rats injected with chimeric serotypes 1 and 2 vector, status epilepticus was abolished, and kindling acquisition was significantly delayed. The experimental findings in rodent models of seizures suggest that targeted gene transfer may provide a basis for development of new gene therapies that may be useful to treat drug-resistant focal seizure disorders.

CONCLUSION

Despite considerable advancements in anti-seizure pharmacotherapy, a substantial proportion of epilepsy patients remain resistant to standard treatments, continuing to experience debilitating seizures. This therapeutic gap underscores the critical need for novel, more effective, and patient-specific interventions. This review has explored the evolving landscape of seizure control strategies, ranging from new pharmacological agents like cannabidiol (CBD) and fenfluramine (FFA) both showing clinical efficacy in drug-resistant syndromes to neuromodulation techniques such as responsive neurostimulation (RNS) and vagus nerve stimulation (VNS), which offer targeted electrical modulation of neural circuits to suppress epileptiform activity.

Equally important are dietary interventions, notably the ketogenic diet and its more accessible variants like the Modified Atkins Diet (MAD) and Low Glycemic Index Treatment (LGIT), which have proven especially beneficial in pediatric and refractory epilepsy. Furthermore, gene therapy, including gene replacement and editing technologies like CRISPR-Cas9, represents a transformative step toward addressing the underlying genetic causes of epilepsy. The development of viral vector systems, particularly adeno-associated viruses (AAV), has made targeted gene delivery to the brain a viable strategy with long-term potential.

In addition, wearable technologies, machine learning-based seizure prediction tools, and brain–computer interface systems are redefining real-time seizure monitoring and individualizing treatment protocols, thereby enhancing patient autonomy and care outcomes.

Altogether, the integration of advanced pharmacology, neurosurgical innovation, metabolic therapy, gene editing, and digital health technologies marks a paradigm shift in epilepsy management. Future progress will depend on ongoing clinical research, regulatory support, and cross-disciplinary collaboration aimed at making these innovations both clinically effective and widely accessible, with the ultimate goal of improving the lives of those affected by epilepsy

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