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Modern approaches to treating drug-resistant epileps- ketogenic diet, innovative drugs and neurosurgery

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Abstract

Introduction and objective
Drug-resistant epilepsy (DRE) is a type of epilepsy where seizures persist despite treatment with multiple antiepileptic drugs being implemented. This condition severely affects the quality of life of those impacted, often leading to difficulties in daily functioning and associated mental health issues such as anxiety and depression. The goal of this study is to investigate the mechanisms behind drug-resistant epilepsy and review the current approaches to its diagnosis and treatment.

Review methods

A thorough literature review was carried out using the PubMed database to explore studies focused on drug-resistant epilepsy. Key search terms included "drug-resistant epilepsy", “DRE”,. The review concentrated on the latest research examining the pathophysiology, diagnostic tools, and treatment strategies for individuals with DRE.

Description of the state of knowledge
Drug-resistant epilepsy is often associated with disruptions in neuronal activity, changes in protein expression, and imbalances in neurotransmitters. These factors contribute to the lack of response to standard antiepileptic medications. Diagnostic procedures currently involve electroencephalography (EEG) to assess brain activity, along with advanced imaging techniques like MRI and CT scans to detect any structural abnormalities. Available treatments encompass a range of drug therapies, surgical options, neurostimulation, and dietary interventions.

Conclusions
The review highlights that, despite notable progress in understanding drug-resistant epilepsy, there are still significant challenges in developing effective treatments. Continued research into the molecular mechanisms and advancements in diagnostic tools are essential for improving the management of this condition and creating more targeted treatment options.

KEYWORDS
drug-resistant epilepsy, CBD, ketogenic diet

Introduction and purpose

Epilepsy is a neurological condition defined by a persistent tendency to experience seizures. This condition significantly impacts the patient’s everyday life due to other symptoms such as anxiety, bad quality of sleep and depression. The exact mechanisms remain under constant research and are not yet fully understood, but are believed to originate from factors such as irregularities in protein expression and imbalances in the function of neurotransmitters. Diagnosis often begins with a detailed assessment of the patient’s medical history and the use of electrophysiological tests, such as electroencephalography (EEG), which monitors brain activity to identify irregular neuronal discharge patterns. In certain cases, additional imaging techniques like CT scans or magnetic resonance imaging (MRI) may be conducted to detect any structural anomalies that might contribute to the occurrence of epilepsy. [1]
One of the most prevalent forms of epilepsy is drug-resistant epilepsy. According to a review of 35 studies, this problem has a prevalence rate of 30% and an incidence rate of 15%. [2]
Despite the introduction of many new anti-convulsant drugs, this figure has not changed. [3]

Due to their high rates of comorbidities, psychiatric dysfunction, social stigma, diminished quality of life, elevated mortality risk, and decreased life expectancy, patients with refractory epilepsy constitute the majority of the population's epilepsy burden. [4]
This review aims to present an overview of new innovative treatments for drug-resistant epilepsy that have emerged in recent years, focusing on pharmacological therapies, surgical interventions, and dietary restrictions.

1. Characteristics of drug-resistant epilepsy

Up to one-third of people with epilepsy may have drug-resistant epilepsy (DRE), which is defined by the inability to achieve long-term seizure control even with the proper administration of two distinct anticonvulsant medication (ASM) regimens, either separately or in combination. [5]
Refractory epilepsy is more common in people who have had more than 20 seizures prior to treatment or who have not responded well to early ASM treatment. Additional risk factors for DRE include neuropsychiatric diseases (mental retardation, concomitant mental illness, neurological abnormalities), usage of several ASMs, younger age at diagnosis, and lack of response to the initial anticonvulsant medication. The incidence of DREs has not decreased significantly over the previous 20 years, highlighting the ongoing burden of unmet demands for those who have DREs. [6,7]
Therapeutic resistance is caused by a variety of circumstances, including genetic background, inflammation, autoimmune diseases, structural defects, and molecular alterations in therapeutic targets. The more coexisting components we have, the more likely DRE is to occur. DRE is realised by a complicated mixture of all of them. But as of yet, there isn't an instrumental test that can accurately forecast DRE. Clinical and EEG data analysis using big data and artificial intelligence will open up a new and genuine opportunity that will enable us to predict the risk of DRE prior to the first ASM and recommend the best course of treatment—such as medication, surgery, or neuromodulation—to each patient earlier. [8]

1.1 Causes of resistance to treatment

A considerable percentage of epileptic patients suffer from drug-resistant epilepsy, which is a severe clinical problem. Numerous pathophysiological processes, such as genetic, structural, biochemical, and immunological elements that influence the body's reaction to medication, might lead to treatment resistance. [9]

1. Changes in the brain's structure

The development of drug-resistant epilepsy is mostly caused by anatomical alterations in the brain. Taylor's localized cortical dysplasia, which was initially identified in 1971, is one instance. It is distinguished by the presence of large and dysmorphic neurons, "balloon cells," heterotopia of neurons in the subcortical white matter, and aberrant layer architecture of the cerebral cortex. In almost half of individuals with drug-resistant epilepsy, focal cortical dysplasia is quite prevalent. Standard antiepileptic medication is ineffective for the aberrant neuronal activity caused by these lesions. [10]

2. Neuroinflammatory processes

Brain damage, regardless of its cause, triggers a cascade of biological events leading to neuroinflammatory processes. Microglia and astrocytes play a key role in these processes,

which, when activated, release cytokines, chemokines, lipid mediators and other inflammatory factors. In the brain, these mediators alter cerebral vascular function, affect infiltration of inflammatory cells, and modify neurotransmission and communication between neurons, which can result in the development of resistance to treatment. [11]

3. Activation of the complement system

The pathophysiology of epilepsy is significantly influenced by the complement, a system of plasma and cell membrane proteins implicated in inflammatory responses. Neuronal dysfunction is caused by complement activation by necrotic cells, cell fragments, or proteins that are improperly folded, including β-amyloid. The complement system may be one cause of treatment resistance, as evidenced by the overexpression of complement proteins in animal models and in the tissues of epileptic patients. [12,13]

4. Cytokine and chemokine functions

Because of their pro-inflammatory properties, cytokines—which are primarily generated by microglia and astrocytes—play a significant part in the development of treatment resistance. The frequency and intensity of seizures are correlated with elevated levels of interleukins, including IL-1β, IL-6, IL-17, and other inflammatory mediators, in epileptic patients. Additionally, by stimulating glial cells and drawing in peripheral monocytes, chemokines and their receptors encourage neuroinflammation. The efficacy of antiepileptic treatment may be compromised by these mechanisms, which intensify abnormal inflammatory processes. [14,15]

5. Molecular and genetic alterations

Drug resistance is also largely influenced by genetic predispositions, such as mutations that impact ion channels, neurotransmission, or drug metabolism. The pharmacokinetics and pharmacodynamics of antiepileptic medications may alter as a result of these alterations, reducing their efficacy. [16]

2. New pharmacological therapies

Drug-resistant epilepsy (DRE) poses a significant challenge in clinical neurology, as approximately one-third of patients still experience seizures despite undergoing treatment with various antiepileptic drugs (ASMs). With the demand for more effective therapies on the rise, new medications are being launched and evaluated for their ability to enhance seizure control and minimize cognitive side effects, which are often associated with conventional treatments. Recent clinical trials and real-world studies have yielded encouraging data on several new ASMs, such as cenobamate and fenfluramine, both of which have demonstrated effectiveness in treating DRE. The results obtained in real-world conditions suggest that cenobamate has great potential to improve seizure outcomes in patients who have failed other treatments. [17]

This study also focused on the cognitive effects of cenobamate, alongside its ability to control seizures. Cognitive impairment is a frequent side effect of many ASMs; however, treatment with cenobamate has resulted in enhancements in verbal and visuospatial episodic memory, which are two crucial areas of cognitive function. After cenobamate treatment, considerable enhancements in cognitive function were noted, especially in assessments of verbal episodic memory (FCSRT) and visual-spatial memory (ROCFT), with statistical significance levels of $p = 0.0056$, $p = 0.0013$, and $p = 0.011$. Nonetheless, a reduction in attentional cognitive ability was noted, underscoring the complexity of ASM's influence on cognitive function. The

enhancement of cognitive function was mainly linked to a decrease in the number of ASMs patients used concurrently, highlighting the significance of reducing polytherapy for cognitive function improvement. [17]

Originally, fenfluramine, a novel drug with encouraging characteristics, was designed to suppress appetite. Nonetheless, it was found to have anticonvulsant effects over time, particularly in individuals with Dravet syndrome, which is a rare and serious type of epilepsy. Studies from the 1980s demonstrated potential for reducing seizure frequency in patients with refractory epilepsy, and recent research has confirmed its efficacy in treating Dravet syndrome. Fenfluramine was found to decrease the occurrence of large motor seizures in individuals with Dravet syndrome by as much as 63.9% at doses of only 0.2 mg/kg/day, according to a significant study. A significant improvement in the context of a disease that has historically resisted treatment is seen in the group of patients treated with higher doses, where as many as 70% experienced at least a 50% reduction in seizures. [18]

Clinical trials of fenfluramine have targeted its safety profile as well as a reduction in seizures. During clinical trials, side effects were typically mild, with decreased appetite, diarrhoea, and fatigue being the most common. It is crucial to note that fenfluramine did not demonstrate any notable long-term cardiovascular effects. This is particularly relevant considering the drug's historical links to heart valve issues associated with higher doses used for weight loss purposes.

The medication functions by adjusting serotonin levels, which is thought to stabilize neuronal excitability—a mechanism different from that of conventional ASM. [18][19]

Clobazam, a benzodiazepine approved for Dravet syndrome and other types of epilepsy, has emerged as a valuable treatment option. While not as recent as cenobamate or fenfluramine, its use alongside other anti-seizure medications (ASMs) has been shown to enhance seizure control in patients with drug-resistant epilepsy (DRE). Clinical trials indicate that clobazam boosts the effectiveness of other ASMs, particularly for refractory seizures. It is generally well tolerated, though some patients may experience sedation or behavioral changes. Adding clobazam to treatment regimens has significantly reduced seizure frequency, especially in those who have not responded to multiple therapies. This combination approach can be particularly beneficial for patients with complex epileptic syndromes, where polytherapy remains a key treatment strategy. [20]

To sum up, the emergence of new ASMs like cenobamate, fenfluramine, and clobazam marks a noteworthy advancement in addressing drug-resistant epilepsy. These medications introduce novel mechanisms of action that can lower seizure frequency and enhance cognitive performance, catering to the varied needs of individuals with epilepsy. While further studies are required to assess their long-term safety and effectiveness, initial findings provide hope for improved DRE management and enhanced quality of life for patients.

2.1 Cannabinoids and their potential in the treatment of refractory epilepsy

Epilepsy is still a difficult neurological condition, particularly when seizures fail to respond to standard therapies. About 30% of patients, particularly those with developmental and epileptic encephalopathies (DEEs), still have refractory seizures in spite of the large variety of antiepileptic medications (ASMs) that are currently on the market. Complex treatment regimens using polypharmacy are frequently necessary for illnesses like Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), which can have serious adverse effects including drowsiness and cognitive impairment. Given the elevated risk of consequences,

including as developmental regression and sudden unexpected death in epilepsy (SUDEP), a more efficient treatment strategy is essential. [21]
By altering ion channels, traditional ASMs mainly target neuronal hyperexcitability; however, this one-target strategy may ignore other intracellular pathways that play a role in seizure production. As a result, there is a rising interest in cannabinoids, especially cannabidiol (CBD), as a therapy alternative due to the need for novel therapeutic approaches that address numerous seizure pathways. CBD is a viable treatment option for people who don't react to traditional medications since studies have shown that it can have anticonvulsant benefits without the euphoria or tolerance development associated with Δ9-tetrahydrocannabinol (THC). [21]
Neuronal excitability can be decreased by CBD's capacity to inhibit GPR55 receptors, which are important in the control of excitatory neurotransmission. Furthermore, CBD has been demonstrated to block calcium influx via voltage-gated T-type calcium channels, which is comparable to how other well-known ASMs like ethosuximide work. Furthermore, by encouraging the inhibitory activity of GABA A receptors, which are essential in halting the excessive neuronal firing that causes seizures, CBD can improve GABAergic signalling. CBD is a great option for treating refractory epilepsy because of these pathways as well as its capacity to influence a variety of biological targets. [22]
According to research conducted between 2018 and 2023, CBD can effectively lower the frequency of seizures; in certain individuals, this can result in a 50% improvement or total seizure freedom. Since CBD does not have any psychotropic effects, it is a popular choice for treating children and teenagers. Despite being typically well-tolerated, CBD may interact with antiepileptic medications like valproic acid or clobazam. Therefore, patient monitoring is crucial to guarantee the security and effectiveness of treatment. [23]

2.2 Ketogenic Diet

Drug-resistant epilepsy (DRE) has been treated with the ketogenic diet (KD), a low-carb, high-fat diet, since the 1920s. By encouraging the synthesis of ketone bodies, which the brain uses as an alternate energy source to glucose, this therapeutic diet simulates the metabolic state of fasting. About 70–80% of the classic ketogenic diet includes fat, 10–20% is protein, and just 5–10% is carbohydrate. Reducing carbohydrate consumption causes the body to use ketones instead of glucose as its primary fuel, which alters brain metabolism and biochemistry. Children with drug-resistant epilepsy, particularly those with disorders like Dravet syndrome, Doose syndrome, and infantile spasms, have seen a notable reduction in seizure frequency while following a ketogenic diet. Although the ketogenic diet has been used for a long time, it is still unclear exactly how it prevents epilepsy. However, some theories suggest that it involves metabolic changes that stabilize neuronal activity, increase mitochondrial function, and modify neurotransmitter systems, such as glutamatergic and GABA-ergic pathways. [24]
Restoring metabolic and energy balance in the brain is thought to be the main way that the ketogenic diet works. The diet lowers neuronal excitability and seizure frequency by boosting the creation of ketone bodies, which divert brain metabolism from glucose. The ketogenic diet may also have antiepileptic benefits since it is believed to influence a number of other biological processes, including gut microbiota, oxidative stress management, and mitochondrial function. [25]
By encouraging inhibitory neurotransmission and blocking excitatory pathways, the ketones themselves can directly alter neuronal activity and stabilize electrical activity in the brain. Despite its promise, the ketogenic diet poses difficulties in clinical practice because of its

severe dietary requirements and its adverse effects, which include kidney stones, loss of bone mineral density, and dyslipidemia. Low glycemic index treatment (LGIT) and the modified Atkins diet (MAD) are two variants of the ketogenic diet that have been created to offer less restrictive alternatives with comparable advantages. The long-term safety and effectiveness of the ketogenic diet, as well as how it might be tailored for various patient populations and used with other therapies, should be the subject of future research. To sum up, the ketogenic diet is still a useful treatment for drug-resistant epilepsy, providing a proven substitute when pharmaceutical treatments are ineffective. However, in order to provide the best possible results for patients, it necessitates careful thought and interdisciplinary supervision. [25]

Although data are still somewhat equivocal due to variations in patient groups and research designs, the effectiveness of the ketogenic diet (KD) in treating drug-resistant epilepsy, especially in adults, has shown encouraging results. A considerable percentage of patients have reported a decrease in the frequency of seizures in clinical studies, which have demonstrated modest effectiveness despite frequently having small sample sizes. For instance, although results varied somewhat, a randomized clinical trial employing the modified Atkins diet (MAD) demonstrated a modest decrease in seizure frequency in people with refractory focal epilepsy. Improved quality of life is a noteworthy advantage of KD, despite its difficult nature, as many patients report feeling more in charge of their health than is usually the case with standard antiepileptic medications. According to studies, a significant portion of adult patients with status epilepticus have seizure remission quickly, indicating that KD may be useful in treating the condition. However, as retention rates tend to fall over time and other studies have demonstrated a decline in patient adherence after six months to a year, long-term effectiveness is still unknown. [26][27]

Despite these difficulties, KD has shown promise in treating drug-resistant epilepsy in both adult and juvenile populations. Response rates vary from 30% to 70%, depending on the particular diet variation and research design. Combining several KD diets, such as the traditional KD diet, MAD, and the medium-chain triglyceride (MCT) diet, has produced a variety of results, such as a decrease in the frequency and intensity of seizures and, in certain situations, even the absence of seizures. Furthermore, KD has been shown to increase mood, motivation, and general quality of life, demonstrating that its benefits go beyond seizure management. To further understand its mechanics and maximize its application in clinical practice, more research is required, including bigger, more standardized clinical studies. [27]

2.3 Neurosurgery and vagus nerve stimulation

In addition to conventional pharmaceutical treatments, neurostimulation techniques and surgery are employed in the management of drug-resistant epilepsy (DRE). For individuals whose seizures are too severe to be managed with medicine alone, or who do not respond to treatment, these methods are advised. Electrical brain stimulation is used in neurostimulation, a type of therapy, to lessen the frequency of seizures. The three most popular techniques are responsive neurostimulation (RNS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS). [28]

Although vagus nerve stimulation (VNS) has become a viable treatment option for medically intractable epilepsy, patient groups continue to differ in how successful it is. Despite being utilized in therapeutic settings for more than 20 years, the exact processes behind VNS's antiseizure benefits are still unclear. Recent developments in computer modeling and neuroimaging have shed light on the brain circuits underlying VNS response, especially when it comes to the "vagus afferent network." The effects of VNS are thought to be mediated in

large part by this network, which is made up of vagal afferent fibers that extend to the nucleus tractus solitarius as well as other brainstem, subcortical, and cortical regions. Dynamic alterations in these brain networks after stimulation have been shown in studies using functional imaging methods, such as BOLD fMRI and PET scans, providing possible biomarkers to predict therapy response. In order to improve therapeutic results for people with drug-resistant epilepsy, more study into the vagus afferent network may improve patient selection criteria and optimize stimulation levels. [29]

Conversely, localized epilepsy responds well to deep brain stimulation (DBS), particularly when the source of the seizure is in a hard-to-reach area of the brain. Electrodes are inserted into important subcortical nuclei during DBS, including the anterior nucleus of the thalamus (ANT), which is linked to limbic and hippocampus epilepsy. Even though research on this technique is ongoing, it has shown great promise in lowering seizures, especially when other therapies have failed. [28]

In contrast, more sophisticated technology underpins responsive neurostimulation (RNS), which enables real-time stimulation impulse adjustments depending on brain activity. RNS has shown promise in the treatment of localized epilepsy, especially in individuals whose seizures originate in particular regions of the brain. By applying stimulation just during a seizure, this method reduces disruption to regular brain activity. When seizures start in a brain region that is accessible, individuals with DRE may potentially qualify for surgical treatments like epileptic focal excision in addition to neurostimulation. For individuals who do not react to medication, surgically removing epileptic foci can result in a notable improvement. Neurostimulation is still a vital option for people who don't fit the requirements for reconstructive surgery. There are drawbacks to both surgical and neurostimulation techniques. Side effects with VNS and DBS include infections, implantation site discomfort, voice changes, and heart problems. However, studies show notable long-term improvements in quality of life and seizure reduction. To improve these techniques and determine which patients will gain the most from these treatments, more research is required. [28]

There are still several obstacles facing modern surgical techniques to treating epilepsy, especially drug-resistant epilepsy (DRE). Data from recent years reveal that surgery is underutilized, despite the fact that surgical procedures have demonstrated excellent effectiveness in appropriate circumstances. Despite the fact that there are now more clinics providing surgical therapy, only 0.35% to 0.63% of patients with DRE actually obtain surgical treatment each year. Social and psychological barriers, as well as patients' and physicians' misunderstandings about the dangers of surgery, are some of the causes of this phenomena. According to recent research, a large number of individuals with DRE are not properly sent to specialized epilepsy facilities, which provide a variety of diagnostic services and alternative treatments. Lack of consultation at such a center is frequently caused by the assumption that the patient won't profit from the therapy, which will exacerbate their epilepsy issues. It should be underlined that all DRE patients should have a proper diagnosis and assessment at a professional facility; not all of them need to decide whether to have surgery. [30]

Modern diagnostic technologies, such as high-resolution MRI, functional imaging (fMRI) and magnetoencephalography (MEG), allow more precise identification of brain areas responsible for triggering seizures. In addition, developments in surgical techniques, such as the use of deep brain stimulation (DBS) electrodes and ablation techniques like laser thermal therapy (LiTT), are increasing the availability and effectiveness of treatments for some types of epilepsy. Surgical outcomes are still encouraging, particularly when it comes to patients' increased quality of life as a result of fewer seizures and better mental health. Furthermore, some research suggests that individuals who are not candidates for standard resection may

have an option with the advent of novel therapies such cerebral nerve stimulation (RNS). It is also important to note that the risk of sudden unconsciousness (SUDEP)-related premature mortality is considerably decreased by surgical treatment of epilepsy. [30]

Conclusions

Recent advancements in drug-resistant epilepsy (DRE) treatments, such as cenobamate and fenfluramine, offer new hope for patients who fail conventional therapies. Cenobamate not only improves seizure control but also enhances cognitive function, particularly in verbal and visuospatial memory, with reduced polytherapy being beneficial for cognitive outcomes. Fenfluramine, originally developed for appetite suppression, shows strong anticonvulsant effects in conditions like Dravet syndrome, with a favorable safety profile compared to past formulations.

Cannabinoids, particularly cannabidiol (CBD), provide a promising alternative for refractory epilepsy, offering anticonvulsant effects without the psychoactive side effects of THC. CBD's multiple mechanisms of action, including modulation of GABAergic signaling and ion channels, enhance its therapeutic potential for patients unresponsive to traditional drugs.

The ketogenic diet (KD), despite its strict requirements, remains an effective option for reducing seizures in DRE patients, particularly children. Modified versions of the diet, like the Modified Atkins Diet (MAD), offer similar benefits with fewer restrictions.

Neurostimulation techniques such as Vagus Nerve Stimulation (VNS), Deep Brain Stimulation (DBS), and Responsive Neurostimulation (RNS) show significant promise in reducing seizure frequency and improving quality of life for patients with refractory epilepsy. However, surgical treatments are still underutilized due to social and psychological barriers, despite their effectiveness. The ongoing development of more precise diagnostic and surgical techniques suggests that these therapies will play an increasingly important role in managing DRE.

Author's contribution Statement

Conceptualization, Robert Rzenno, Monika Brzozowska; methodology, Wiktoria Wardal; software, Natalia Furlepa; Karolina Wojciechowska; check, Marcelina Matuszewska and Katarzyna Wicha; formal analysis Natalia Sidz; investigation, Magdalena Tomaszewska and Wiktoria Jedlikowska; resources, Robert Rzenno; data curation Monika Brzozowska, Natalia Furlepa and Karolina Wojciechowska; writing - rough preparation, Robert Rzenno; writing - review and editing, Robert Rzenno and Natalia Sidz; visualization, Wiktoria Jedlikowska, Marcelina Matuszewska; supervision, Robert Rzenno; project administration Katarzyna Wicha

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