TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 17
Number 1 *Fall 2023*

33-42

2023

Epilepsy and Treatment Resistance

Eva Kowalsky

Epilepsy and Treatment Resistance

Eva Kowalsky

Eva Kowalsky graduated with a Bachelor of Science degree in Honors Biology in June 2023 planning to attend medical school in May of 2025.

Abstract

Epilepsy is one of the most common debilitating neurological conditions. Individuals with epilepsy experience frequent seizures. Seizures are caused by hyperexcitable and hyper-synchronized neurons. Anti-seizure medications typically work to normalize the electrical activity in the brain. Many epileptic disorders are caused by genetic mutations, most of which cause mutations in ion channel mechanics. 30% of individuals with epilepsy do not respond to classic anti-seizure medications. A combination of factors typically contributes to treatment resistance. Individuals with drug-resistant epilepsy must turn to novel approaches for seizure relief. These approaches include following a ketogenic diet, using CBD products, utilizing a neurostimulator device, or resorting to epilepsy surgery. These approaches are usually successful in providing seizure relief. The purpose of this review is to give an overview of epilepsy, discuss its mechanism of action, review the concept of drug resistance, and consider novel therapeutic options for those individuals.

Introduction

The average human brain contains 86 billion neurons intricately linked by synapses, which serve as contact sites for electrochemical transmission. Synaptic connection patterns produce functional ensembles of neurons, which control information processing in the brain. The coordinated firing of neurons in the brain gives rise to our cognitive capacities. The opposing forces of excitation and inhibition are generally kept in balance by several homeostatic processes. Seizures are caused by excessive electrical activity in the brain and are a typical clinical manifestation of neural circuit failure. Seizures can be caused by a variety of genetic disorders or brain structure malformations and can occur in any region of the cerebral cortex. Epilepsy is a clinical disorder defined by a persistent proclivity to spontaneous seizures. Epilepsy affects 0.5-1% of the world's population and is associated with significant physical and psychological morbidity as well as increased death (Rao & Lowenstein, 2015). Antiepileptic medications either decrease excitation or enhance inhibition of the electrical activity in neurons in order to prevent seizures. However, many individuals experience drug-resistant epilepsy, which is characterized by failing two or more antiepileptic medications. This review will give an overview of epilepsy and explain some possible reasons why some individuals experience drug resistance. Additional topics of novel approaches to relieve epileptic seizures will also be discussed.

Methods

Through the usage of databases such as Google Scholar, Touro's Library, the National Center for Biotechnology Information, and the Epilepsia journal database, articles were chosen and reviewed for inclusion purposes. Each article was analyzed and assessed to determine validity and complete topic relevance. Key phrase searches included "epilepsy," "drug resistance," "anti-seizure medications," "ketogenic diet," and "cannabis for epilepsy."

What is Epilepsy?

Epilepsy is a chronic medical condition in which one experiences recurrent seizures. Epilepsy disorders are one of the most common neurological disorders in childhood; however, the elderly can acquire epilepsy as a consequence of conditions such as stroke, tumors, Parkinson's, or Alzheimer's disease. It is important to clarify that the term "epilepsy" signifies the disease and "seizures" as the symptom. A single seizure can occur as a result of an injury, a tumor, or a high fever. Those seizures would be considered reactive seizures occurring in normal nonepileptic tissue. Epilepsy is diagnosed after a person has had two or more unprovoked seizures (Epilepsy and seizures). Epilepsy is often caused by genetic disorders or brain structure malformations and can be comprised of a specific seizure type or multiple seizure types.

History of Epilepsy

The word seizure is derived from the Greek meaning "to take hold." In ancient cultures, seizures were viewed as experiences of demonic possession or evidence of a spiritual connection. In the 19th century, epilepsy was conclusively widely accepted as a physical medical condition, and patients were separated into dedicated hospitals to receive proper medical care. Additionally, the discovery and use of EEG greatly enhanced physicians' understanding of epilepsy. The International League Against Epilepsy (ILAE) developed and periodically updates the classification systems for seizures (Patel & Moshé, 2020).

Diagnosis of Seizures and Epilepsy

Epilepsy can be diagnosed by a range of medical practitioners. With a first seizure, a person is typically examined by a physician in an emergency room. After ruling out life-threatening diseases and conditions, the individual will often be referred to their primary care provider or a neurologist for follow-up. The two monitoring techniques typically used to diagnose epilepsy are EEG (electroencephalogram) and video monitoring. An EEG is a test that monitors the electrical activity in the brain, detecting an anomaly or shift in brain waves during a seizure. Seizures are usually accompanied by very large EEG patterns. EEG can also assist in determining where the seizure began, if

it spreads, and the type of seizure. CT and MRI scans are utilized to see if there is an area of scarring, tumor, or structural malformation that could be causing the seizure. Genetic testing can be done to determine if a genetic mutation is causing the seizures. An individual would be given a diagnosis of epilepsy following two or more unprovoked seizures.

Types of Seizures

There are two basic categories of seizure types, generalized seizures, and partial/ focal seizures. Additionally, a distinction must be made between simple vs complex seizures. Focal seizures have a specific focus or source or origination, such as a scarred region of the brain or a malformed blood vessel. They are usually restricted to a small area of the brain and are often caused by structural lesions or abnormalities. In contrast, generalized seizures are widespread and involve most of the brain. In some cases, generalized seizures can spread from a specific focus, but typically, they spread from many areas. Generalized seizures are more often linked to genetic causes. Simple seizures cause changes in consciousness but not loss of consciousness, while complex seizures lead to loss of consciousness. Subcategories of seizures include infantile spasms, absence seizures (petite-mal), clonic, myoclonic, atonic, tonic, and tonic-clonic (grand-mal). Combinations of seizure types can also be used to identify complex seizures. Motor seizures cause shifts in muscular activity, such as jerking, rigidity, loss of muscle tone, or automatisms. Non-motor seizures can cause changes in heart rate, breathing, or color; a blank stare, inability to speak or move; cognitive changes that cause difficulty speaking and understanding; emotional changes that cause sudden fear, dread, or even pleasure; or sensory changes that cause numbness, tingling, or pain (Obsorne-Shafer, 2016)

The Pathophysiology of Seizures

Ion channels control the excitability of the neuronal membrane and are responsible for action potential propagation. A mutation in an ion channel can affect channel kinetics, channel activation or inactivation, or recovery from inactivation. Electrical impulses, known as action potentials, are used by neurons to communicate. The neuronal membrane depolarizes or changes in voltage as a result of a net positive inward ion flow. Normally, many inhibitory processes involving negative ions, such as chloride ions, help brain tissues prevent hyperexcitability. However, mutations in the ion channels cause depolarization to occur in excess. In this condition, the excitatory impulses are increased while inhibitory transmission is reduced. Therefore, the voltage differential across the neuronal membrane is altered favorably, and the ion channels stay open for longer than normal, causing hyperexcitability. Another group of mutations that lead to epilepsy impairs synaptic inhibition, also causing hyperexcitability. The mechanism of seizure formation can be caused by the excitation of a group of nerves caused by the inward flow of positive ions and involvement of excitatory neurotransmitters, too little inhibition, or epileptogenesis, hyperexcitability, and hyper synchronization of neurons that facilitates spread (Mandal, 2019). A hyperexcitable neuron alone cannot generate a seizure; rather, there must be abnormal synchronization in addition.

Seizure Mortality

Seizures are associated with significant physical and psychological morbidity as well as increased death. The amount of brain damage an individual with epilepsy accrues is usually correlated with seizure frequency and severity. The presumed mechanism of damage is the excessive release of glutamate, the most abundant excitatory neurotransmitter, during the seizure, which can cause glutamate excitotoxicity, a cell death mechanism. Significant damage can be caused during an episode of status epilepticus, which is a potentially fatal condition in which a person either has an excessively lengthy seizure or fails to fully recover consciousness in between recurrent seizures. Rescue medications are administered in order to prevent an episode of status epilepticus. Additionally, for reasons unclear, individuals with epilepsy are more likely to die unexpectedly and without apparent cause. This condition is called Sudden Unexplained Death in Epilepsy. Individuals with uncontrolled or drug-resistant epilepsy are at a higher risk of dying from Sudden Unexplained Death in Epilepsy.

Genetic Mutations and Epilepsy

Genetic mutations cause around 70% of epileptic disorders. Genetic testing can identify a cause for a patient's epilepsy that was previously thought to have been idiopathic (without known cause). The genetic alterations range from large-size chromosomal copy number variants, to small insertions or deletions, and single nucleotide variations (Tsang et al., 2019). Additionally, combinations of mutations in multiple genes can also cause epilepsy (Chambers et al., 2016). Whole exome sequencing allows for rapid analysis of many genes and plays an important role in clinical diagnostics. Whole exome sequencing has become a promising and cost-effective tool in genetic diagnosis for patients with epilepsy (Tsang et al., 2019). In addition, genomic testing supports the application of

precision medicine to epilepsy care by allowing the tailoring of medication and management recommendations (Graifman et al., 2023). Whole exome sequencing can guide providers in choosing the appropriate anti-seizure medications (ASM), suggest additional screenings based on co-morbidities discovered via genetic diagnosis, and help individuals gain access to specific clinical trials. For example, in patients with SCN8A, sodium channel blockers were found to be especially beneficial in reducing seizures; however, they were found to worsen seizures and increase their frequency in patients with SCN1A (Tsang et al., 2019, Graifman et al., 2023). This is why genetic diagnosis can be essential in clinical management. Additionally, a genetic diagnosis can give families greater peace of mind, connect them with support and advocacy groups, and provide options for future reproductive decisions. Another benefit of WES is that it can help identify other diseases a patient might be suffering from that mimic epilepsy (Chambers et al., 2016). The usage of numerous commercial epilepsy panels is becoming more commonplace as a first step in epilepsy management. Nearly all the genetic mutations that cause epilepsy cause mutations in ion channels. A mutation in the SCN1A gene and the HCN1 gene causes a mutation in the sodium channel. A mutation in the KCNQ2/3 genes causes mutations in potassium channels. These mutations can cause changes in membrane excitability. Additionally, other genetic mutations can cause problems with neurotransmitter release, synapse development, postsynaptic response, neuronal growth and nutrient sensing, neuronal metabolism, and neuronal proliferation and migration (Rao & Lowenstein, 2015).

Classical Epilepsy Treatments- Anti-Seizure Medications (ASM)

The first line of treatment for seizure disorders is anti-seizure medications (ASM), also known as antiepileptic drugs (Kaeberle, 2018). Common ASM include valproic acid (Depakote), levetiracetam (Keppra), topiramate (Topamax), oxcarbazepine (Trileptal), and lamotrigine (Lamictal). The choice of ASM should be tailored to the specific seizure type, epileptic syndrome, co-morbidity, co-medication, lifestyle, and preferences of the patient and, if necessary, their family or caregivers. ASM are not cures for epilepsy and do not treat the underlying cause. They are used continuously to prevent seizures and must be taken consistently every day. ASM are introduced gradually and increased until seizures are controlled, or adverse effects are unacceptable. Side effects of ASM can include grogginess, double vision, dizziness, nausea, unsteady gait, depression, hyperactivity, and rash. In addition to ASM, most individuals with an epilepsy disorder have a rescue medication. Rescue medications are administered in order to stop excessively lengthy seizures and to prevent an episode of status epilepticus. Each individual has a different recommendation from their provider as to when a rescue medication should be administered (Kaeberle, 2018). Rescue medications include Diazepam, which is given rectally, Clonazepam, which is administered in the form of a dissolvable tablet or strip in the mouth, and Midazolam, which is given as a nasal spray.

Mechanisms of Action of ASM

The mechanism of action for many ASM is the modulation of voltage-gated ion channels (sodium, calcium, and potassium). Additionally, other ASM aim to prolong the inhibitory actions of inhibitory neurotransmitters such as GABA, while others decrease the tendency for certain neurons to fire action potentials at high frequencies, and others directly modulate synaptic release by affecting components of release machinery (Löscher et al., 2020). By altering neurons' bursting characteristics and lowering synchronization in localized neuronal ensembles, ASMs lower the likelihood that a seizure will occur. Additionally, ASMs prevent abnormal neuronal activity from transferring to nearby brain regions (Löscher et al., 2020).

Drug-Resistant Epilepsy (DRE)

Despite the usage of many ASM, approximately one-third of individuals with epilepsy suffer from uncontrolled seizures. According to Talevi (2022), despite the increasing number of options for epilepsy treatment, the portion of epilepsy patients that remain drug-resistant has stayed the same during the last 100 years. DRE is associated with increased morbidity and mortality, serious psychosocial consequences, cognitive problems, and reduced quality of life (Tang et al., 2017). Additionally, individuals with uncontrolled or drug-resistant epilepsy are at a higher risk of dying from Sudden Unexplained Death in Epilepsy and the risk of other negative consequences related to seizures, such as falling or drowning is increased. Seizures are also associated with brain damage due to episodes of status epilepticus, which they are at higher risk for. Patients with DRE often resort to unconventional treatments for seizure relief, such as following a ketogenic diet, surgical removal of the seizure focus, neurostimulation devices, and the use of cannabis. Drug resistance is hard to predict at diagnosis. The related risk factors are younger onset age, abnormal EEG findings (both slow wave and epileptiform discharges), neurological deficits at the time of diagnosis, symptomatic etiology, high-frequency seizures, an episode of status epilepticus, multiple seizure

types, and non-response to the first ASM (Xue-Ping et al., 2019). Interestingly females are more likely to develop drug-resistant epilepsy than males (Cepeda et al., 2022).

Criteria for Drug-Resistant Epilepsy

To improve patient care and facilitate clinical research, the International League Against Epilepsy (ILAE) formulated a consensus definition of drug-resistant epilepsy. Drug-resistant epilepsy, also called refractory or intractable epilepsy, is defined as failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. The failure of an unconventional treatment would not count as an appropriate trial for drug resistance determination. Additionally, the individual must have been taking the medication at an adequate strength/dosage for a sufficient amount of time without experiencing significant adverse effects (Kwan et al., 2010). A drug that failed due to serious adverse side effects would not either be considered a trial for drug resistance determination. Studies have shown that after failure of two appropriate, well-tolerated ASM, the chance of success from further trials of ASM becomes less likely (Löscher et al., 2020).

Factors Contributing to Treatment Resistance

There are six main hypotheses for the possible underlying mechanisms of ASM resistance. The two most discussed are the transporter hypothesis and the target hypothesis. The other hypotheses include the gene variant hypothesis, the intrinsic severity hypothesis, the neural network hypothesis, and the pharmacokinetic hypothesis. Other factors discussed are epigenetics and neuroinflammation. In an individual, it is not one of these factors that contribute to treatment resistance, but rather a combination, complicating successful treatment outcomes. While the mechanisms proposed in the transporter, pharmacokinetic, target, neuronal network, and intrinsic severity hypotheses may offer a more direct association between alterations and drug resistance, mechanisms proposed in the gene variant and neuroinflammatory hypotheses offer a more integrative view that could serve as the basis for the emergence of the other mechanisms (Servilha-Menezes & Garcia-Cairasco, 2022).

Transporter Hypothesis

The transporter hypothesis states that drug resistance originates from the increased or altered expression of efflux transporters across the blood-brain barrier (BBB), leading to decreased availability of ASMs at their site of action (Servilha-Menezes & Garcia-Cairasco, 2022). The supporting evidence for this hypothesis is that P-Glycoprotien, multidrug resistance proteins, and breast cancer resistance protein are found in higher concentrations in epileptic brain tissue. These transporters have been shown to hinder chemotherapeutic drugs from entering cancer cells. Therefore, it is hypothesized that these transporters use those same mechanisms to hinder ASMs from crossing the BBB (Tang et al., 2017).

Target Hypothesis

The target hypothesis states that acquired molecular level alterations to the structure and functionality of ASM targets, such as compositional changes in voltage-gated ion channels, and neurotransmitter receptors, could result in decreased drug sensitivity (Tang et al., 2017)(Servilha-Menezes & Garcia-Cairasco, 2022). Loss of use of dependent blockade of sodium channels by the ASM carbamazepine was observed in carbamazepine-resistant patients. Additionally, GABAA receptor subunits were observed to be altered in epileptic brain tissue, and therefore, ASM that act on the GABA receptors would not work properly (Tang et al., 2017).

Gene-Variant Hypothesis

The gene-variant hypothesis states that endogenous variance in genes involved in the pharmacodynamics and pharmacokinetics of ASM or genes associated with the epileptic phenotype could be the source of drug resistance (Servilha-Menezes & Garcia-Cairasco, 2022). For example, mutations in the SCN1A gene are the main cause of Dravet Syndrome, a syndrome characterized by its drug resistance.

Intrinsic Severity Hypothesis

The intrinsic severity hypothesis states that neurobiological factors contribute to define epilepsy in a range from mild to severe and determine its response to ASM treatment (Servilha-Menezes & Garcia-Cairasco, 2022). In other words, DRE is inherent to the disease severity (Tang et al., 2017). The supporting evidence for this hypothesis is that increased seizure frequency and severity have been correlated to higher instances of DRE.

Neural Network Hypothesis

The neuronal network hypothesis states that epilepsy-related structural alterations can lead to the state of drug resistance through the formation of an abnormal neuronal network. The structural changes could prevent the ASM from reaching their targets and contribute to a reduced inhibitory effect of the endogenous antiepileptic system (Servilha-Menezes & Garcia-Cairasco, 2022). Structural

changes include axonal sprouting, synaptic reorganization, aberrant neurogenesis, and neurodegeneration.

Pharmacokinetic Hypothesis

The pharmacokinetic hypothesis states that peripheral overexpression of efflux transporters in organs such as the liver, intestine, and kidney increases drug metabolism and the clearance of ASM, thereby reducing plasma levels and availability to cross the blood-brain-barrier (Servilha-Menezes & Garcia-Cairasco, 2022). In addition, some drugs exhibit nonlinear pharmacokinetics induced by the medication itself. For example, valproic acid is highly and concentration-dependent bound to plasma albumin. The ability of albumin to bind to valproic acid diminishes with increasing valproic acid concentration. This means that with increasing dosage, the total valproic acid available to cross the blood-brain-barrier decreases (Vázquez & Fagiolino, 2022).

Epigenetic Hypothesis

Epigenetics is the study of changes in organisms caused by modification of gene expression rather than alteration in the genetic code itself. Studies have shown that seizures can cause histone modifications, and DNA methylation changes have been observed in epileptic tissue (Fonseca-Barriendos et al., 2022). These epigenetic changes can cause alterations in ASM target receptors, leading to DRE. Additionally, epigenetic changes can be induced by the ASM itself. For example, phenobarbital is associated with a decreased expression of methyltransferases and increased gene expression (Fonseca-Barriendos et al., 2022).

Neuroinflammatory Hypothesis

Neuroinflammatory processes can provoke dysfunction in the blood-brain-barrier and cause overexpression of efflux transporters, resulting in loss of responsiveness to ASM. The supporting evidence for this hypothesis is that inflammatory mediators released by neurons during a seizure are shown to increase the expression of efflux transporters. This is why the neuroinflammatory hypothesis can be seen as the possible underlying mechanism of the transporter hypothesis (Servilha-Menezes & Garcia-Cairasco, 2022, Vázquez & Fagiolino, 2022)

Models and Research on Drug Resistance

Developing novel treatments and management strategies for DRE has been a longstanding goal of clinicians and researchers (Löscher et al., 2020). In vivo and in vitro models have considerably contributed to researchers' understanding of DRE. Models of DRE are important not only for the identification of the mechanisms of DRE and its treatment failure but also for novel drug testing. Rodents and zebrafish are genetically modified to be drug-resistant for researchers to understand the mechanism behind DRE and to test novel drugs. Dogs with spontaneous seizures are also used in rare cases; however, ethical approval and the complexity of canine clinical trials limits their usage. In vitro, models such as lab-grown neurons are also used (Löscher et al., 2020).

How To Overcome Drug Resistance

The mechanism of resistance is not specific to a single ASM but rather affects a variety of drugs. Thus, overcoming DRE is extremely challenging. One of the current approaches for identifying more effective treatments for DRE is the development of new ASM using a new drug screening program. The data generated from these programs creates a pharmacological profile that identifies promising investigational compounds for further development and potential treatment of DRE. Additionally, precision medicine is being investigated as a possible avenue of therapy for individuals with DRE. Furthermore, add-on treatment with drugs that act on the mechanisms of ASM resistance, such as efflux transporter inhibitors or anti-inflammatory drugs, is also a hopeful therapeutic possibility (Löscher et al., 2020).

The Ketogenic Diet and Epilepsy

A ketogenic diet (KD) is a high-fat, low carbohydrate, diet that mimics the metabolism of a fasting state to promote the production of ketone bodies. This state is known as ketosis, which means that the body shifts from breaking down carbohydrates to breaking down fats. The KD is often utilized in cases of DRE. Prior to the introduction of ASM, the KD was used in many cases of epilepsy. Currently, due to its difficult maintenance and side effects, the KD is typically used in cases of DRE. A KD is initiated, monitored, and, if needed, modified, by a physician and nutritionist. Potential side effects of the KD include impaired growth due to nutritional deficiency and a buildup of uric acid in the blood, which can lead to kidney stones (Epilepsy and seizures). There are four different types of KDs, the classic long-chain triglyceride KD, medium-chain triglyceride KD, modified Atkins diet, and low glycemic index treatment (Zhu et al., 2022).

Long-Chain Triglyceride (LCT) KD

The classic long-chain triglyceride KD is the most common KD for epilepsy management. The LCT KD is very restrictive and follows a 4:1 ratio of fat to carbohydrates. A 3:1 ratio can be used for infants or specific children

who require higher amounts of protein or carbohydrates. The LCT is often unpalatable, difficult to prepare, and difficult to maintain (Zhu et al., 2022).

Medium-Chain Triglyceride (MCT) KD

The medium-chain triglyceride KD is a slightly more flexible KD than LCT KD. In MCT KD, the calorie intake is calculated based on the percentage of energy derived from MCTs (Zhu et al., 2022). A typical MCT diet should consist of 30%-60% of calories from MCTs. MCT fat is more ketogenic than LCT fat; this means that it produces ketone bodies easier. Therefore, the MCT diet requires less total fat to be consumed, allowing more carbohydrates and proteins to be included.

The Modified Atkins Diet (MAD)

The modified Atkins diet is based on the Atkins diet and is similar to the classic KD; however, it does not require the precise weighing of ingredients. This diet requires less carbohydrates than the traditional Atkins diet and encourages high levels of fat intake (Zhu et al., 2022). Even though there are no strict ketogenic ratios on the MAD, ratios typically range from 1:1 to 2:1 but sometimes can also reach 4:1.

Low Glycemic Index Treatment (LGIT)

The low glycemic index treatment for epilepsy was developed as an alternative to KD. The LGIT is based on the concept that the protective effect of the KD relies on stable glucose levels (Zhu et al., 2022). Therefore, the LGIT monitors not only the total amount of carbohydrates consumed but also focuses on carbohydrates that have a low Glycemic Index.

Potential Mechanisms of Action of the Ketogenic Diet

The potential mechanisms of the KD are based on the role of neurotransmitters, brain energy metabolism, ion channels, and oxidative stress. Under KD conditions, the reduction of brain glucose utilization and glycolytic ATP production may induce potassium channels that are sensitive to ATP opening, which leads to hyperpolarization of the neuronal membrane, consequently reducing the electrical excitability of the brain. Reducing the overall electrical excitability of the brain can reduce seizure frequency and severity. Additionally, the KD diet can improve mitochondrial function, elevate ATP levels, reduce oxidative stress, and reduce inflammation (Zhu et al., 2022). Though not yet fully understood, the combination of beneficial factors leads to an increase in GABA expression. GABA is an inhibitory neurotransmitter, and therefore, its increase can reduce seizure frequency and severity.

Efficacy of the Ketogenic Diet in Epilepsy Management

The Core Outcomes in Refractory childhood Epilepsy treated with Ketogenic Diet Therapy (CORE-KDT) study was initiated to develop a core outcome set on outcomes for childhood epilepsy treated with KD (Carroll et al., 2023). This helps clinicians appropriately report patient outcomes leading to more accurate statistics on KD efficacy and tolerability. Currently, studies show that the KD for DRE has demonstrated high efficacy rates, with many individuals showing a 50% reduction in seizure frequency and some even a 90% reduction in seizure frequency (Tang et al., 2017). Some children, up to 10-15%, become seizure-free (Kossoff, 2017). KD is also used in infantile spasm treatment. Infantile spasms are typically treated with high levels of hormones (ACTH) or steroids which have many adverse side effects. According to Dressler et al. (2019), the KD diet has been shown to be as effective in controlling infantile spasms as ACTH when pretreated with vigabatrin. KD is also associated with significantly less severe adverse side effects than ACTH, making it a more desirable treatment option. The KD has even been shown to be effective, safe, and well-tolerated in premature neonates (who had still not yet reached full gestational term) (Phitsanuwong et al., 2023). Low adherence to the KD diet is often due to the fact that it is unpalatable, difficult to prepare, and difficult to maintain.

Cannabis and Epilepsy

For many years, researchers have looked at the potential benefits of using cannabis to treat epilepsy and other neurological disorders. Cannabis refers to all products derived from the plant Cannabis sativa. Cannabis contains compounds known as cannabinoids, which interact with cannabinoid receptors to produce various effects. The psychoactive effects of "getting high" are caused by tetrahydrocannabinol, or THC. Cannabidiol, or CBD, does not produce euphoric or intrusive side effects; rather, it has been shown to have positive effects. CBD is part of the Cannabis sativa plant that has been shown to be effective in reducing seizures in some people with epilepsy. In 2018, the FDA approved the drug Epidolex, which is a purified CBD extract from the cannabis plant. Epidolex is under strict pharmaceutical supervision and contains >98% highly purified pharmaceutical-grade CBD. Epidolex has been approved for Dravet Syndrome and Lennox-Gastaut Syndrome, which are two epilepsy syndromes that are highly drug-resistant. Common adverse side effects of CBD treatment may include sleepiness, reduced appetite, and diarrhea. However, in most cases, parents and caregivers reported these side effects as mild

and did not stop treatment. There are also drug interactions associated with CBD. CBD has been shown to raise blood plasma levels of clobazam, an ASM.

Cannabinoids and the Endocannabinoid System

The mechanism of action for cannabinoids anticonvulsant effects have been studied and debated extensively, and the mechanism of action for CBD is still not fully understood. While THC has a high affinity for endocannabinoid receptors, at which agonist activity has demonstrated anticonvulsant effects, CBD has a low affinity for these receptors and therefore does not modulate them directly. However, CBD may modulate the receptors indirectly by blocking ANA uptake and hydrolysis (ANA also acts on endocannabinoid receptors), making it more available to activate the endocannabinoid receptors (Gaston & Szaflarski, 2018). Additional targets include modulation of intracellular calcium ion mobilization by GPR55 and TRPV1 as well as modulation of adenosine-mediated signaling pathways (von Wrede et al., 2021). By reducing pro-inflammatory activities and signaling in astrocytes to prevent the increase of inflammatory cytokines, CBD also seems to have an anti-inflammatory effect in the neurological system, which has been shown to help reduce seizure activity.

Evidence for the Use of Cannabidiol in Epilepsy

In a study done by Devinsky et al. (2018), patients with Lennox-Gastaut Syndrome were randomly assigned to either receive 20mg of cannabidiol, 10mg of cannabidiol, or a placebo. The median percent reduction from baseline in frequency of drop seizures was 41.9% in the 20mg cannabidiol group, 37.2% in the 10mg cannabidiol group, and 17.2% in the placebo group. Additionally, 7% of patients in the 20mg cannabidiol group and 4% of patients in the 10mg cannabidiol group became seizure-free during the maintenance period (Devinsky et al., 2018). Additional positive effects of CBD treatment include improved behavior and alertness, improved language, improved motor skills, and improved sleep and mood (Gaston & Szaflarski, 2018). Studies done on other epileptic disorders showed that add-on treatment of CBD was associated with a significant reduction in baseline monthly seizure frequency (Lattanzi et al., 2021). However, CBD was not shown to be effective in the treatment of infantile spasms, possibly due to their unique etiology (Hussain et al., 2020).

Neurostimulation Devices for Epilepsy

Neurostimulation devices are devices that act directly upon nerves. In this therapy, the nervous system is exposed to brief electric currents. A neuromodulation device sends an electrical signal to change what a nerve or the brain does. The purpose is to make the brain cells work the way they are supposed to (Shafer & Dean, 2018). Neurostimulation devices have been developed to prevent or lessen seizures.

Vagus Nerve Stimulation

Vagus nerve stimulation uses the vagus nerve to provide regular, gentle electrical pulses to the brain in an effort to prevent or decrease seizure activity. The treatment entails implanting a device under the skin in the left chest region. A wire or electrode is inserted beneath the skin and connected to the generating device. The wire is then wrapped around or linked to the vagus nerve. In the outpatient clinic, the device is set up to give pulses or stimulation at regular intervals. Operation of the vagus nerve stimulator requires no action from the user. When a seizure occurs, the individual or caregiver can use a magnet to further stimulate the brain by swiping it over the generator in the left chest region. A review of 65 people who had a vagus nerve stimulator for ten years or more, showed improvements in seizure control over time. Seizures decreased by 36% after six months, 58% after four years, and 75% by ten years after the vagus nerve stimulator was placed (Shafer & Dean, 2018).

Responsive Neurostimulation

Responsive neurostimulation is a closed-loop system of neuromodulation that continuously monitors neuronal activity at seizure focus and responds with stimulation only when epileptiform activity is detected. The responsive neurostimulation system is indicated in patients with a known seizure focus. The responsive neurostimulation system includes cortical strip leads, each containing four electrode contacts, surgically placed at the seizure focus, and a cranially seated neurostimulator. Using a special tablet that communicates with the neurostimulator, the physician can program the device's settings tailored to the individual. Studies have shown that the responsive neurostimulation system reduces the frequency of seizures (Skarpaas et al., 2019). Additionally, with treatment with the responsive neurostimulation system, patients' quality of life significantly improved.

Deep Brain Stimulation

Deep brain stimulation is similar to responsive neurostimulation; however, with deep brain stimulation, the stimulation is supplied in a predetermined cycle and not directly in response to a seizure. Many patients who receive deep brain stimulation therapy don't experience an immediate reduction in seizures; rather, they experience a reduction in seizures over time.

Epilepsy Surgery

When ASM and other interventions such as KD, CBD, and neurostimulation devices are not effective, epilepsy surgery is often utilized as a last-ditch effort to achieve seizure relief. The objective of epilepsy surgery is to remove the area of the brain responsible for seizure activity. Patients with DRE who received epilepsy surgery had greater rates of seizure cessation, improved behavior, and a better quality of life. Reported rates of complete seizure freedom range from 40%-80% depending on the study and location of surgery (Hsieh et al., 2023). The potential to reduce or eliminate the need for seizure drugs is another benefit of epilepsy surgery. Since the adverse effects of anti-seizure drugs can have an impact on a person's quality of life, this advantage is significant to many people considering surgery. However, not every individual is a candidate for epilepsy surgery. Epilepsy surgery is used when all other methods for seizure relief have failed. While epilepsy surgery has a very high success rate, it also has many adverse side effects, and therefore care must be taken to make sure that the individual is an appropriate candidate for surgery.

Surgical Procedures for Epilepsy

Evaluation for surgery is done via EEG, electrical source localization, functional MRI imaging, and PET and SPECT imaging. Tailored resections are done for focal epilepsy where seizures have been localized within the hemisphere and the lobe. Often, only a portion of the area is resected though in some cases, the entire lobe is removed. For example, in drug-resistant temporal lobe epilepsy, the entire temporal lobe is removed. A hemispherectomy is indicated in epileptic disorders that are known to affect only one hemisphere of the brain. This surgery is often only done before the age of six, as after the age of six, the ability of the dominant hemisphere to acquire language may decline (Galan et al., 2021). A hemispherectomy involves removing the cerebral lobes on one side of the brain. Deeper brain structures are typically left in place. A hemispherectomy can also be a disconnection procedure, where the hemispheres are disconnected from each other, rather than a resection procedure. A corpus callosotomy is another surgical procedure for epilepsy treatment. This procedure involves cutting the corpus callosum, which is the primary communication pathway between the two hemispheres. This procedure is typically indicated in individuals who suffer from atonic drop seizures. Additionally, for corpus callosotomy, thermal ablation via lasers can also be used as a safe, less invasive, and effective modality (Mallela et al., 2022).

Outcomes and Effectiveness of Epilepsy Surgery

In nother study, 77% of patients who received epilepsy surgery achieved seizure freedom, while 4% of patients who solely received ASM achieved seizure freedom. Patients who received surgery either received a tailored resection of the seizure focus, a hemispherectomy, or a corpus callosotomy. Surgery in patients with DRE resulted in higher rates of cessations of seizures, better scores on measures of behavior, and better scores on measures of quality of life (Dwivedi et al., 2017). While there are adverse side effects to epilepsy surgery, such as motor, sensory, and cognitive deficits related to the area of the brain resected or disconnected, the positive effects of seizure freedom typically outweigh the negative ones. Additionally, while many patients don't achieve full seizure remission, many experience a reduction in their seizure frequency of 75% relative to their preoperative baseline (Hsieh et al., 2023).

Conclusion

Management of seizures and epilepsy has seen tremendous advancements in the last century. However, despite the introduction of several new ASM, 30% of epileptic patients continue to have medication resistance. When treating individuals with DRE, treatment options such as the KD, cannabis, neurostimulation devices, and epilepsy surgery should be considered. Living with epilepsy can be emotionally and physically draining for patients and caregivers. Many aspects of epilepsy can impact one's lifestyle and independence. Spreading awareness about epilepsy can help bystanders understand what a seizure looks like and know what to do if they encounter someone having a seizure. Advancements in epilepsy research focus on cures for genetic epilepsy disorders, studying new ASM with more potent results and fewer side effects, and focusing on novel treatment options for the DRE community.

References

Carroll, J. H., Cross, J. H., Hickson, M., Williams, E., Aldridge, V., & Collinson, A. (2023). A core outcome set for childhood epilepsy treated with ketogenic diet therapy (CORE-KDT study): International parent and health professional consensus. Epilepsia. https://doi.org/10.1111/epi.17513

Cepeda, M. S., Teneralli, R. E., Kern, D. M., & Novak, G. (2022). Differences between men and women in response to anti-seizure medication use and the likelihood of developing treatment resistant epilepsy. Epilepsia Open, 7(4), 598–607. https://doi.org/10.1002/epi4.12632

Chambers, C., Jansen, L. A., & Dhamija, R. (2016). Review

of Commercially Available Epilepsy Genetic Panels. In Journal of Genetic Counseling (Vol. 25, Issue 2, pp. 213–217). Springer New York LLC. https://doi.org/10.1007/s10897-015-9906-9

Devinsky, O., Patel, A. D., Cross, J. H., Villanueva, V., Wirrell, E. C., Privitera, M., Greenwood, S. M., Roberts, C., Checketts, D., VanLandingham, K. E., & Zuberi, S. M. (2018). Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. New England Journal of Medicine, 378(20), 1888–1897. https://doi.org/10.1056/nejmoa1714631

Dressler, A., Benninger, F., Trimmel-Schwahofer, P., Gröppel, G., Porsche, B., Abraham, K., Mühlebner, A., Samueli, S., Male, C., & Feucht, M. (2019). Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: A single-center parallel-cohort randomized controlled trial. Epilepsia, 60(3), 441–451. https://doi.org/10.1111/epi.14679

Dwivedi, R., Ramanujam, B., Chandra, P. S., Sapra, S., Gulati, S., Kalaivani, M., Garg, A., Bal, C. S., Tripathi, M., Dwivedi, S. N., Sagar, R., Sarkar, C., & Tripathi, M. (2017). Surgery for Drug-Resistant Epilepsy in Children. New England Journal of Medicine, 377(17), 1639–1647. https://doi.org/10.1056/nejmoa1615335

Fonseca-Barriendos, D., Frías-Soria, C. L., Pérez-Pérez, D., Gómez-López, R., Borroto Escuela, D. O., & Rocha, L. (2022). Drug-resistant epilepsy: Drug target hypothesis and beyond the receptors. In Epilepsia Open (Vol. 7, Issue S1, pp. S23–S33). John Wiley and Sons Inc. https://doi.org/10.1002/epi4.12539

Galan, F. N., Beier, A. D., & Sheth, R. D. (2021). Advances in Epilepsy Surgery. Pediatric Neurology, 122, 89–97. https://doi.org/10.1016/j.pediatrneurol.2021.06.004

Gaston, T. E., & Szaflarski, J. P. (2018). Cannabis for the Treatment of Epilepsy: An Update. In Current Neurology and Neuroscience Reports (Vol. 18, Issue 11). Current Medicine Group LLC 1. https://doi.org/10.1007/s11910-018-0882-y

Graifman, J. L., Lippa, N. C., Mulhern, M. S., Bergner, A. L., & Sands, T. T. (2023). Clinical utility of exome sequencing in a pediatric epilepsy cohort. Epilepsia. https://doi.org/10.1111/epi.17534

Hsieh, J. K., Pucci, F. G., Sundar, S. J., Kondylis, E., Sharma, A., Sheikh, S. R., Vegh, D., Moosa, A. N., Gupta, A., Najm, I., Rammo, R., Bingaman, W., & Jehi, L. (2023). Beyond seizure freedom: Dissecting long-term seizure control after surgical resection for drug-resistant epilepsy. Epilepsia, 64(1), 103–113. https://doi.org/10.1111/epi.17445

Hussain, S. A., Dlugos, D. J., Cilio, M. R., Parikh, N., Oh, A., & Sankar, R. (2020). Synthetic pharmaceutical grade cannabidiol for treatment of refractory infantile spasms: A multicenter phase-2 study. Epilepsy and Behavior, 102. https://doi.org/10.1016/j.yebeh.2019.106826

Kaeberle, J. (2018). Epilepsy Disorders and Treatment Modalities. In NASN school nurse (Print) (Vol. 33, Issue 6, pp. 342–344). NLM (Medline). https://doi.org/10.1177/1942602X18785246

Kossoff, E. (2017). Ketogenic Diet. Epilepsy Foundation. https://www.epilepsy.com/treatment/dietary-therapies/ketogenic-diet

Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Hauser, W. A., Mathern, G., Moshé, S. L., Perucca, E., Wiebe, S., & French, J. (2010). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. In Epilepsia (Vol. 51, Issue 6, pp. 1069–1077). https://doi.org/10.1111/j.1528-1167.2009.02397.x

Lattanzi, S., Trinka, E., Striano, P., Rocchi, C., Salvemini, S., Silvestrini, M., & Brigo, F. (2021). Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox–Gastaut Syndrome. In CNS Drugs (Vol. 35, Issue 3, pp. 265–281). Adis. https://doi.org/10.1007/s40263-021-00807-y

Löscher, W., Potschka, H., Sisodiya, S. M., & Vezzani, A. (2020). Drug resistance in epilepsy: Clinical impact, potential mechanisms, and new innovative treatment options. Pharmacological Reviews, 72(3), 606–638. https://doi.org/10.1124/pr.120.019539

Mallela, A. N., Hect, J. L., Abou-Al-Shaar, H., Akwayena, E., & Abel, T. J. (2022). Stereotactic laser interstitial thermal therapy corpus callosotomy for the treatment of pediatric drug-resistant epilepsy. Epilepsia Open, 7(1), 75–84. https://doi.org/10.1002/epi4.12559

Mandal, Dr. A. (2019, February 27). Epilepsy Pathophysiology. News Medical Life Sciences. https://www.news-medical.net/health/Epilepsy-Pathophysiology.aspx

Obsorne-Shafer, P. (2016). New terms seizure classification. Epilepsy Foundation. https://www.epilepsy.com/what-is-epilepsy/seizure-types/new-terms-seizure-classification

Patel, P., & Moshé, S. L. (2020). The evolution of the concepts of seizures and epilepsy: What's in a name? In Epilepsia Open (Vol. 5, Issue 1, pp. 22–35).

Wiley-Blackwell Publishing Ltd. https://doi.org/10.1002/epi4.12375

Phitsanuwong, C., Kim, J. A., Schimpf, S., & Nordli, D. R. (2023). Experience with the ketogenic diet in premature neonates. Epilepsia Open, 8(1), 200–204. https://doi.org/10.1002/epi4.12673

Rao, V. R., & Lowenstein, D. H. (2015). Epilepsy. Current Biology, 25(17), 742–746.

Servilha-Menezes, G., & Garcia-Cairasco, N. (2022). A complex systems view on the current hypotheses of epilepsy pharmacoresistance. In Epilepsia Open (Vol. 7, Issue S1, pp. S8–S22). John Wiley and Sons Inc. https://doi.org/10.1002/epi4.12588

Shafer, P. O., & Dean, P. M. (2018). Vagus nerve stimulation (VNS) therapy. Epilepsy Foundation. ttps://www.epilepsy.com/treatment/devices/vagus-nerve-stimulation-therapy

Shafer, P. O., & Dean, P. M. (2018). Seizure Devices. Epilepsy Foundation. https://www.epilepsy.com/treatment/devices

Skarpaas, T. L., Jarosiewicz, B., & Morrell, M. J. (2019). Brain-responsive neurostimulation for epilepsy (RNS ® System). In Epilepsy Research (Vol. 153, pp. 68–70). Elsevier B.V. https://doi.org/10.1016/j.eplepsyres.2019.02.003

Talevi, A. (2022). Anti-seizure medication discovery: Recent and future paradigm shifts. In Epilepsia Open (Vol. 7, Issue S1, pp. S133–S141). John Wiley and Sons Inc. https://doi.org/10.1002/epi4.12581

Tang, F., Hartz, A. M. S., & Bauer, B. (2017). Drug-resistant epilepsy: Multiple hypotheses, few answers. In Frontiers in Neurology (Vol. 8, Issue JUL). Frontiers Media S.A. https://doi.org/10.3389/fneur.2017.00301

Tsang, M. H.Y., Leung, G. K. C., Ho, A. C. C., Yeung, K. S., Mak, C. C.Y., Pei, S. L. C., Yu, M. H. C., Kan, A. S.Y., Chan, K. Y. K., Kwong, K. L., Lee, S. L., Yung, A. W.Y., Fung, C. W., & Chung, B. H.Y. (2019). Exome sequencing identifies molecular diagnosis in children with drug-resistant epilepsy. Epilepsia Open, 4(1), 63–72. https://doi.org/10.1002/epi4.12282

U.S. Department of Health and Human Services. (n.d.). Epilepsy and seizures. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures

Vázquez, M., & Fagiolino, P. (2022). The role of efflux transporters and metabolizing enzymes in brain and peripheral organs to explain drug-resistant epilepsy. In Epilepsia Open (Vol. 7, Issue S1, pp. S47–S58). John Wiley and Sons Inc. https://doi.org/10.1002/epi4.12542

von Wrede, R., Helmstaedter, C., & Surges, R. (2021). Cannabidiol in the Treatment of Epilepsy. In Clinical Drug Investigation (Vol. 41, Issue 3, pp. 211–220). Adis. https://doi.org/10.1007/s40261-021-01003-y

Xue-Ping, W., Hai-Jiao, W., Li-Na, Z., Xu, D., & Ling, L. (2019). Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis. In Medicine (United States) (Vol. 98, Issue 30). Lippincott Williams and Wilkins. https://doi.org/10.1097/MD.0000000000016402

Zhu, H., Bi, D., Zhang, Y., Kong, C., Du, J., Wu, X., Wei, Q., & Qin, H. (2022). Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. In Signal Transduction and Targeted Therapy (Vol. 7, Issue 1). Springer Nature. https://doi.org/10.1038/s41392-021-00831-w