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Examining the Efficacies of Contemporary Treatments for Combating Epilepsy

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ABSTRACT

It is estimated that 1 in 26 individuals will develop epilepsy at some point during their lifetime. Despite extensive research, a cure for epilepsy is yet to be found. However, the condition can be mitigated through a variety of treatment options. This review will critically examine the efficacies of various treatment options that are available for the patient today including medications such as anti-epileptic drugs (AEDs), dietary therapies such as ketogenic & modified Atkins diets, surgical intervention, and vagus nerve stimulation (VNS) therapy. By evaluating the strengths and limitations of these treatments, this review aims to provide insights into optimizing epilepsy management and improving patient outcomes.

Introduction

Epilepsy is a chronic, non communicable nervous disorder characterized by recurring seizures due to abnormal electrical activity in the brain. During an epileptic seizure, a multitude of neurons in a specific region of the brain fire simultaneously, causing an electrical storm. Since each of the approximately 100 billion cerebral neurons can have more than 1,000 connections with other neurons (Gulati, 2015), electrical activity in one region of the brain is likely to spread to other regions as well. Depending on the type and severity as well as the region of the brain affected, epilepsy can have detrimental side effects and impede quality of life. For instance, patients may experience a loss of memory function as well as have cognitive triggers preventing them from partaking in certain activities (ex. Reading aloud) (Letcher et al., 2020). Many individuals, particularly in low-income and poorly educated countries, face stigma and discrimination around the disorder. This further decreases quality of life, especially in those with particularly active epilepsy causing them to experience numerous seizures per day. Additionally, 1 out of every 1,000 adult epilepsy patients and 1 out of every 4,500 pediatric epilepsy patients experience sudden unexpected death in epilepsy (SUDEP) (Elmali et al., 2019), resulting in loss of life for no other apparent physiological causes.

In addition to having profound, negative effects on the lives of diagnosed individuals, epileptic disorders are quite common. According to data from the World Health Organization (WHO), around 50 million patients have been diagnosed with epilepsy (*Epilepsy*, 2024), making epilepsy the second most common neurological disorder worldwide (Letcher et al., 2020). As such, it is imperative that the multitude of patients living with epilepsy are able to control their seizures safely and effectively. In this paper we review and summarize the effectiveness of different epilepsy management options available for patients today. We begin by discussing the least invasive methods, antiepileptic drugs and the ketogenic diet, in Sections 2 and 3 respectively. Highly invasive methods, vagus nerve stimulation and surgery, are discussed in Sections 3 and 4 before concluding in Section 5.

Anti-Epileptic Drugs (AEDs)

Introduction

As of the time of this review, AEDs are the most common way of treating epilepsy. The usage of AEDs is a symptomatic treatment rather than a curative one. Although referred to as "antiepileptic drugs", AEDs do not combat epilepsy itself but rather provide seizure relief as opposed to treating the underlying cause. The development and approval of antiepileptic medication throughout these past decades and centuries have been slow with periods of hiatus. However, as of today there are far more options, allowing for increased customization to meet unique needs. Table 1 gives examples of some of the 30+ FDA approved AEDs.

Table 1. Examples of Commonly Used Antiepileptic Drugs

Anticonvulsant	Brand Name
Lamotrigine	Lamictal
Gabapentin	Neurontin
Phenytoin	Dilantin
Topiramate	Topamax
Carbamazepine	Tegretol
Levetiracetam	Keppra

The following table lists some of the most commonly used anticonvulsants and their brand names.

Mechanism of Action

The mechanism of action of AEDs is dependent on the type of drug. There are 4 main categories that anticonvulsants fit into: a) Sodium channel blockers, b) calcium channel inhibitors, c) GABA system and receptor agonists, and d) glutamate blockers.

Sodium channel blockers are among the most common types of AEDs (e.g. phenytoin, carbamazepine, and lacosamide). By blocking the sodium channels embedded in cell membranes, the channels aren't able to return to an active state, significantly reducing the activities that would otherwise result in seizure development (Louro & Odle, 2023).

Calcium plays a crucial role in synaptic activity (Marambaud et al., 2009) and as a result, so do the channels that control it. Similar to the mechanism of action of sodium channels blockers, calcium channel inhibitors slow down seizure-like impulses. This makes them an effective way to control petit mal (also known as absence) seizures (Louro & Odle, 2023). Common examples of calcium channel inhibitors include topiramate, lamotrigine, and ethosuximide.

Gamma-aminobutyric acid, or GABA, is the primary inhibitory neurotransmitter in the brain. Increased GABA concentrations lead to less cerebral and seizure activities. GABA agonists such as phenobarbital and primidone mimic GABA's inhibitory tendencies while drugs like tiagabine work to slow GABA reuptake, increasing the amount available to neurons (Louro & Odle, 2023).

Glutamate blockers work similarly to sodium channel blockers and calcium channel inhibitors. Glutamate and aspartate are excitatory neurotransmitters and blocking their ability to bind works to prevent seizure-like activity (Louro & Odle, 2023).

Efficacy

AED monotherapy (treatment using only one kind of AED) has already been established as effective in helping 60%-70% of patients control their seizures (Singh et. al, 2020). AED polytherapy can be utilized for patients with drug-resistant epilepsy however not without risk. The already existing side effects of AEDs can be amplified through the

drugs' interactions (Belete, 2023). Additionally, 30% of those diagnosed with epilepsy do not respond effectively to anticonvulsants and have refractory (drug resistant) epilepsy, making AEDs an unsuitable therapy for them.

Side Effects

Along with their anticonvulsant properties, AED usage comes with adverse side effects. Drowsiness and dizziness are the most common side effects (Louro & Odle, 2023) across all types of anticonvulsants. However, there are specific side effects unique to individual drugs or drug groups that must be mitigated. When used in conjunction with other drugs, the effects of AEDs are often exacerbated. For instance, alcohol and other inhibitory substances should be strictly avoided. AEDs such as ethosuximide increase the amount of other anticonvulsants in the blood, thereby increasing the severity of their side effects. Other AEDs such as phenobarbital increase the metabolism of steroids such as estrogen, which can cause long lasting damage (Louru & Odle, 2023).

Table 2. Side Effects of Example Antiepileptic Drugs

Anticonvulsant	Most Common Side Effects
Lamotrigine	Rashes, drowsiness, irritability, difficulty sleeping, diarrhea, tremors
Gabapentin	Drowsiness, headaches, memory issues, weight gain, diarrhea, blurred vision
Phenytoin	Drowsiness, constipation, swollen/sore gums, unsteadiness, headaches
Topiramate	Nausea, drowsiness, diarrhea, blurred vision, weight loss, appetite loss, depression
Carbamazepine	Dizziness, drowsiness, headaches, weight gain, dryness of the mouth
Levetiracetam	Irritability, headaches, drowsiness, nausea

The following table lists common drugs and their side effects as sourced from the NHS (NHS, 2024).

The Ketogenic Diet

Introduction

Ketogenic diet (KD) consists of a high amount of fat (~70%-80%), moderate amounts of protein (~20%), and a very low amount of carbohydrates (~5%-10%). The metabolism of fat results in the formation of ketone bodies, which are normally excreted in urine. However, excessive amounts of ketone bodies results in a state of ketosis, which is the primary goal of the diet. The mechanism behind how exactly a state of ketosis helps control epileptic seizures is poorly understood (Frey, 2023) although the fact that it does has been known since the time of the Romans.

KD fell out of practice after the discovery of the first AED (phenytoin) in 1938 and many considered it an alternative treatment not worth the trouble until its reemergence in the mid-1990s (Frey, 2023). As of today, multiple hospitals KD primarily to treat pediatric epilepsy. Unlike "fad" keto diets aimed at weight loss, KDs for seizure relief are modified and only undergone with strict dietary supervision.

Types of Ketogenic Diets

Although all ketogenic diets aim at inducing a state of ketosis, significant variations in their macromolecular breakdowns exist. In this study, we discuss the effectiveness of two variations of the diet.

The Classical Ketogenic Diet (KD)

Classical KD diet was first proposed by Wilder et al. in 1921 as a way to treat epilepsy and consisted of a 3:1 to 4:1 ratio of fats to carbohydrates and proteins. Regardless of efficacy, the diet is extremely restrictive, limiting even fluid intake. This restrictive nature makes it difficult for patients to continue the KD diet long-term. (D'Andrea Meira, Isabella, 2019).

In 2008, Neal et al. followed 145 children aged 2 to 16 with refractory epilepsy for 3 months in a randomized controlled trial to assess the effectiveness of KD for seizure relief. Data from 54 patients treated with the diet and 49 controls (42 were unable to complete the study or provide adequate data) revealed that the treatment group had a 75% decrease in the baseline average amount of seizures compared to the controls (Neal et al., 2008). 28 children had greater than 50% seizure reduction compared to 4 controls and 5 children had greater than 90% seizure reduction compared to no controls (compared to themselves) [Neal et al., 2008]. Children undergoing the KD diet reported side effects such as constipation, lack of energy, and hunger.

Similar to the study conducted by Neal et al., numerous other studies have also found the classical KD diet to be efficacious with a vast majority of treated patients achieving either seizure freedom or greater than 50% reduction in seizure frequency (Wells, 2020). Despite its effectiveness, few studies and clinical trials have been done on adults with refractory epilepsy. This is mainly due to a lack of participation as the rigor of the diet is difficult to follow, especially for adult patients. Additionally, the KD diet is not recommended for infants due to the calorie deficit hindering crucial growth.

The Modified Atkins Diet (MAD)

First introduced in 2003 as a less restrictive alternative, MAD initiation does not require prior fasting, restriction, or hospitalization characteristic of the KD diet. The intensity of the classical KD diet makes it difficult to follow through with the diet over an extended period. As a result, the modified Atkins diet (MAD) is more appealing and more likely to be utilized to its full potential. Unlike the KD diet, there are no calorie or fluid restrictions. Fats are strongly encouraged in the form of dairy and oils and make up roughly 65% of total calories (Goswami & Sharma, 2019).

In 2013, Sharma et al. analyzed the efficacy of the MAD in treating childhood refractory epilepsy in a randomized controlled study of 102 patients. There was a significant reduction in the mean number of seizures in the treatment group compared to the controls. Side effects were minimal with constipation being the most adverse (affecting 46% of the treatment group). Overall, it was concluded that the MAD was effective and tolerable (Sharma et al, 2013).

In addition, MAD has been found to be effective in treating children with Lennox-Gastaut Syndrome, a rare and severe form of childhood epilepsy (Kim et al., 2015). The MAD could be used as an effective, yet less rigorous, method to achieve seizure relief while still maintaining a higher standard of quality of life.

The Classical KD vs the MAD

Kim et al. released a study in 2015 comparing the efficacy, safety, and tolerability of the classical KD diet from the MAD in children with refractory epilepsy. 104 patients were randomly assigned into either a KD group or MAD group. 6 months after the study's start date, it was found that the KD group experienced less seizures on average than

the MAD group though the difference was not statistically significant at a 95% confidence interval (Kim et al., 2015). However, a statistically significant difference was found between the average number of seizures in patients 1-2 years old with the KD group experiencing a significantly higher reduction (Kim et al., 2015). Along with increased effectiveness, the KD group experienced a greater number of side effects and the MAD regimen was found to be safer and tolerable (Kim et al., 2015).

In 2023, El-Shafie et al. compared the efficacy of the classic ketogenic diet (KD) against the efficacy of the modified Atkins diet (MAD) in treating childhood drug-resistant epilepsy (DRE). 40 patients diagnosed with DRE were randomly assigned to one of KD or MAD groups. Treatments persisted for 24 months along with regular check-ups. Analysis after the 24 month period showed that 60% of the KD group and 53.33% of the MAD became seizure free. Additionally, the remaining participants showed 50% or greater seizure reduction Furthermore, side effects were also minimal. The study concluded that both the KD and MAD diets are effective in treating childhood DRE with KD having a greater impact compared to MAD.

Thus, the KD diet and the MAD diet are effective in the treatment of refractory epilepsy. The KD diet is found to be more efficacious overall but more taxing on the body. Further, the numerous restrictions associated with the KD diet may hinder quality of life. MAD and other lenient variations of the KD diet may be suitable for some patients with some degree of seizure control.

Vagus Nerve Stimulation Therapy (VNS)

Introduction

The vagus nerve is the 10th and longest cranial nerve and it is responsible for controlling much of the parasympathetic (involuntary) nervous system as well as some motor function. The human body contains two vagal nerves (right and left) that run down the sides of the body starting from the medulla oblongata and passing through the neck, chest, heart, lungs, and abdomen/GI tract. As such, the vagus nerve is considered the “pacemaker for the brain”.

In 1997, VNS was approved by the FDA as an adjunctive therapy for seizure control for adults and adolescents over 12 years of age with refractory partial or focal epilepsy. Approval for pediatric treatment (older than 4) was granted in 2017. VNS consists of an implant placed in the left side of the chest that sends electrical impulses at programmed intervals, stimulating the vagal nerves.

Mechanism of Action

The exact mechanism of action of VNS is unknown. However, there are numerous theories detailing the role stimulation of the vagus nerve has in reducing seizure strength. For instance, VNS is thought to stimulate the nodes of the “Vagus Afferent Network”, modulation of which is thought to reduce seizure spreading and mass firing (Afra et al., 2021).

Efficacy

VNS has been reported to decrease seizure frequencies when used in adjunct to drug therapy. In 2020, Tsai et al. followed 95 newly implanted patients of all ages and demographics over a period of 36 months. A statistically significant reduction in seizure frequency emerged as early as 3 months after the start of the study. From 3 to 36 months, the reduction rate ranged from 26.1% to 36.1% (Tsai et al., 2020). Furthermore, randomized controlled trials using VNS therapy have resulted in greater than 50% seizure reduction in 26% to 40% of patients within one year, with better results suggested in longer, uncontrolled trials (Pérez-Carbonell et al., 2020).

In addition to immediate relief, the long-term effects of VNS seem promising. In 2011, Elliot et al. tracked 436 children and adults of all demographics and ages (ranging from 1-76 years) with refractory epilepsy. The treatment varied from 10 days to 11 years with an average of 4.94 years. Following implantation, a statistically significant reduction in seizure frequency emerged (55.8%) (Chen & Meng, 2017). 255 patients (63.75%) experienced 50% or greater reduction, 162 (40.5%) patients experienced 75% or greater reduction, and 90 patients (22.5%) experienced 90% or greater reduction. However, 2.8% of patients also experienced permanent injury to the vagus nerve (Chen & Meng, 2017). VNS was used adjunct to aggressive AED regimens and surgery if fit. It was concluded that VNS therapy is a safe and effective supporting treatment for generalized and focal drug-resistant epilepsy when used in conjunction with other treatment options.

Since VNS is a relatively new treatment option, more studies are required to assess its long-term effects. However, as of 2024, VNS therapy has been shown to provide significant seizure relief.

Surgery

Introduction

Currently, neurosurgery for epilepsy treatment is considered a last resort. Due to the nature of the procedures, there are significantly more risks associated with surgeries compared to alternative forms of treatment. Additionally, epileptic surgery is not suitable for every patient and is primarily aimed at those with focal epilepsy (patients whose seizures are localized) (Jayalakshmi et al., 2014). Despite this, epileptic surgery remains underutilized and with proper caution and care can lead to tremendously beneficial outcomes.

Approximately 60% of patients with epilepsy suffer from focal epilepsy (Jayalakshmi et al., 2014). Among them, 15% do not respond adequately enough to AEDs to warrant surgery (Jayalakshmi et al., 2014). After the appropriate phases of presurgical testing to determine suitability, only 30% to 40% of those patients are eligible for surgery (Rugg-Gunn et al., 2020). As shown, only a small percentage of patients are candidates for epilepsy surgery and those who are often suffer from extreme, debilitating variants and are left with little other choice.

Methods, Risks, & Efficacy

Methods involving the focal resection of the region where seizures are prevalent are implemented most often. This, in other words, is the removal of the region of the brain where the seizures arise from. Temporal, frontal, and parietal lobectomies are among the most common focal resections. According to the Epilepsy Foundation, temporal lobe resection has the highest rate of success with 60% to 70% of patients achieving remission. Less successful are frontal and parietal lobe resections, which have a roughly 50% remission rate (Kiriakopoulos et al., 2018). Most patients who do not receive full remission do experience a significant decrease in seizure frequency (70% to 80% of patients) while only a small percentage do not (Kiriakopoulos et al., 2018). In addition to the potential tissue damage and complications caused by the operation itself, numerous side effects can arise depending on the region of the brain operated on. Memory loss, double vision, mood problems, peripheral vision loss, motor skill issues, and speech difficulties have all been associated with epileptic surgery (Kiriakopoulos et al., 2023). In children and adolescents, a perioperative mortality rate of about 1.3% has been reported (Jayalakshmi et al., 2017). Although the side effects can seem extreme, in many cases surgery still improves overall quality of life as untreated, uncontrollable epilepsy is often debilitating and can lead to worse brain damage and a higher chance of mortality (Kiriakopoulos et al., 2023).

Epileptic surgery should be seen as a treatment option rather than a last resort, especially for pediatric patients. Wyllie et al. analyzed the postsurgical outcomes of 136 pediatric patients who had undergone epileptic surgery between 1990 and 1996. Extratemporal, multilobar, and hemispherectomies constituted about 50% of the procedures while temporal resections constituted the other 50%. Overall, 69% of adolescents, 68% of children, and 60% of infants

achieved seizure freedom, with the temporal resections having the highest remission rate (56 out of 72, or 78%) (Wyllie et al., 1998). 4 of the 136 patients developed wound infections from the surgery and 1 required further surgery to repair the damage. 1 patient experienced language defects (resolved after 6 weeks) and several patients experienced minor vision and memory loss, among other minor side effects (Wyllie et al., 1998). Despite the extant side effects, surgery is often more cost-effective and beneficial for quality of life and seizure control than AEDs and alternative forms of therapy (Thijs et al., 2019).

Misconceptions and fears result in surgery being drastically underutilized. Greater independence and a reduced risk of death have been shown in numerous randomized controlled trials (Thijs et al., 2019), showing that surgery is a viable option for treating focal epilepsy.

Conclusion

This review critically examined the efficacy of various treatments, focusing not only on seizure control but also on quality of life. Epilepsy treatment has significantly evolved over the years, offering a broad spectrum of options that can be tailored to individual needs. Ongoing research into deep brain stimulation and other emerging therapies aims to enhance current treatment regimens, with the ultimate goal of ending the battle against epilepsy. While antiepileptic drugs remain the cornerstone of epilepsy treatment today, the development of alternative therapies such as neurostimulation and dietary interventions broadens the possibility for safer and more effective seizure control, particularly for those with drug-resistant epilepsy. Continued research and a multidisciplinary approach are essential to ensuring the safety and quality of life for patients living with this complex and nuanced neurological disorder.

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