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## The Effectiveness of Treatments for Drug-Resistant Epilepsy: A Review of Literature

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The Effectiveness of Treatments for Drug-Resistant Epilepsy: A Review of Literature

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Author's Note

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### **Abstract**

Epilepsy is a neurological disorder characterized by abnormal brain activity that results in seizures (World Health Organization, 2022). Patients with epilepsy expect epilepsy-specific costs to range from \$1,022 to \$19,749 and healthcare costs from \$10,192 to \$47,862 (Begley & Durgin, 2015). About one-third of epilepsy patients cannot control their seizures with existing antiseizure medication (Xue et al., 2022). This population has an increased mortality rate because of their drug-resistant epilepsy. This review aims to examine and compile evidence for six alternative drug-resistant epilepsy treatments. The quality of each treatment was evaluated based on the number of patients who had seizure freedom, had a seizure reduction, had adverse events, and had changes in a Quality of Life score. The six treatments examined were: deep brain stimulation, ketogenic diet, medical *Cannabis* and delta-9-tetrahydrocannabinol, stereotactic radiosurgery, resective surgery, and vagus nerve stimulation.

## Introduction

Epilepsy is one of the most common neurological disorders and affects about 50 million people globally (World Health Organization, 2022). This disorder is caused by abnormal brain activity, and the type of seizure that appears depends on what area(s) of the brain are affected. Seizures resulting from one area of the brain are called focal seizures, and seizures that appear to involve multiple areas of the brain are called generalized seizures (Mayo Clinic, 2022a). For a person to be diagnosed with epilepsy, they must have two or more unprovoked seizures. Compared to the general population, the risk of premature death in people with epilepsy increases up to three times higher (World Health Organization, 2022), and the leading cause of death in people with uncontrolled seizures is a complication called “Sudden Unexpected Death in Epilepsy,” or SUDEP (Epilepsy Foundation, 2022a). The most significant risk for a person dying from SUDEP is having uncontrolled generalized tonic-clonic seizures (previously known as grand mal seizures) and having seizures at night (Epilepsy Foundation, 2022b). While uncontrolled seizures can occur from missing doses of medication, alcohol use, or both, about one-third of epilepsy patients cannot control their seizures with existing antiepileptic drugs (AEDs) (Xue et al., 2022). This type of epilepsy is considered drug-resistant epilepsy (DRE).

As a population at an increased risk of premature mortality due to this condition, people diagnosed with DRE need alternative therapies to reduce the frequency of seizures. Many studies examine the treatment options for drug-resistant epilepsy (Buchanan-Peart et al., 2020; Conte et al., 2018; Devinsky et al., 2022; Hsieh et al., 2022; Kishk et al., 2021; Muthiah et al., 2020; Xie et al., 2022; Yan et al., 2018); however, there is a lack of reviews that compile and evaluate the current treatments offered. This review focuses on the current body of research of the past five years and compiles a list of treatments currently used for drug-resistant epilepsy patients. The

research questions addressed in this literature review are: (1) What are the current treatments available in high-income countries for DRE? (2) What is the effectiveness of each treatment? (3) Should any significant analyses be investigated more thoroughly? (4) Where are the gaps in research that scientists can investigate?

## **Methods**

In this review, multiple databases were examined for primary research sources about treatments for drug-resistant epilepsy in high-income countries. The EBSCOhost, PubMed Central, Google Scholar, and Elsevier databases were used to find relevant references. The following keywords were used with “AND” as a Boolean operator: drug-resistant epilepsy AND treatment; AND surgery; AND diet; AND Vagus Nerve Stimulation; AND Deep Brain Stimulation; AND medial temporal disconnection. The selection of studies was considered by the following criteria: peer-reviewed journals, human studies, date of publication, type of study, methodology, and measurement of results. References that supported and contradicted the treatment options researched were included, along with studies of epileptic encephalopathies. Studies that did not mention drug-resistant epilepsy or treatment-resistant epilepsy were not included in the review, as the treatments must be pertinent to epilepsies that meet the “drug-resistant” criteria.

## *Definitions*

Published studies of treatments for epilepsy use various measures for efficacy, which can impose difficulties when comparing results across studies. This review considers both quantitative and qualitative measures for each treatment option. The term “drug-resistant” is used

to describe seizures that are not controlled with antiseizure medications (Epilepsy Foundation, 2022a); however, the International League Against Epilepsy (ILAE) has proposed these criteria for drug-resistant epilepsy: occurs when a person has failed to become (and stay) seizure-free with adequate trials of two antiseizure medications (ASMs) and the seizure medications have been chosen appropriately for the person's seizure type, tolerated by the person, and tried alone or together with other seizure medications (Kwan et al., 2009). The studies used in this review will examine two types of disorders: epileptic encephalopathies and seizure disorders. Epileptic encephalopathies are a specific disorder characterized by drug-resistant seizures and a diagnosis of any brain disease (Epilepsy Foundation, 2022e). Seizure disorders are chronic brain disorders characterized by recurrent ( $\geq 2$ ) seizures that are unprovoked and occur  $> 24$  hours apart (Adamolekun, 2022). The standard quantitative measurement for the efficacy of epilepsy treatments is the frequency of seizures before and after treatment. Some studies also include data about seizure severity, rescue medication use, and postictal recovery time. Postictal refers to the time between when a seizure ends and when the patient returns to baseline without symptoms of disorientation, drowsiness, headache, nausea, or a combination of symptoms (Abood & Bandyopadhyay, 2022). This review will look at the statistical change in seizure frequency as the primary quantitative measure. For qualitative studies, this review will examine the quality of life of the patient, the International League Against Epilepsy (ILAE) Outcome Scale (Appendix), the Engel Classification Scale (Appendix), the adverse events (AEs) experienced, or a combination of these measures to determine the efficacy of the treatment. This review will also examine these measures when looking at the effectiveness of treatments for drug-resistant epilepsy.

### **Deep Brain Stimulation (DBS)**

Deep brain stimulation (DBS) involves surgically implanting electrodes into specific brain regions of a patient (Epilepsy Foundation, 2022c). The electrodes produce electrical impulses from a pacemaker-like device placed under the skin in the upper chest that regulate abnormal impulses in the brain. DBS is used frequently for treating conditions such as Parkinson's disease, dystonia, epilepsy, and obsessive-compulsive disorder (Mayo Clinic, 2022b). DBS has the potential to be an effective treatment for patients with DRE, but it does not have much promise in relieving patients of seizures completely. Conte et al. (2018) found that in four patients treated with DBS for drug-resistant epilepsy, none were seizure-free with an ILAE class 1 outcome (Appendix). Another study found that 5 of 40 patients (12.5%) had an ILAE class I outcome after being treated with DBS, although 85% of the patients reported seizure reduction (Yan et al., 2018)(Appendix). A few studies also examined the seizure frequency of patients with DBS after their stimulator battery had depleted. One study found that out of nine patients, two did not have changes in their seizure frequency, and seven had an increase in seizure frequency, which suggests that a portion of, but not all, seizure relief is due to the lesional effect of DBS, which is the inhibition of neurons surrounding the electrodes (Cukiert et al., 2015).

Overall, the outcomes analyzed by numerous studies show promise for bilateral DBS of the anterior nucleus of the thalamus (ANT) or the centromedian nucleus of the thalamus (CMT) to achieve a reduction in seizure frequency (Yan et al., 2018). The ANT is a critical component of the hippocampal system for episodic memory. Experimental models have shown its possible role in the propagation of seizure activity due to its central connectivity (Child & Benarroch, 2013). The CMT is a significant source of direct input to the basal ganglia, brainstem, and

cortex. Its connectivity and diverse physiologic role make it an excellent target for the treatment of generalized epilepsy (Ilyas et al., 2019). Patients with partial or secondarily generalized seizures may benefit more from ANT DBS. In contrast, those with generalized epilepsy, such as in Lennox-Gastaut syndrome, may benefit more from CMT DBS (Klinger & Mittal, 2018). This treatment appears to depend more on the type of epilepsy for electrode placement and the consequential frequency of seizures post-implant. The AEs reported from studies of DBS varied, but the percentage of patients that experienced these AEs was relatively low. In 110 implanted patients, Salanova et al. (2015) found that 39 had device-related serious adverse events (SAEs), with a majority occurring in the first few months following implantation. The most frequent SAEs reported were implant site infection in 10% and stimulator lead(s) not within the target area of the brain in 8.2%, with all other reported SAEs being 1.8% or less (Salanova et al., 2015).

### **Ketogenic Diet (KD)**

The ketogenic diet is a special high-fat, low-carbohydrate diet that helps control seizures in some people with epilepsy. It is usually prescribed by a physician and monitored by a dietician (Epilepsy Foundation, 2022d). The ketogenic diet promotes ketosis, which is the process of burning fat for energy rather than glucose. Ketosis then promotes the liver and brain to produce adenosine and gamma-aminobutyric acid (GABA), which can inhibit seizure activity (Sharma et al., 2015). GABA is an inhibitory neurotransmitter that affects vertebrate species' central nervous system. Studies of the ketogenic diet show it is a more successful way of promoting GABA in the body rather than direct injections or using GABA agonists because those treatments can aggravate seizure activity (Snodgrass, 1992).



A study completed by Kishk et al. (2021) examined patients on a 2:1 lipid: non-lipid KD and a 3:1 lipid: non-lipid KD for two months. This study found that both the 2:1 and 3:1 treatment groups showed a statistically significant lower seizure frequency and severity compared to the control group and their baseline scores, in addition to improvement of all aspects (physical function, social function, and general health) of the QOL score (Kishk et al., 2021). Kishk et al. (2021) also found that 22.5% of patients had  $\geq 50\%$  seizure reduction after one month, and 60% had  $\geq 50\%$  after three months for both treatment groups. Another study found that 35.6% of their patients were seizure-free at one month, 39.8% at three months, 38.3% at six months, and 43.1% at 12 months with lipid: non-lipid ratios ranging from 2.5:1 to 4:1 (Guzel et al., 2019).

IJff et al. and Raju et al. also found similar results in studies completed in 2016 and 2011, respectively. Ten percent of the participants in the KD group (no specific lipid: non-lipid ratio) of the IJff et al. (2016) study were seizure-free at four months compared to 7% in the usual care (control) group, and 34% of the KD group experienced  $\geq 50\%$  seizure reduction at four months compared to 7% of the control group. Twenty-six percent of the participants following a 4:1 KD group and 21% following a 2.5:1 KD of the Raju et al. (2011) study were seizure-free at three months. Fifty-eight percent of the participants in the 4:1 KD group and 63% in the 2.5:1 KD group saw  $\geq 50\%$  seizure reduction at three months (Raju et al., 2011).

Many of these studies had a high rate of participants dropping out or refusing treatment. Kishk et al. (2021) found that 61.9% of participants who matched the inclusion criteria refused treatment, and 63.8% of the participants in the study dropped out at different times due to the taste of the food and adverse events such as abdominal pain, diarrhea, and constipation. In the study completed by Guzel et al. (2019), nearly half the patients (48%) who stopped the diet did

so due to compliance problems. This study also found that 50.8% of patients had hyperlipidemia, 26.9% had a selenium deficiency, and 26.2% had constipation due to the treatment (Guzel et al., 2019). Another study found that adults receiving KD most commonly reported vomiting, constipation, and diarrhea (Martin-McGill et al., 2020). Although studies showed the QOL increased from treatment with KD, the compliance issue among participants and the adverse events from the diet show it may not be a suitable treatment for most patients with DRE.

### **Medical Cannabidiol (CBD) and Delta-9-Tetrahydrocannabinol (THC)**

*Cannabis* (marijuana) is a plant that has increased in popularity over the years for its diverse biological activities. In recent years, the cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been studied as a treatment for DRE. THC is the primary psychoactive compound found in *Cannabis*. Its psychoactive properties have limited its clinical use due to the AEs it causes, such as altered senses, hallucinations, changes in mood, impaired body movements, and difficulty with thinking. Therefore, more research has been dedicated to exploring the therapeutic use of CBD in treating DRE (Buchanan-Peart et al., 2020). A few studies have demonstrated the anticonvulsant properties of CBD; however, most of those are either retrospective or small-scale observational studies (Buchanan-Peart et al., 2020). A recent study examined potential mechanisms for CBD's antiseizure activity: the Transient receptor potential vanilloid-1 (TRPV1), the G protein-coupled receptor-55 (GPR55), and through the inhibition of adenosine reuptake (Raucci et al., 2020). CBD decreases extracellular calcium influx through the TRPV1 channel, acts as a GPR55 antagonist by inhibiting intracellular calcium release, reduces adenosine reuptake, and increases extracellular adenosine concentration

(Raucci et al., 2020). These potential mechanisms lead to a decrease in neuronal excitability or hyperactivity (Raucci et al., 2020).

Buchanan-Peart et al. (2020) found in their review that studies show the use of CBD resulted in at least a 50% reduction in seizures for patients with DRE. However, one study in that review demonstrated that the patients with a more significant reduction in seizures had epileptic encephalopathies with or without a known genetic mutation (Tzadok et al., 2016). While Tzadok et al. (2016) reported that 66 of 74 patients in their retrospective study saw some reduction in seizure frequency, five patients reported aggravation of seizures, and only 14 of 31 patients without an epileptic encephalopathy showed a similar response to the treatment. In a small cohort study completed by Devinsky et al. (2022), there was no statistically significant difference in average seizure frequency between their maximal THC: CBD dose phase and the pre-intervention phase 90 days before the first dose of the study medication. Twenty-one percent of the patients had a  $\geq 50\%$  reduction in convulsive seizures, while 13.8% had a  $\geq 50\%$  increase in convulsive seizures during the maximal dose period (Devinsky et al., 2022).

Many studies show a more significant reduction of seizures in patients with epilepsy encephalopathies than in patients with epilepsy syndromes from CBD treatment (Mazurkiewicz-Bęldzińska & Zawadzka, 2022). In their study, Klotz et al. (2019) saw that more than 60% of their children population had epileptic encephalopathies, such as Lennox-Gastaut syndrome, Dravet syndrome, and Doose syndrome, whereas more than 60% of their adult population had focal/multifocal epilepsy. Klotz et al. (2019) also saw a greater number of children with known genetic and structural etiologies compared to adults. The results of this study found that seizure frequency reduction was significantly higher in children than adults; therefore, etiology might be an important factor in treatment response (Klotz et al., 2019). While the publications examined

show great promise for the use of CBD as an alternative treatment for DRE in patients with epileptic encephalopathies, there is still a need to investigate the use of CBD.

One study found in the review by Buchanan-Peart et al. (2020) examined the quality of life reported by patients with certain forms of treatment-resistant epilepsy during a study with cannabidiol. The researchers found that there was an improvement in the domains of physical function, cognitive function, emotional well-being, social function, and behavior, but the score improvements did not correspond with AEs or changes in seizure frequency with CBD use (Buchanan-Peart et al. 2020). This discrepancy indicated that cannabidiol's impact on a patient's quality of life might be independent of its effect on seizure reduction. Buchanan-Peart et al. (2020) also found studies that revealed adverse events associated with the use of CBD, including sedation, decreased appetite, increases in transaminases, diarrhea, behavioral changes, skin rashes, fatigue, and sleep disturbances. Although, one small cohort study found that no adverse or serious adverse events were deemed related to the study drug and were consistent with patients' histories and diagnoses (Devinsky et al., 2022).

### **Stereotactic Radiosurgical Interventions**

Stereotactic radiosurgery (SRS) is a treatment used for epilepsy that uses many focused radiation beams to treat the area of the brain where seizures begin, or the seizure focus (Epilepsy Foundation, 2022c). SRS is a minimally-invasive procedure because the surgeon does not have to open the skull. In many studies, SRS is compared with other surgical interventions for treating DRE, such as resective surgery. Conte et al. (2018) found that in a study of 9 patients treated with radiosurgery, three were seizure-free under ILAE class 1 and Engel class IA (Appendix). One study found that seizure remission was achieved in 52% of the patients that

underwent SRS and in 78% of the patients that underwent anterior temporal lobectomy (ATL) (Mustafa & Zaben, 2022). The pattern of seizure remission was apparent immediately following the procedure for the ATL group, but maximal remission of 74% occurred 34 to 36 months post-intervention for the stereotactic surgery group (Mustafa & Zaben, 2022). Another systematic review found that 12 of 16 studies reported radiotherapy had a positive effect on seizure outcomes defined by the total percentage of patients categorized as Engel class I and II (Appendix), ranging from 25%-95% patients per study with an overall average of 57% (98 patients) (Eekers et al., 2018). This review's highest level of evidence was from a randomized control trial comparing SRS to ATL. The trial was terminated earlier than scheduled due to poor recruitment; nevertheless, the results showed seizure-free outcome rates following ATL were superior to SRS (Barbaro et al., 2018).

Eekers et al. (2018) found in their review study that, in total, 20% (34 patients) of the patients across their study needed subsequent surgery due to radionecrosis, cyst formation, edema, and intracranial hypertension or remaining seizures. In the study completed by Mustafa and Zaben (2022), there were 14 adverse events recorded in 39% of the SRS group, of which five events were considered serious. Those events included seizure exacerbation, headache, cerebral edema, and new neurological deficits (Mustafa & Zaben, 2022). Side effects reported in other studies included headaches, pin-site infections, dizziness, nausea, vomiting, severe seizure exacerbation, status epilepticus, and visual field defects (Marathe et al., 2021). While SRS has some effectiveness in treating drug-resistant epilepsy, it does not compare favorably to a resective surgery such as an anterior temporal lobectomy.

### **Resective Surgery (RS)**

The most common type of surgery for epilepsy is called focal resection, which involves removing the area of the brain where seizures start or the seizure focus (Epilepsy Foundation, 2022c). Other types of resection surgery include the temporal lobe, frontal lobe, occipital lobe, and parietal lobe. Conte et al. (2018) found that out of 109 patients treated with resective surgery, 58 were seizure-free under ILAE class 1 and Engel class IA (Appendix). Among the 111 patients with ongoing seizures, 10 had ILAE class 2 outcomes, 12 had class 3 outcomes, and 89 had class 4-6 outcomes (Conte et al., 2018)(Appendix). The study completed by Conte et al. (2018) also saw 24 patients underwent more than one surgical treatment procedure and found that ten patients were in the ILAE class 1 outcome or Engel class IA, 4 in ILAE class 3, and 10 in ILAE class 4-6 (Appendix).

A study of nine systematic reviews and two large case series of patients with unmanageable epilepsy revealed, on average, 62.4% of patients were seizure-free after epilepsy surgery; however, surgery was found to be less effective for epilepsy associated with structural pathology, extratemporal lesions, or both (Jobst & Cascino, 2015). In a study completed by Hsieh et al. (2022), with a median of 14.7 years of follow-up, 232 (92.4%) patients achieved a period of at least one year of seizure freedom, and 234 (93.2%) patients achieved at least six months of seizure freedom. One hundred sixty-seven (66.5%) of patients were still seizure-free when the threshold of seizure freedom was increased to >2 years (Hsieh et al., 2022). Of the 155 patients who still had postoperative seizures, 59 (38.2%) had seizures within six months, and 71 (45.8%) had seizures within one year, with the median longest period of seizure freedom being 6.9 years (Hsieh et al., 2022).

Sixteen (6.4%) of patients in the Hsieh et al. (2022) study experienced surgery-related AEs, which were defined as a permanent disabling neurological deficit, an unplanned reoperation (excluding epilepsy surgery), a major thromboembolic, or a cardiopulmonary event within 30 days of surgery. Of these, the majority (56%) were reoperation for infection, which in some cases required multiple surgeries, bone flap removal, cranioplasty, or a combination of these (Hsieh et al., 2022). During the last follow-up of the study, 97 (39.3%) patients had a reduction in their antiseizure medication compared to their preoperative baseline. Nineteen (7.7%) patients had an increase, and 131 (53.0%) had a mixed change in their medication (Hsieh et al., 2022).

### **Vagus Nerve Stimulation (VNS)**

Vagus nerve stimulation (VNS) is a treatment for DRE similar to deep brain stimulation in that it uses a small electrical generator implanted under the chest's skin. A wire from the generator is then attached to the vagus nerve in the neck (Epilepsy Foundation, 2022c). The vagus nerve is a crucial part of the autonomic nervous system, which controls functions of the body that are not under voluntary control (Epilepsy Foundation, 2022f). Researchers speculate that affecting this nerve can help control seizure activity by increasing blood flow to key brain areas, raising levels of neurotransmitters important for regulating impulse hyperactivity, and changing electroencephalogram patterns during a seizure (Epilepsy Foundation, 2022f). The generator stimulates the vagus nerve at certain times to help reduce the number of seizures a person has. In a study completed by Conte et al. (2018), 5 of 46 patients that use VNS were seizure-free under ILAE class 1 and Engel class IA (Appendix). Another study found that the number of patients with a >50% reduction in seizure frequency was 8 of 20 (40.0%) at six months, 11 of 20 (55.0%) at 12 months, 7 of 12 (58.3%) at 18 months, and 5 of 8 (62.5%) at 24

months (Xie et al., 2022). In a study completed on children ages 0-6 years, 23 of 39 (59.0%) patients aged 0-3 years achieved seizure reduction at one year, 23 of 37 (62.0%) at two years, and 23 of 37 (62.0%) at four years (Muthiah et al., 2020). The investigators also found that for patients implanted at ages 4 to 6 years, 30 of 54 (56.0%) achieved seizure reduction at one year, 35 of 53 (66.0%) at two years, and 27 of 52 (52.0%) at four years (Muthiah et al., 2020).

A few studies showed AEs as a result of the VNS treatment. Xie et al. (2022) found that six months after stimulator implantation, 4 of 20 (20.0%) patients had adverse events, including hoarseness and a cough. At 12 months after stimulator implantation, only 3 of 20 (15.0%) patients had mild hoarseness (Xie et al., 2022). In the study completed by Muthiah et al. (2020), major complications required additional corrective surgeries for those that resulted in significant structural injuries, and minor complications were all other complications associated with VNS implantation or activation. The major complication rate was 5.5% and included fractured lead wires and deep infection necessitating device removal (Muthiah et al., 2020). The minor complication rate was 6.5% and included vocal changes with activation or vocal cord paresis, coughing with device activation, vomiting or gagging, and neck pain (Muthiah et al., 2020).

### **Review of Literature**

The studies chosen for this review focused on patients with seizure disorders and epileptic encephalopathies of various origins, such as genetic mutations, trauma, or unknown. Each treatment studied was analyzed for its effectiveness in reducing seizure frequency, improving quality of life metrics, and limiting the number of AEs experienced by patients. Deep brain stimulation (DBS) has much promise as a treatment for drug-resistant epilepsy. A systematic review by Yan et al. (2018) showed that of the 40 patients who received deep brain



stimulation, five (12.5%) had an ILAE class I outcome (completely seizure-free, see Table of ILAE Outcome Scale in Appendix), 34 (85.0%) had seizure reduction with DBS, and 6 (15.0%) had no seizure reduction. In a study completed by Salanova et al. (2015), 39 of the 110 implanted subjects (35.5%) had device-related serious adverse events (SAEs), with the majority occurring in the first few months following the implant procedure.

DRE treatment studies that used the ketogenic diet (KD) saw more patients reduce their frequency of seizures rather than completely relieve them of seizure activity. Nine of 40 (22.5%) patients in one study had  $\geq 50\%$  seizure reduction after one month on KD, and 24 of 40 (60%) on KD had  $\geq 50\%$  seizure reduction after three months (Kishk et al., 2021). Another study found that 5 of 19 (26.0%) participants following a 4:1 KD and 4 of 19 (21.0%) following a 2:5 KD were seizure-free at three months (Raju et al., 2011).

Studies using medical *Cannabis* as a treatment for DRE show contradicting results on its effectiveness in reducing seizure frequency in patients. One study found that 89.0% of their patients reported some reduction in seizure frequency, but 38.0% had between 0-50% reduction and 7% of patients reported seizure aggravation from the treatment (Tzadok et al., 2016). Another study found no statistically significant difference in the average seizure frequency between the study's maximal dose of THC: CBD medication and the pre-intervention phase (Devinsky et al., 2022).

A systematic review of radiosurgical interventions showed that 12 out of 16 studies had an outcome of patients achieving Engel class I or II (See Table of Engel Classifications in Appendix) that ranged from 25%-95% per study (Eekers et al., 2018). Of those patients, 34 (20.0%) needed subsequent surgery due to SAEs (Eekers et al., 2018). Another study completed by Mustafa & Zaben (2022) recorded 14 AEs in 39% of the group that underwent stereotactic

radiosurgery (SRS). Fifty eight of 109 patients that received resective surgical treatment for their DRE were classified as seizure-free under ILAE class 1 and Engel class IA (Appendix), according to Conte et al. (2018). In a study completed by Hsieh et al.(2022), 16 (6.4%) patients experienced surgery-related AEs, and the primary (56.0%) adverse event was infection.

Vagus nerve stimulation (VNS) as a treatment for DRE showed that 8 of 20 (40.0%), 11 of 20 (55.0%), 7 of 12 (58.3%), and 5 of 8 (62.5%) of patients had a >50% reduction in seizure frequency for six, 12, 18, and 24 months, respectively (Xie et al., 2022). The authors also found that 4 of 20 (20.0%) of patients had AEs six months after implantation, which then dropped to 3 of 20 (15.0%) at twelve months (2022). Another study completed by Muthiah et al. (2020) found that a small percentage of patients had major complications (5.5%) and minor complications (6.5%) after implantation of the vagus nerve stimulator.

## **Discussion**

Of all six treatments for DRE examined in this review, the resective surgery treatment appears to have the highest percentage of seizure-free patients after surgery, the highest percentage of patients with a reduction in seizure frequency, and the lowest percentage of adverse events due to surgery. There is still the possibility of needing subsequent surgery if the first operation was unsuccessful. However, it is the most successful choice for an alternative treatment for DRE overall. DBS appeared to have the second-highest percentage of patients with a reduction in seizures and the third-lowest percentage of adverse events due to implantation. VNS appeared to have the third-highest percentage of patients with a reduction in seizure frequency and the second-lowest percentage of adverse events due to implantation. SRS appeared to have the second-highest percentage of seizure-free patients after the procedure, but

the adverse event rate was higher and included some severe conditions. The ketogenic diet appeared to have the third highest percentage of seizure-free patients after the treatment; however, many participants experienced adverse events, and the dropout rate was incredibly high due to the lack of compliance from the participants to adhere to the diet. The complete list of rankings can be found in **Table 1**. It should be noted that these rankings are based on the statistics provided from the literature used in this review. A meta-analysis would be needed to make any statistical claims about the data provided.

Table 1: Rankings of Treatments. Each DRE treatment ranked based on the statistics provided from the literature

Rating	Highest percentage of seizure-free patients	Highest percentage of patients with seizure frequency reduction	Lowest percentage of adverse events
1.	Resective Surgery	Resective Surgery	Resective Surgery
2.	Stereotactic Radiosurgery	Deep Brain Stimulation	Vagus Nerve Stimulation
3.	Ketogenic Diet	Vagus Nerve Stimulation	Deep Brain Stimulation
4.	Cannabidiol	Cannabidiol	Stereotactic Radiosurgery
5.	Vagus Nerve Stimulation	Ketogenic Diet	Ketogenic Diet
6.	Deep Brain Stimulation	Stereotactic Radiosurgery	Cannabidiol

As noted above, each treatment had advantages and limitations, and the studies examined for this review noted a few limitations in their findings. DBS, VNS, and resective surgery had studies that needed larger sample sizes and randomized control trials (RCTs). Cannabidiol had evidence that supported but also contradicted its use as a treatment option for DRE. One considerable limitation was the legalization status of cannabis, so there are limits to the amount patients can receive depending on the location of the study. Many retrospective studies were also used, which may not accurately reflect its efficacy for drug-resistant epilepsy. The ketogenic diet treatment was one of the least invasive, but had a very high number of patients drop out of the studies at various points, and it is not an effective treatment if the participant does not comply

with the diet. SRS was effective for some DRE patients, but it had a more significant number of SAEs in their study groups. In addition, SRS is considered an inferior treatment when compared to resective surgery. Other limitations of the studies include using ASMs or AEDs while being tested with the research treatment and the need for research on mechanisms that pertain to drug-resistant epilepsy.

A few prevailing limitations found in most of these studies were a need for large sample sizes, more RCTs, and limiting the number of retrospective studies. The use of retrospective studies can give insight into how effective these treatments are, but the severe lack of current studies with large sample sizes hinders that progress. RCTs are also needed to ensure minimal bias when completing these studies. Another limitation found in the reviewed studies was the number of patients that discontinued the treatment during the study. Many studies note that a certain number of patients dropped out of the research at specific intervals but do not necessarily consider this when compiling data, skewing the data. It is also important to note the possibility of patient overlap in these studies depending on the participant regulations for the study.

### **Recommendation**

Any future research on the efficacy of treatment options for DRE should have large sample sizes, include RCTs, and complete long-term follow-ups. More research should be conducted for each of these treatments, especially to understand the general mechanism of the treatment and epilepsy as a disorder. This review aims to compare the effectiveness of treatments for DRE and should not be used as a recommendation for those seeking alternative treatments. There are many types of seizure disorders and epileptic encephalopathies, and treatments should

be patient-specific. Neurologists and physicians that treat DRE should be consulted when examining alternative treatment options.

### **Conclusion**

Epilepsy is a neurological disorder with no current cure, but many forms of epilepsy respond well to medication to alleviate symptoms. Although medication has little to no effect on patients with DRE, evidence suggests that there are alternative treatments for managing symptoms. The purpose of this study is to compare the effectiveness of treatments for DRE. According to the studies examined, resective surgery has the highest percentage of patients that were seizure-free after the procedure, the highest percentage of patients that had a seizure reduction after the procedure, and the lowest percentage of adverse events experienced by patients. All of the treatments have been proven to reduce seizure activity for patients with DRE, but more research is needed to find any common factors in the mechanisms of the treatments. While the studies examined offer some crucial insights into alternative treatment options for DRE, more research is needed to confirm these results on larger cohorts and understand the physiological mechanisms responsible for epileptic conditions and their treatments.

### **Abbreviations**

AE: adverse event

AED: antiepileptic drugs

ASM: antiseizure medication

ATL: anterior temporal lobectomy

CBD: cannabidiol

DBS: deep brain stimulation

DRE: drug-resistant epilepsy

GABA: gamma-aminobutyric acid

ILAE: International League Against Epilepsy

KD: ketogenic diet

QOL: quality of life

RCT: randomized controlled trial

RS: resective surgery

SAE: serious adverse event

SRS: stereotactic radiosurgery

THC: delta-9-tetrahydrocannabinol

VNS: Vagus nerve stimulation

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## Appendix

*Table of Engel Classifications*

Class I: Free of disabling seizures	IA: Completely seizure-free since surgery	IB: Non disabling simple partial seizures only since surgery	IC: Some disabling seizures after surgery, but free of disabling seizures for at least 2 years	ID: Generalized convulsions with antiepileptic drug withdrawal only
Class II: Rare disabling seizures (“almost seizure-free”)	IIA: Initially free of disabling seizures but has rare seizures now	IIB: Rare disabling seizures since surgery	IIC: More than rare disabling seizures after surgery, but rare seizures for at least 2 years	IID: Nocturnal seizure improvement
Class III: Worthwhile improvement	IIIA: Worthwhile seizure reduction	IIIB: Prolonged seizure-free intervals amounting to greater than half the follow-up period, but not less than 2 years		
Class IV: No worthwhile improvement	IVA: Significant seizure reduction	IVB: No appreciable change	IVC: Seizures worse	

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*Table of International League Against Epilepsy (ILAE) Outcome Scale*

<b>Class</b>	<b>Description</b>
Class 1	Completely seizure free; no auras
Class 2	Only auras; no other seizures
Class 3	1 to 3 seizure days per year; $\pm$ auras
Class 4	4 seizure days per year to 50% reduction of baseline seizure days; $\pm$ auras
Class 5	Less than 50% reduction of baseline seizure days; $\pm$ auras
Class 6	More than 100% increase in baseline seizure days; $\pm$ auras

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