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A Review of the Surgical Procedures for the Treatment of Drug-Resistant Epilepsy and Their Seizure Control Outcomes

Talal Salem, Cohen Chetty, Ochran Chetty

Faculty of Medicine, Masaryk University, Brno, Czech Republic
Email: talalsalem.med@gmail.com

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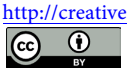

Abstract

Background: Drug-resistant epilepsy can be defined as the existence of seizures within 6 months, despite adequate therapy regimens with one or more antiepileptic drugs. Epilepsy surgery has been the standard therapy to help those patients who suffer from drug-resistant epilepsy. The goal of this surgery is to halt or reduce the intensity of seizures. This literature review aims to provide an overview of existing surgical procedures for the treatment of drug-resistant epilepsy and the degree of seizure control they provide based on available literature. **Methods:** Data were collected from medical journal databases, aggregators, and individual publications. The most used databases were PubMed, Medline and NCBI. Some of the keywords used to search these databases include: "drug resistant epilepsy", "seizure control", and "neurosurgery". **Results:** Epileptic surgery is divided into resective and non-resective procedures. Studies have shown that a full resection of the epileptogenic brain area increases the probability of seizure eradication, however, the risks of postoperative impairments grow as the resection area is extended. On the other hand, patients who are unsuitable for seizure focus removal by resective surgery, such as those with multifocal seizures or overlapping epileptogenic zone with a functional cortex, may benefit from non-resective surgical options such as Vagus Nerve Stimulation and Responsive Neurostimulation. **Conclusion:** This literature review discusses the comprehensive treatment of epilepsy, especially the surgical treatment of drug-resistant epilepsy. The reviewed studies have shown that epilepsy surgery has promising outcomes in achieving seizure freedom/reducing seizure frequency with minimal adverse effects when performed correctly with the appropriate choice of surgical candidates.

Keywords

Drug-Resistant Epilepsy, Vagus Nerve Stimulation, Seizure Control, Neurostimulation

1. Introduction

1.1. General

Epilepsy is a neurological illness in which brain activity becomes abnormal, resulting in seizures or episodes of unusual behavior, feelings, and even loss of awareness. It affects over 50 million patients globally and accounts for a considerable amount of the global illness burden [1]. Patients with epilepsy can be treated by antiepileptic drugs (AEDs), some of them require lifetime treatment to manage their seizures, while in others' the seizures ultimately go away. However, when AEDs fail to control the seizures, a condition known as drug-resistant epilepsy develops. This occurs in one-third of epileptic patients and can result in early mortality, brain injury, or a lower quality of life [2].

Epilepsy surgery has been the standard therapy to help those patients who suffer from drug-resistant epilepsy. The goal of epilepsy surgery is to halt or reduce the intensity of seizures. This article aims to review existing surgical procedures for the treatment of drug-resistant epilepsy and the degree of seizure control they provide based on available literature.

1.2. History of Epilepsy

Epilepsy is an ancient disease, its history is interwoven with the history of human existence; however, it was not always recognized as a pathology of neurological origin [3] [4]. It was a controversial disease often being associated with demonic spiritual possession, genius, and divinity, and was often referred to as the "sacred disease" [4]. Epilepsy's history can be traced back to the Assyrian texts, almost 2000 B.C found in Mesopotamia on an Akkadian tablet with the inscription describing a person with "his neck turning left, hands and feet are tense, and his eyes wide open, and from his mouth froth is flowing without him having any consciousness" [5]. The description of epilepsy as a disease was found in many ancient texts, the most important being described in the *Corpus Hippocraticum*, a collection composed of 60 treaties dating to 400 B.C. in Ancient Greece. It is here where Hippocrates first hypothesizes that epilepsy is a disease of the brain and is caused by an excess of "phlegma" in the brain, that when in contact with blood causes epileptic seizures [4]. The work of John Hughling Jackson (1835-1911), the father of "modern epileptology", set the scientific base of epileptology by studying it on an anatomical and pathological basis, leading to his correlation of epileptic seizures to localized lesions in the cortex [6]. In 1873 Jackson gave the following definition of epilepsy: "Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey Mat-

ter" [4].

1.3. History of Epileptic Surgery

May 25, 1886, marks the beginning of the modern era of epileptic surgery at the National Hospital for Paralysed and Epileptic in London. Sir Victor Horsley (1857-1916) performed his first successful craniotomy for focal seizures secondary to a depressed skull fracture [7]. By the end of 1886, he would complete 9 epileptic surgeries and establish the efficacy of the procedure. He had operated on these patients with the support and help of John Hughling Jackson (1835-1911) and David Ferrier (1843-1928) [3]. By performing brain-mapping experiments using electrical stimulation of the Rolandic cortex on monkeys, Horsley was able to perform these operations without stimulating the cortex of his patients [5]. The collaborative work of Foerster and Altenburger in Germany, Penfield and Jasper in Canada, and other interdisciplinary teams greatly influenced our understanding of cerebral electrophysiology and function [7]. This served as the basis for the diagnostic and operative techniques for modern epilepsy surgery.

2. Pathogenesis of Drug-Resistant Epilepsy

Epilepsy can be caused by various reasons, including genetic susceptibility/abnormalities, brain tumors, vascular lesions, traumatic brain injuries, chemical exposure, hypoxia, or stroke. Many of these disorders are linked to neurodegeneration. The release of cytokines, chemokines, lipid mediators, and proteins in the neuronal microenvironment is triggered by brain injury, resulting in a cascade of biological events defined by neuroinflammatory processes. In the brain, these mediators activate microglia and astrocytes, modify cerebrovascular function, influence peripheral inflammatory cell infiltration, increase cell proliferation or death, change ion transport, neurotransmission, and neuronal communication [8]. In addition to this, the complement system's significance in the pathophysiology of epilepsy has recently been demonstrated. Necrotic cells, cellular fragments, or a misfolded protein, such as the fibrillar form of amyloid-peptide in Alzheimer's disease, can activate complement [9]. Various complement proteins have been shown to be overexpressed in surgically excised tissue from epileptic patients [10].

In epileptic patients, several cytokine secretion and receptor expression regulatory mechanisms have been discovered [11]. For instance, serum IL-1b, IL-1Ra, IL-6 concentrations have all been found to be higher in epileptic patients [12]. The production of cytokines, chemokines, reactive oxygen species, and secondary messengers are all involved in neuroinflammation. Glial cells in the central nervous system, endothelial cells, and peripheral immune cells all produce these mediators which have immunological, physiological, biochemical, and psychological effects. Hence, the role of neuroinflammation is essential when we look at the mechanisms of epileptogenesis.

There are various hypotheses proposed to describe the pathogenesis of drug-resistant epilepsy. **Table 1** contains a summary of these hypotheses.

Table 1. Summary of drug-resistant epilepsy pathogenesis hypotheses.

Hypothesis	Summary
Pharmacokinetic Hypothesis [13]	Anticonvulsant levels are reduced when drug efflux vectors are over expressed in peripheral organs.
Transport Hypothesis [14]	Anticonvulsant levels are reduced when drug efflux vectors are over expressed in the blood brain barrier.
Neural Network Hypothesis [15]	The brain's seizure control mechanism is suppressed by neuron loss and synaptic network reorganization, preventing drug access to targets.
Intrinsic Severity Hypothesis [16]	Both the severity of epilepsy and drug resistance are influenced by neurobiological variables.
Genetic Variants Hypothesis [17]	Drug resistance develops because of genetic polymorphisms related to pharmacodynamics, metabolic pathways, enzymes, ion channels, and neurotransmitter receptors, which may inhibit drug binding, metabolism, and transport.
Epigenetic Hypothesis [18]	Drug resistance patterns may be influenced by epigenome alterations.
Target Hypothesis [19]	Drug efficacy is reduced because of quantitative and qualitative alterations in potential-dependent ion channels and neurotransmitter receptors.
Neuroinflammation Hypothesis [20]	Neuroinflammation can cause blood brain barrier disruption leading to decreased transport of antiepileptic drugs.

3. Diagnosis of Drug-Resistant Epilepsy and Its Classification

3.1. Diagnosis

The most important part of epilepsy surgery is the presurgical assessment phase. All patients suspected of drug-resistant epilepsy should be sent to an epilepsy center. The patients will be assessed again during this stage to confirm the diagnosis and define the seizure type.

Epilepsy's course does not remain stable and there are apparent variations in response to AEDs. Therefore, the categorization of a patient's epilepsy as drug-resistant at a certain moment in time is only valid at that time, it does not necessarily suggest that the patient will never be seizure-free on AEDs. This led to a significant debate within the medical community on the number of required AEDs that must fail before categorizing the condition under drug-resistant epilepsy. However, the International League Against Epilepsy (ILAE) suggested in 2017 that drug-resistant epilepsy can be defined as the existence of seizures within 6 months, despite adequate therapy regimens with one or more medications [2]. The suggested definition arose from the desire among medical doctors and clinical researchers to establish a uniform terminology in detecting drug-resistant epilepsy in the face of rapidly expanding treatment choices.

3.2. Classification of Seizures

Seizures are currently classified into three types:

1) Seizures with a generalized onset impact both sides of the brain or groups

of cells on both sides of the brain at the same time. This term was previously used and still encompasses seizure forms such as tonic-clonic, absence, and atonic, just to mention a few.

2) Focal onset seizures begin in a single region or cluster of cells on one side of the brain. They are divided into 2 types:

- *Focal onset aware seizures* which occur when a person is awake and aware during a seizure.
- *Focal onset impaired awareness seizures* occur when a person is confused, or their awareness is compromised during a focal seizure.

3) Unknown onset seizures occur when the start of a seizure is unknown. These types of seizures usually occur at night when no one is around to witness the start of the seizure.

4. Diagnostic Methods to Determine Epileptogenic Zones

4.1. Preoperative Diagnostic Methods

The main purpose of preoperative tests is to determine the epileptogenic zone and the safety of a potential brain surgery so that the procedure may be conducted with minimal functional damage and seizure cessation.

To evaluate the various cortical zones, a range of diagnostic methods can be used. Seizure semiology, Video-EEG recording, neurofunctional testing and neuroimaging methods are used to identify the cortical zones involved in seizure production and propagation. Video-EEG is considered as the ultimate tool in detecting the epileptogenic zone, it can be significantly aided by high resolution MRI for structural integrity, diffusion tensor imaging for cellular integrity, magnetic resonance spectroscopy for biochemical data, or physiological imaging modalities such as PET and single-photon emission EEG, magnetoencephalography (MEG), and functional MRI methods [21]. Despite the availability of a variety of diagnostic methods, various instances may necessitate different diagnostic procedures, therefore the assessment process should be personalized to each patient.

4.2. Perioperative Diagnostic Methods

Perioperative invasive methods can be employed during epilepsy surgery. These methods are performed in an awake craniotomy to help the neurosurgeon distinguish between the epileptogenic zones from eloquent areas of the brain [21]. Intraoperative electrophysiology examinations, with the help of a neurologist, can be done after obtaining Intracranial EEG (iEEG) recordings. There are several iEEG recording methods, including electrocorticography (ECoG) through subdural grids, strips, depth electrodes and stereoencephalography (SEEG), each with its own restrictions and advantages [22]. The choice to utilize iEEG is motivated by the goal to enhance the likelihood of the patient becoming seizure-free.

5. Surgical Options for Drug-Resistant Epilepsy and Their Seizure Control Outcomes

The right surgical choice can be determined after completing preoperative ex-

aminations, identifying the epileptogenic zone, and establishing the risk assessment of the surgery in each specific case. Different surgical procedures can be used depending on the seizure type, location, or the presence or absence of a detectable abnormality on brain imaging. Broadly speaking, epileptic surgery can be divided into resective and non-resective procedures. A full resection of the epileptogenic brain area increases the probability of seizure freedom; nevertheless, the risks of postoperative impairments grow as the resection area is extended. As a result, the degree of resection should be assessed against such risks and tailored to each individual patient. On the other hand, patients who are unsuitable for seizure focus removal by resective surgery, such as those with multifocal seizures or overlapping epileptogenic zone with a functional cortex, may benefit from non-resective surgical options.

Many surgical outcomes classification systems can be used by epilepsy centers. The most common ones are the Engel classification system, see **Table 2** [23] and ILAE classification system, see **Table 3** [24].

6. Resective Surgical Options

6.1. Anterior Temporal Lobectomy (ATL) & Anteromedial Temporal Resection (AMTR)

In 1936, Wilder Penfield conducted the first temporal lobe excision for epilepsy.

Table 2. Engel outcome scale classification system [25].

Engel Outcome Scale	
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 seizures only.
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	Seizure worse.

Table 3. ILAE outcome scale classification system [25].

ILAE Outcome Scale	
Class 1	Completely seizure-free; no auras.
Class 2	Only auras; no other seizures.
Class 3	1 to 3 seizure days per year; with/without auras.
Class 4	4 seizure days per year to 50% reduction of baseline seizure days; with/without auras.
Class 5	Less than 50% reduction of baseline seizure days; with/without auras.
Class 6	More than 100% increase of baseline seizure days; with/without auras.

Several surgical treatments and procedures for temporal lobe epilepsy have subsequently been suggested; the earliest one being the anterior temporal lobectomy. ATL has been shown in a landmark trial to be superior to long-term pharmacological treatment in individuals with drug-resistant temporal lobe epilepsy [26]. After ATL, 60% - 80% of patients reach seizure-free status, compared to less than 5% who do not have surgery but instead seek medicinal treatment [27]. Due to the temporal lobe being a vital location for memory functions, one of the major risks of this operation is memory impairments. Results from a meta-analysis revealed memory decline on neuropsychological tests of verbal memory occurred in 44% of patients undergoing dominant hemisphere ATL, compared to 20% of patients undergoing nondominant hemisphere ATL [28].

Spencer introduced AMTR in 1984 with the goal of preserving the lateral temporal cortex while still treating the temporal lobe epilepsy. This offered a great advantage over the classical ATL as it minimized the above-mentioned side effects caused by ATL [29]. Nowadays, AMTR is a common surgical procedure to treat temporal lobe epilepsy. A randomized controlled clinical trial showed that at the second year of follow-up, AMTR surgery combined with AEDs resulted in a decreased risk of seizures compared to AEDs alone. During the trial, zero out of 23 patients was seizure free in the AEDs group, compared to the 11 out of 15 patients who achieved seizure freedom in the surgical group [30].

6.2. Extratemporal Resections

Extratemporal epilepsy is a group of seizures outside the temporal lobe. To treat it, lesions (such as tumors, focal cortical dysplasia and cavernomas) in other parts of the brain such as the occipital, frontal, or parietal lobes, may be removed by neurosurgeons. This therapy is most effective when the lesions are in certain brain regions with abnormal electrical activity causing seizures.

In a study on 34 patients with lesional/non-lesional drug-resistant extratemporal epilepsy who underwent extratemporal resections found that 55.8% of these patients had a favorable seizure outcome (Engel class I - II), with 84.2% in Engel class I one year after surgery [31]. In a study following 24 patients who suffered from epilepsy originating from the insular cortex, after at least a 12

month follow up it was found that 62.5% of patients obtained seizure-free status (ILAE I, LAO), while more than three-quarters reached a seizure-satisfactory status (ILAE1-3). Although, a few mild postoperative deficits were noted [32]. In another longitudinal study of surgical outcomes following posterior cortex epilepsy surgery, 57 patients were studied. 6 months after surgery, 75% of patients remain seizure-free. After one year, this percentage drops to roughly 70%, and after 8 years, it is slightly more than 50% [33]. 70% of patients with frontal lobe encephalomalacia became seizure-free after epilepsy surgery in a small group of 14 patients at the Mayo Clinic [34]. Seizure-free outcomes were observed in individuals with lesional and non-lesional frontal lobe epilepsy. The total seizure-free rate was 56% after the first year, 45% after three years, and 30% after five years [35]. Regarding functional outcomes, a 2018 study of 42 patients who had occipital lobe resection to treat epilepsy indicated that 57.6% had satisfactory visual function after the surgery. Resection of the lateral occipital lobe was more likely to impair vision [36].

6.3. Laser Interstitial Thermal Therapy (LiTT)

LiTT is a minimally invasive surgical alternative for patients with drug-resistant epilepsy, particularly those with focal epilepsy. The method might help reduce the surgical risks associated with typical open epilepsy surgery, such as postoperative discomfort, extended recovery times, and cognitive impairments following surgery [37]. LiTT was primarily developed to be used in brain tumor surgeries, although during recent years it started to be adopted in epilepsy surgery [38]. LiTT can be used and repeated several times in several indications causing epilepsy such as drug-resistant mesial temporal lobe epilepsy [39], hypothalamic hamartoma [40], complex and deep focal cortical dysplasia [41]. LiTT can also be utilised to perform a minimally invasive robotic laser corpus callosotomy [42]. LiTT works by the insertion of a catheter via a fiber optic probe under MRI-guidance which transmits laser energy through a tiny 3.2 mm (about 0.13 in) hole in the skull. Because of its tolerance and minimal morbidity, LiTT appears to be a well-tolerated approach for ablation of a range of epileptogenic lesions, and it reduces seizures in many patients [43]. The overall picture, however, reveals that the seizure outcomes for LiTT looks to be good, albeit poorer than open resective procedures (difference of 10% - 20%) [44]. In a prospective multicenter study, 60 epileptic patients were treated with LiTT. 42 patients were followed-up after one year, 64.3% of those patients were classified as Engel I outcome [45]. Moreover, in many cases, preliminary findings show that MRI-guided LiTT may provide a much superior cognitive outcome than open resection [46].

6.4. Stereotactic Radiosurgery

Stereotactic radiosurgery is a new therapeutic method that combines stereotactic localization with numerous cross-fired beams from a highly collimated radiation source. It can be used for selected patients with brain tumors, arteriovenous

malformations, trigeminal neuralgia, and other illnesses.

Radiosurgery is a promising treatment option for drug-resistant focal epilepsy. The combination of non-invasive localization and radiosurgery is an appealing alternative approach to lesions that have historically been treated with open brain resection. When the seizure focus is in eloquent or surgically problematic brain areas, which are associated with an unacceptably high frequency of complications following open surgery, stereotactic radiosurgery can be considered as a therapeutic option [47]. Radiosurgery enables the neurosurgeon to administer a precise and correct dose of radiation with minimum danger to neurological functions and without damaging neighboring healthy parenchyma [48].

Mesial temporal lobe epilepsy (MTLE) caused by mesial temporal sclerosis is the best focus for radiosurgery since targets can be shown on MRI [49]. Radiosurgery has recently been investigated as an alternative to open resective surgery for MTLE. In 1995, the first case of MTLE was treated by radiosurgery [50]. Since then, many trials have been published in the medical literature. The long-term outcomes were published in a study containing 15 patients with a mean follow-up duration of 60 months (about 5 years). 60% of those patients were seizure-free plus no patient was suffering from recurrent disabling seizures [51]. In a randomized controlled trial, 20 patients had been treated for MTLE by radiosurgery. Follow-ups were conducted after 36 months (about 3 years), 67% of patients were seizure-free [52]. In a prospective multicenter study, 21 patients were studied and followed up for 2 years and 65% of them were seizure-free [53]. According to a meta-analysis that included 13 studies, 50% of the patients treated for MTLE by radiosurgery were seizure-free in a follow-up duration between 6 months and 9 years. The meta-analysis also reported some adverse events of the procedure which included visual impairments and headache, memory impairments, psychosis, non-epileptic seizures, and dysphasia [54].

Currently, stereotactic radiosurgery stays as a very controversial therapeutic method for drug-resistant epilepsy despite the numerous clinical trials described above. The risks and adverse events might outweigh the clinical benefits in many cases since it is associated with severe memory disorders especially when used to treat MTLE. However, a literature review published in the Epilepsia Journal showed promising long-term cognitive outcome after the treatment of epileptic hypothalamic hamartomas using this method [55].

7. Non-Resective Surgical Options (Neuromodulation-Based Interventions)

7.1. Vagus Nerve Stimulation (VNS)

The Vagus nerve is an essential component of the autonomic nervous system that regulates metabolic homeostasis and works with the neuroendocrine-immune axis to maintain balance via its afferent and efferent pathways. Any approach that stimulates the Vagus nerve, including manual or electrical stimulation, is called Vagus Nerve Stimulation (VNS). VNS is a therapeutic option for drug-resistant

epilepsy and depression [56] [57]. In a meta-analysis, VNS was also found to be beneficial in treating chronic heart failure [28]. The effectiveness of non-invasive transcutaneous VNS methods for epilepsy, tinnitus, migraine, and pain needs more evidence to be proven [58] [59].

It was noticed in the 1880s that hand massages and compression of the carotid artery in the cervical area of the neck could control seizures. This action is considered a primitive method of Vagus nerve activation [60]. During the 1930s and 1940s, electrical VNS research was conducted to better understand the role of the Vagus nerve in controlling brain activity. It was shown that VNS altered brain electrical activity in animals. Hence, anticonvulsant effects were found on experimentally produced seizures in dogs [61]. This led to the FDA authorization of VNS for use as an adjunctive therapy in patients over the age of 12 who have drug-resistant seizures in 1997. Following that, in 2017, it was FDA approved in children as young as 4 years old. However, nowadays VNS has no age restriction.

The VNS consists of a pulse generator implanted below the collarbone and a lead wrapped around the left Vagus nerve. It must be mentioned that achieving seizure freedom with VNS seems to be rare, but still, it may be effective in lowering seizure frequency and increasing quality of life [62]. In a systematic review of the literature including the registry of 5554 patients, 63% of patients had more than 50% reduction in seizure frequency after 24 - 48 months follow-up, while 8.2% achieved seizure freedom [63]. In a literature review published in 2019, it was found that within one year, VNS resulted in a more than 50% decrease in seizure frequency in 26% - 40% of patients [64]. An observational study noticed that VNS managed to reduce seizure-related hospital admissions from 91.3% to 43.5% in 17 patients with genetic generalized epilepsy (GGE). Also 12 out of 29 patients with Lennox-Gastaut Syndrome (LGS) had more than 50% decrease in seizure frequency after VNS therapy [65]. In a recent retrospective study of 41 patients published in 2022, a drop of median seizure frequency from 1.5/day to 0.3/day in the focal epilepsy group after implantation of VNS was observed. Comparatively, a drop from 0.6/day to 0.2/day in the generalized epilepsy group after the same treatment was observed [66].

7.2. Responsive Neurostimulation (RNS)

RNS consists of an implanted neurostimulator and intracranial leads that detect seizures and respond with electrical stimulation to stop them [67]. The FDA has approved the RNS System in 2013 as an additional treatment in lowering the incidence of seizures in those over the age of 18 under three conditions. These conditions include:

- The patient is resistant to 2 or more AEDs,
- The patient has had 3 or more seizures per month for 3 consecutive months.
- The patient has no more than 2 epileptogenic foci [68].

All patients who received RNS during a randomized controlled trial had seen a decline in their seizure rates. The average reduction in seizure frequency was

44% after 1 year, going up to 53% after 2 years [69]. In another randomized controlled trial providing Class IV evidence, seizure frequency reduction reaches 60% - 66% after 3 to 6 years [70]. In a recent prospective study published in 2020 looking at 230 participants, the median reduction in seizure frequency reached 75% at the 9th year follow-up [71]. RNS demonstrates improved seizure frequency reduction with time. Therefore, it can be considered as a therapeutic option for specific patients suffering from drug-resistant epilepsy.

7.3. Deep Brain Stimulation (DBS), Anterior Thalamic Nucleus Stimulation

Several animal investigations in the second half of the 20th century led to the discovery of the possible significance of the anterior thalamic nucleus in epilepsy [72] [73]. The first clinical case of thalamic lesioning to treat epilepsy was published in 1967 [57]. Nowadays, DBS can be used for the treatment of essential tremor, Parkinson's disease, dystonia, psychiatric disorders, as well as drug-resistant epilepsy. DBS is utilized in cases when medications fail to control symptoms. It works by preventing electrical impulses from being sent to certain areas of the brain. An electrode is implanted in the brain by surgery which is connected to a neurostimulator implanted beneath the skin. The neurostimulator transmits electrical signals to the electrode [74]. DBS was officially approved by the FDA for the treatment of drug-resistant epilepsy in 2018 [75].

Due to the small number of patients who have had DBS implants, we have a limited understanding of the short- and long-term outcomes. Nevertheless, a randomized double-blind controlled trial referred to as SANTE (The Stimulation of the Anterior Nuclei of Thalamus for Epilepsy), involved 110 patients with drug-resistant epilepsy was the biggest trial with promising findings in 2010 [76]. This trial published follow-up findings after 5 years which revealed that the average seizure reduction rate gradually increased to 69%, with 11 patients achieving seizure freedom for at least 6 months. Also, the number of patients with a 50% reduction in seizure frequency had increased to 68% [77].

SANTE was updated again in 2021 with a retention rate of 56% (62/110 patients). Long-term seizure control outcomes after 7 years and safety outcomes after a decade were reported. At 7 years, the average seizure frequency decreased from baseline by 75%. Also, 74% of patients had 50% or more reduction in seizure frequency.

Following implantation, the most often reported adverse events were hardware-related, paresthesia, implant site discomfort, implant site infection, intracerebral hematoma, and electrode misplacement. Although, after the 10-year follow-up, no worsening of adverse events was found, indicating a consistent long-term safety profile [78].

8. Conclusions

Drug-resistant epilepsy arises from various factors, including genetic abnormalities, brain tumors, injuries, and neurodegenerative disorders. Neuroinflamma-

tion, involving microglia and astrocyte activation, alters cerebrovascular function and neurotransmission. Hypotheses suggest drug resistance can be due to overexpressed drug efflux vectors in peripheral organs or at the blood-brain barrier, hindering drug access. Understanding these diverse pathogenic mechanisms is crucial for developing targeted treatments and interventions to manage drug-resistant epilepsy effectively.

In this paper, the latest literature regarding seizure control outcomes in surgical procedures for the treatment of drug-resistant epilepsy was reviewed. The treatment of drug-resistant epilepsy requires multidisciplinary care and referral to epilepsy facilities for prompt clinical assessment. Along with these management difficulties, determining the pathophysiology of drug-resistant epilepsy is important for our understanding of the illness. Moreover, effective utilization of diagnostic tools to evaluate the patient's eligibility for surgical therapy (preoperative evaluation) is critical in the management of drug-resistant epilepsy patients. This can help in identifying the type of surgical procedure that would be the safest and most advantageous to each specific patient.

As demonstrated in this review, epilepsy surgery shows promising outcomes in achieving seizure freedom/reducing seizure frequency with minimal adverse effects when performed correctly with the appropriate choice of surgical candidates. Preoperative examinations and surgical procedures will continue to improve as technologies advance and hopefully, the implementation of epilepsy surgery will increase in the future.

Conflicts of Interest

The authors of this paper declare no conflicts of interest regarding the publishing of this paper.

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