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Epilepsy: Surgical and Non-Surgical Management and Treatment

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Abstract

Epilepsy (in Ancient Greek ἐπιλαμβάνειν, meaning literally to seize, possess, or afflict) is one of the most common serious neurological disorders encompassing a group of such disorders. It has been historically associated with evil spirits and mystery, and still to this day often carries social stigmas. Its long history, along with its social implications, makes epilepsy a unique disorder. Yet, epilepsy is a common neurological condition. It affects people of all ages, more commonly the elderly. It is characterized by recurrent seizures or vigorous shaking that can be brief and nearly undetectable, or last for long periods of time. Epilepsy can occur for a variety of reasons and can start at any age. In children, it is the result of the child's brain having been injured in some way. Despite a basic understanding of the pathophysiology of epilepsy, its causes can be complex, hard to identify, and not fully understood. I had posited that epilepsy is but an autoimmune disease run amok, the seizures being only its symptoms. Treatment usually proceeds along four threads: Pharmacology; neurosurgery and neurostimulation; gene therapy and immunotherapy; and other therapies. While interest here is principally on neurosurgery and neurostimulation, the complete therapeutic portfolio is considered.

Keywords: *Autoimmune disease; Epilepsy; Seizures; Gene therapy; Immunotherapy; Neurosurgery and neurostimulation*

Running Title: Management and Treatment of Epilepsy.

Abbreviations: AANS: American Association of Neurological Surgeons; AAVV: Adeno-Associated Virus Vector; AD: Alzheimer's Disease; AD: Atkins' Diet; ADK: Adenosine kinase; ALS: Amyotrophic Lateral Sclerosis; ANS: Autonomous Nervous System; ASM/D: Anti-Seizure Medication/Drug; ATP: Adenosine Triphosphate; BBB: Blood-Brain Barrier; CBD: Cannabidiol; CNS: Central Nervous System; CAT: Complementary & Alternative Therapy; CKT: Classic KD; CT: Computed Tomography: DREADD: Designer Receptor Exclusively Activated by Designer Drugs; DS: Dravet's Syndrome; EEG: Electroencephalogram; DNA: Deoxyribonucleic Acid; EEG: Electroencephalography; EF: Epilepsy Foundation; EM: Electro Magnetic; EMU: Epilepsy Monitoring Unit; FDA: (U.S.) Food & Drug Administration; fMRI: functional MRI; GABA: Gamma-Aminobutyric Acid; GEL: Genetics, Environment, Lifestyle; GKRS: Gamma Knife RS; Ig: Immunoglobulin; GT: Gene Therapy; IT: Immunotherapy; ILAE: International League Against Epilepsy; ION: Ion Oxide Nanoparticle; IVIg: Intra-Venous Ig; KD: Ketogenic Diet; LITT: Laser Interstitial Thermal Therapy; lfMS: low-field MS; MAD: Modified AD; MCT: Medium-Chain Triglyceride; MRI: Magnetic Resonance Imaging; MS: Magnetic Stimulation; MST: Multiple subpial transection; MST: Magnetic Seizure Therapy; NCP: Neurocybernetic Procedure; NINDS: (U.S.) National Institute for Neurological Disorders and Stroke; NS: Neuro Stimulation; PEMFET: Pulsed EM Field Therapy; PET: Positron Emission Tomography; PNS: Peripheral Nervous System; RNA: Ribonucleic Acid; RNS: Responsive NS; rRS: radioRS; PD: Parkinson's disease; RS: Radio Surgery; sEEG: stereo EEG; rTMS: repetitive TMS; SPECT: Single Photon Emission Computed Tomography; SPION: Super Paramagnetic ION; TMS: Transcranial Magnetic Stimulation; TTF: Tumor-Treating Field; VNS: Vagus Nerve Stimulation; WHO: World Health Organization.

Drugs: Anticonvulsants; Benzodiazepine; Bromides; Cannabidiol; Carbamazepine; Clobazam; Clozapine; Ethosuximide; Epidiolex (non-psychoactive made from CBD); Gabapentin; Lamotrigene; Levetiracetam; Lyrica; Methohexital; Olanzapine; Phenobarbitol; Phenytoin (Dilantin); Sodium Amobarbital; Sodium Valproate; Sultiame. Valium.

Diseases/Disorders: Agranulocytosis; Alzheimer's disease; Amyotrophic lateral sclerosis; Anaphylaxis; Angioedema; Ataxia; Bradycardia; Cardiac arrest; Diplopia; Dravet's Syndrome; Encephalitis; Epileptic partialis continua; Epilepsy (benign Rolandic; focal; generalized; lesional; non-lesional; partial-onset; pediatric; refractory); Epileptic syndromes; Hyponatremia; Leukopenia; Pancytopenia; Seizures (atonic; epileptic and non-epileptic; focal; generalized; myoclonic; tonic); Fatigue; Meningitis; Migraine; Parkinson's disease; Seizure-related disorders; Stroke; Status epilepticus; Tuberous sclerosis neurofibromatosis; Vertigo.

Introduction

As defined by the International League against Epilepsy (ILAE), "*epilepsy is a disease of the brain that results in at least two unprovoked seizures occurring at least 24 hours apart. A person may also be diagnosed with epilepsy if they have one unprovoked seizure and have a high chance (>60%) of having another seizure within the next 10 years or if they have an epilepsy syndrome*". This pragmatic definition only relates to events or occurrences - not to signs, symptoms, mechanisms, or especially causes. Other definitions have been provided by the (U.S.) National Institute for Neurological Disorders and Stroke (NINDS), the American Association of Neurological Surgeons (AANS), and others. It is important to note that not all seizures are epileptic and not all are caused by disrupted brain activity (e.g., syncope, drop in blood pressure, etc.). These recurrent, unprovoked seizures might affect, for example, the muscles, the senses, consciousness, or their combination. A seizure can be "focal" (confined to a specific part of the brain) or "generalized" (spread widely throughout the brain and leading to a loss of consciousness). Epilepsy can occur for a variety of reasons; some forms have been classified into epileptic syndromes, most of which begin in childhood. Even though epilepsy can start at any age, in children, it is the result of the child's brain having been injured in some way (a severe head injury, difficulties at birth, an infection which affects the brain such as meningitis, etc.).

Epilepsy is considered refractory (not yielding to treatment) when two or three anticonvulsant drugs have failed to control it. About 60% of patients achieve control of their epilepsy with the first drug they use, whereas around 30% do not achieve control with drugs. When drugs fail, other options include neurosurgery, vagus nerve stimulation, gene therapy, immunotherapy, the ketogenic or other diets, and lifestyle changes. Treatments of particular interest here will be neurosurgery and neurostimulation.

According to the World Health Organization (WHO), around 50 million [65 million according to the Epilepsy Foundation (EF)] people worldwide have epilepsy, making it one of the most common neurological diseases globally after migraine and stroke. Between 2% to 3% of the world's population will be diagnosed with epilepsy at some time in their lives. In the developed world, the onset of new cases occurs most frequently in babies and the elderly and is more common in older children and young adults, due to differences in the frequency of the underlying causes. In the developing world, which accounts for 80% of all cases, between 4 and 10 out of 1,000 of them live with active seizures at any one time. In the U.S., 3.4 million people have epilepsy with 150,000 new cases occurring each year. Of these, the cause remains unknown for 6 out of 10 of them, and 1 in 26 will develop the condition at some point in their lifetime. Further, one-third of them live with uncontrollable seizures because existing medications do not work in their cases. Still further, epilepsy occurs more commonly in the elderly, affecting 1% of the population by age 20 and 3% of the population by age 75. Also, it is more common in males than females with a small overall difference. It is estimated that up to 70% of people living with epilepsy could live seizure- free if properly diagnosed and treated. However, since the very first anti-seizure drug was prescribed over 150 years ago, there have been few improvements in efficacy despite the development of several iterations and generations of such drugs. By contrast, in low-income countries, three quarters of people with epilepsy do not get the treatment they need.

For a variety of reasons, seizures occur as the result of excessive and abnormal nerve cell activity in the brain cortex when cortical neurons fire excessively, hyper-synchronously, or both, leading to temporary disruption

of normal brain function. This might affect, for example, the muscles, the senses, consciousness, or their combination. Some forms have been classified into epileptic syndromes, most of which beginning in childhood.

In this article, I will review the causes of epilepsy, how a diagnosis is arrived at, and the available treatment portfolio that includes pharmacotherapy, neurosurgery and neurostimulation, gene therapy and immunotherapy, complementary and alternative therapies, and other therapies.

Causes of Epilepsy

There is a basic understanding of the pathophysiology of epilepsy, especially of forms characterized by the onset of seizures from a specific area of the brain (so-called "partial-onset epilepsy"). Nonetheless, the causes of epilepsy can be complex and sometimes hard to identify, and we still do not fully understand the mechanisms by which the brain becomes epileptic.

Epileptic seizures have no immediate underlying cause, some occurring as the result of brain pathology (injury, stroke, tumors, infections), genetic mutations, or birth defects through a process known as "epileptogenesis" with a long term risk of recurrent seizures depending on the part of the brain affected and on the person's age. They result from excessive and abnormal nerve cell activity (excessive electrical discharge) in hyper-excitable neurons in the brain cortex. Many neurological insults (neuroinfection, neurotrauma, and stroke) are known to be associated with a high-risk of both blood-brain barrier (BBB) disruption and epilepsy.

Like for most diseases/disorders, there are three main categories of causes: genetics, environment, and lifestyle (acronym: GEL). A genetic tendency can either be inherited (it is passed down from one or both parents), not inherited (it consists of a new change in the person's genes), result from changes due to genetic conditions (such as, for example, tuberous sclerosis, neurofibromatosis), or else be due to an improperly developing or damaged brain. Alternatively, epilepsy can have both innate (genetic) and acquired (environmental and lifestyle lumped together) causes, with interaction of these factors in many cases.

Genetic causes are more common among younger people, including problems with the way the brain developed before birth. Serious brain trauma (stroke, tumors, infection) are more likely causes in older people. Other factors may be a brain injury or tumor, abnormal blood vessels in the brain, bleeding in the brain, meningitis, encephalitis, or any other type of infection that affects the brain. Notwithstanding these genetic causes, epilepsy is not contagious. It can run in families but that is not a necessary condition for it to develop in siblings or descendants. Other factors, known as "acute symptomatic seizures" may also occur as a consequence of other health problems (stroke, head injury, toxic ingestion or metabolic problems). These are included in the broader classification of "seizure-related disorders" rather than epileptic seizures. Epilepsy that occurs as a result of other issues may be preventable.

Environmental factors consist of triggers or stimuli, including flashing or bright lights, a lack of sleep, stress, overstimulation (like staring at a computer screen or playing video games for too long), fever, some medicines, and hyperventilation (breathing too fast or too deeply).

Beyond genetic susceptibility, I posited elsewhere that the root cause of neurodegenerative diseases, including epilepsy, is an autoimmune disease that had run amok, damaging the brain normal functions. Under this theory, the seizures are but the manifestation of this process, the symptoms of that disease, not its cause. The recent suggestion that the immune system, and how it responds to injury, may play an important role in triggering epilepsy conforms with my autoimmune theory. Under this interpretation, if it is assumed that the brain's response is 'linear', the treatment would (naively) consist of either preventing the said massive insults from occurring or/and appropriately modulating the immune system - pointing to the strong need for the development of such innovative methods for treating epilepsy.

Drugs developed so far attempt to regulate the excitation/inhibition imbalance, not what provoked that imbalance. To this day, the rationale is to use anti-seizure medications/drugs (ASM/Ds) that either increase inhibitory activity (so-called GABA enhancers) or decrease excitatory activity (glutamate blockers) in the brain. They further (naively) assume that brain function is 'linear' so that remedying this imbalance will stop the seizures. However, the situation is considerably more complex as the brain's response is highly

'nonlinear', and there is evidence to that. It is not, therefore, too surprising that the above pharmaceutical approach has largely been palliative only.

Diagnosis of Epilepsy

A diagnosis of epilepsy is aided (but not necessarily ruled out) by brain imaging and confirmed by an electroencephalogram (EEG). Although a substantial fraction of seizures are controllable with medication, approximately 20%–30% of patients do not improve with, or fail to tolerate, antiepileptic drugs. For such patients, neurostimulation, neurosurgery, or lifestyle and dietary changes may be considered. While surgery to remove the epileptogenic zone can be offered, it is not feasible if the seizures arise from brain areas that are essential for language, vision, movement or other important functions. As a result, many people with epilepsy are left without any treatment options to consider. Fortunately, not all cases of epilepsy are lifelong, and many people do improve to the point that treatment is no longer needed.

If medication does not stop all seizures, or only stops some of them, other types of treatment might be considered instead of, or alongside ASM/Ds. The diagnosis may also be reviewed for correctness to confirm the type of epilepsy or seizures as well as the treatment followed so far. Referral to a tertiary service (hospital or unit that focuses on specific care for different conditions) or a more specialized treatment may be considered.

Pharmacotherapy

Treatment usually proceeds along four threads: Pharmacology; neurosurgery and neurostimulation; gene therapy and immunotherapy; and other therapies. While interest here is principally on neurosurgery and neurostimulation, it will be helpful to also briefly address the other therapies.

Epilepsy is a long-term or even a lifetime condition that cannot generally be 'cured'. Medications are the initial treatment choice for almost all patients with multiple seizures. Some patients who only have a single seizure and whose tests do not indicate a high likelihood of seizure recurrence may not need medications. The medications treat the symptoms of epilepsy (the seizures), rather than the cause and do not cure the underlying condition. They are highly effective and completely control seizures in the majority (approximately 70%) of patients. The drugs prevent seizures from starting by reducing the tendency of brain cells to send excessive and confused electrical signals.

For most people, seizures can be 'controlled' (stopped) and treatment is often about managing seizures in the long-term. Treatment is usually considered only after repeated seizures and a diagnosis of epilepsy. In those cases where there is suspicion of a likelihood of repeated seizures, treatment may at times be started after a single seizure. The aim is to arrest all seizures with the lowest doses of the lowest number of ASM/Ds starting with the lowest dose and increasing it progressively (s0-called "titration") until seizures are controlled. If seizures are not controlled, a different ASM/D is usually tried (by adding in the new drug while slowly withdrawing the first one). Epilepsy is considered refractory (not yielding to treatment) when two or three anticonvulsant drugs have failed to control it. About 60% of patients achieve control of their epilepsy with the first drug they use, whereas around 30% do not achieve control with drugs. When drugs fail, other options include neurosurgery and neurostimulation, gene therapy and immunotherapy, complementary and alternative therapies (including the ketogenic diet and its variants), and lifestyle modifications.

Numerous ASM/Ds have been introduced over the past decades. They are usually the first-line treatment for epilepsy and are selected based on the type of seizure one has as well as the patient's other pertinent medical history. With many different ASM/Ds currently available, choosing the right medication for an individual patient has become complicated. Choice of medication depends on a variety of factors, some of which include the type of seizure and type of epilepsy, the likely side effects of the medication, other medical conditions the patient may have, potential interactions with the patient's other medications, age, gender, and cost of the medication. There are dozens of medications available, ranging all the way from *Lyrica* to *Valium*. For severe cases, the FDA has also recently approved *Epidiolex*, a non-psychoactive medication made from *Cannabidiol* (CBD) oil. Each ASM/D has its own profile with

specific pros and cons. These prescriptions work by targeting the excessive electrical activity in the brain that causes seizures. Basic side effects such as drowsiness, headaches, and nausea are common.

During the 1920s and 1930s, when the only anticonvulsant drugs were the sedatives *Bromides* (discovered in 1857) and *Phenobarbitol* (discovered in 1912), the ketogenic diet was widely used and studied. This changed in 1938 when H. Houston Merritt, Jr. and Tracy Putnam discovered Phenytoin (*Dilantin*), and the focus of research shifted to discovering new drugs. A few anticonvulsants (*Benzodiazepines, Levetiracetam* and *Valproate*) have shown antiepileptogenic properties in animal models of epileptogenesis. With the introduction of *Sodium Valproate* in the 1970s, effective drugs across a broad range of epileptic syndromes and seizure types were available. However, while they suppress epileptic seizures, anticonvulsants neither cure nor prevent the development of seizure susceptibility.

How is the Course of Treatment Determined?

Initial treatment is usually a 'monotherapy', that is the treatment is started with a first-line ASM/D that is tried first and taken on its own. Once the most appropriate ASM/D has been identified, it will usually be prescribed on a very low dose. This helps the body get used to the medication and makes side effects less likely. The dose is then increased slowly over a number of weeks until the seizures are stopped. The right dose may be different for different individuals (this is referred to as the 'individual therapeutic concentration').

How the body absorbs, uses, and removes medication changes with age. For children, ASM/D doses are based on their body weight and so the dose increases as they get older (up to around 12 years of age). For adults, doses are not based on body weight.

For most people, once the right ASM/D for them is found, it will stop their seizures. Although it can take time for some, the aim is always to stop the seizures by just taking one ASM/D. However, if the seizures do not stop when the dose is increased, or there are side effects, the ASM/D will be changed. Because different ASM/Ds work in different ways, if one does not control the seizures, it does not mean that other ASM/Ds will not work. If the seizures are not controlled with a single ASM/D, a combination of ASM/Ds may be taken (this is called 'polytherapy'). Some ASM/Ds added to a first-line ASM/D are called second-line ASM/Ds. This is slightly different for children because ASM/Ds are not split into first- and second-line for treating children age 12 and under.

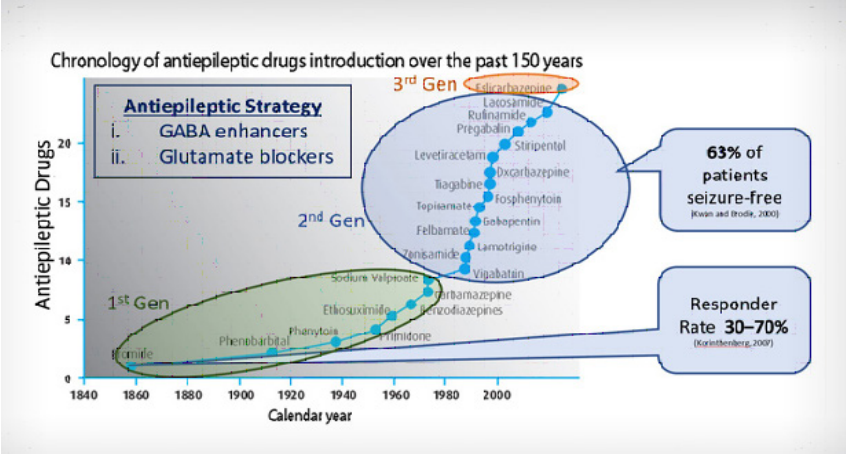
Some people continue to have seizures despite taking ASM/Ds. In this case, they may continue to take ASM/Ds to reduce their seizures as much as possible and consider trying other types of treatment.

Rationale for the Use of Anti-Seizure Medications

To this day, the rationale is using ASM/Ds that either increase inhibitory activity (GABA enhancers) or decrease excitatory activity (glutamate blockers) in the brain. These pharmaceutical strategies have been successful in treating two-thirds of epilepsy patients (Kwan and Brodie, 2000). However, since the very first anti-seizure drug was prescribed over 150 years ago, there have been few improvements in efficacy despite the development of several iterations and generations of ASM/Ds (see Figure 1).

Paradoxical new findings demonstrate that brief inhibitory activity can trigger electrographic seizure activity in the brain under certain conditions (Magloire, Mercier, Kullmann, and Pavlov, 2018). Although counterintuitive, these findings are expected when considering that brain function and response is non-linear (Breakspear, 2017), being composed of nearly 100 billion cells connected in 100 trillion ways.

The first generation of such medicines was introduced from 1810 to 1980, totaling 14 drugs. The second generation introduced from approximately 1980 to 2020 included 19 other drugs. The third and current generation beyond 2020 includes only 1 additional drug.



Source: M. Chang, Times Science (2021)

Figure 1: *Chronology of anti-seizure medications introduction (1850-2010)*

Available anti-seizure medications/drugs (ASM/D)

Available ASM/Ds, their particulars, effectiveness, and recommendations for their use are summarized in Table 1:

Anti-Seizure Medications	Particulars	Recommendations
1. Anticonvulsants: - Single agent initially - Second agent helps in ~ 13% of cases - Third agent or two agents combined helps an additional 4% of cases	Mainstay treatment (possibly for entire life). Choice based on: - Seizure type - Epilepsy syndrome - Other medications - Other health problems - Person's age - Person's lifestyle	~ 30% of people continue to have seizures despite treatment
2. Carbamazepine	• Cause increased risk of birth defects • May induce opercular *status epilepticus*, usally in children with atypical evolution	- Recommended first treatment line of focal seizures - Also for treatment for benign Rolandic epilepsy in children
3. Clobazam	Prevention and control of seizures	No benefits over other ASMs
4. Ethosuximide	Prevention and control of absence or petit mal seizures	Controls the abnormal electrical activity in the brain
5. Gabapentin	Causes increased risk of birth defects	For treatment of benign Rolandic epilepsy in children
6. Lamotrigine	• Lowest risk of causing birth defects • May induce opercular *status epilepticus*, usally in children with atypical evolution	Recommended second treatment line of both focal and generalized seizures
7. Levetiracetam	Lowest risk of causing birth defects	- Recommended first treatment line for generalized seizures - Also for treatment for benign Rolandic epilepsy in children
8. Phenobarbitol	Causes increased risk of birth defects	Least expensive ($5/year). WHO-recommended first treatment line in the developing world
9. Phenytoin	Equally effective in both focal and generalized seizures	- Controlled release may have fewer side effects - Also for treatment for benign Rolandic epilepsy in children

10. Sodium valproate	Causes increased risk of birth defects (physical disabilities, developmental issues)	- Also first treatment line for generalized seizures - Effective in myoclonic and tonic or atonic seizures - Also for treatment for benign Rolandic epilepsy in children
11. Sultiame (Riker 594; Ospolot)	A carbonic anhydrase inhibitor used to treat benign Rolandic epilepsy in children	For treatment for benign Rolandic epilepsy in children

Source: A. L. Fymat (2022)

Table 1: *Anti-seizure medications – particulars and recommendations*

Adverse effects from medications

Adverse effects from medications include essentially:

- Dose-related: mild (mood changes, sleepiness, unsteadiness in gait).
- Not dose related: rashes, liver toxicity, suppression of the bone marrow.

They are reported in 10%-90% of people and cause ~ 25% of people to stop treatment.

The most common adverse reactions in pediatric and adult patients (≥4% and ≥2% greater than placebo) are: dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. However, safety and efficacy in patients <4 years of age have not been established. Other effects include: Suicidal behavior and ideation; serious dermatologic reactions; multi-organ hypersensitivity; anaphylaxis and angioedema. hyponatremia; neurological adverse reactions; hepatic effects; abnormal thyroid function; and hematologic adverse reactions. Rare cases of pancytopenia, agranulocytosis, and leukopenia have been reported.

Four of the available ASMs (*Carbamazepine, Gabapentin, Phenobarbitol*, and *Valporate*) cause an increased risk of birth defect while two others (*Lamotrigine* and *Levetiracetam*) have the lowest such risk.

Most pregnant women with epilepsy will have a normal pregnancy and labor and over a 90% chance of having a healthy baby. However, they have a slightly higher chance of having a baby with a birth defect due to genetic conditions, injury during seizures, and use of ASM/Ds.

Neurosurgery & Neurostimulation

Approximately 70% of epileptic patients have well-controlled seizures with medications. The remaining 30% are considered medically-resistant and, for them, surgery provides the best chance of complete control of their seizures. However, not all patients with refractory epilepsy are suitable candidates for surgery. Two main qualifying conditions are: (1) having partial, rather than generalized epilepsy (i.e. their epilepsy arises from a single part of the brain, rather than from both sides or from all over the brain); and (2) the epileptic region should be in a part of the brain that, if removed, is unlikely to result in major neurological complications. Whether or not patients are likely to benefit from surgery is then determined by detailed testing (pre-surgical evaluation).

The two-phase (non-invasive and invasive) pre-surgical evaluation and the several neurosurgical and neurostimulation procedures will now be discussed, Of the surgeries to be presented, surgical resection offers the best chance of rendering a patient seizure-free. However, the benefits of surgery should always be weighed carefully against its potential risks.

Pre-Surgical Non-Invasive Evaluation – Phase I

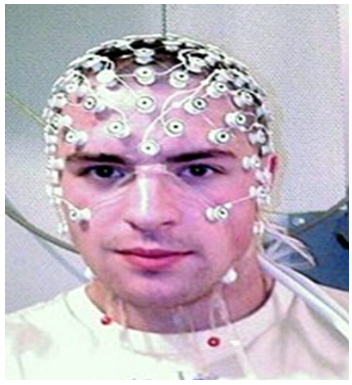
Pre-surgical evaluation consists of a one- or two-phase process to determine if surgery is the best option and can provide good seizure control with minimal risk. Phase I involves all non-invasive (non-surgical) tests whereas Phase II involves (surgical) invasive tests that are used in selecting patients.

Phase I evaluation is designed to find the area of the brain that is likely to be generating the seizures (the focus), to determine if that area can be safely removed, and to predict what kind of outcome might be expected with regard to seizure reduction or seizure freedom.

There are generally six tests involved in Phase I, but not every patient requires every test available in this evaluation. For the selection of the necessary and appropriate tests, adult and pediatric epilepsy patients are evaluated by epileptologists who prescribe such tests on an individualized basis. The tests provide separate independent information that can be correlated in order to zero-in on the location of origin of the seizures. These tests comprise:

Inpatient Video-EEG Monitoring

This is the recording of seizures with simultaneous video and EEG. The aim is to identify the likely location in the brain where seizures originate. It is the most important pre-surgical test and is generally conducted in an inpatient setting in an Adult and Pediatric Epilepsy Monitoring Unit (EMU). It is performed with electrodes attached to the scalp (noninvasive monitoring) as in Figure 2.



Reference: Thuglass at Wikipedia

Figure 2: *The electroencephalogram recording setup*

All the data are interpreted by a trained epileptologist who analyzes in detail the symptoms from the beginning and during seizures, the location of EEG changes during seizures (ictal EEG onset), and the abnormalities noted in between seizures (interictal) to evidence the likely location where seizures originate within the brain.

Magnetic Resonance Imaging (MRI)

The aim is to detect abnormalities in the brain that could be the cause of the epilepsy (lesional epilepsy) or may be normal (non-lesional epilepsy). With more powerful MRI machines and use of special protocols and software, subtle brain abnormalities are increasingly being identified.

Positron Emission Tomography (PET)

The aim is to localize brain regions with decreased brain function, which is indicative of the location of the seizures. PET scans record the metabolic activity of the brain to determine if it is functioning normally. In patients with epilepsy, decreased brain function is seen in the region where seizures originate when the patient is not actually having a seizure. On the other hand, if the patient has a seizure during the test, increased brain function is seen. PET scan may show abnormalities even if the brain MRI is normal. PET scans are usually done in the outpatient setting.

Single-Photon Emission Computed Tomography (SPECT)

The aim is to identify brain regions with increased blood flow, which is indicative of the location of seizures. When a person has a seizure, an increased amount of blood flows to the brain region where the seizure begins. SPECT scans performed during seizures can

identify the brain region where blood flow increases and, thus, indicate where they begun. They are performed when the patient is admitted to the hospital for video-EEG monitoring.

Neuropsychological Evaluation and Functional MRI (fMRI)

The aim of this combination test is to predict cognitive deficits after surgery. Neuropsychological evaluation and fMRI are used to assess cognitive functions, especially language and memory function prior to surgery to determine which side of the brain is dominant for language and if there is decreased memory function in the epileptic region. This allows prediction of cognitive deficits after surgery. fMRI measures blood flow changes in areas of the brain during the performance of specific cognitive tasks.

Intracarotid Amobarbital/Methohexital (Wada test)

The aim is to predict language and memory function post-surgery. Performed in selected cases, the test involves the injection of a medication such as *Sodium Amobarbital* or *Methohexital* into one carotid artery at a time. The medication causes temporary (1-5 minutes) paralysis of one-half of the brain allowing independent testing of language and memory function in the other half. This test is also used to predict post-operative deficits in language and memory function.

If all tests performed point to the same region of the brain as being the origin of epileptic seizures, the patient is likely to be a good surgical candidate.

Based on the results of the Phase I evaluation, patients may be deemed good or poor surgical candidates. In some cases, despite all prior tests, the seizure focus may not be defined well enough for surgical treatment so that more testing would be needed (called Phase II evaluation).

Presurgical Invasive Evaluation - Phase II

Phase II evaluation involves video-EEG monitoring with electrodes that are placed inside the skull (invasive monitoring). As there is more risk from invasive monitoring, the decision about the necessity for a Phase II evaluation is usually made by the epilepsy team as a whole and discussed in detail with the patient.

There are six surgical implantation options, each involving the implantation of electrodes either on the surface of the brain, or within the brain. The benefit of these electrodes is that they are closer to the area producing the seizures than those placed simply on the scalp. After surgical placement of electrodes, the patients are transferred to the EMU where epileptologists perform video- EEG monitoring in a similar fashion to the phase I monitoring.

The electrode types and implantation arrays differ and may include:

Subdural Electrodes

A subdural electrode grid is a thin sheet of material with multiple small (couple millimeters in size) recording electrodes implanted within it. The electrodes are placed directly on the surface of the brain. They have the advantage of recording the EEG without the interference of skin, fat tissue, muscle, and bone that may limit scalp EEG. Shapes and sizes of these sheets are chosen to best conform to the surface of the brain and the area of interest.

Depth Electrodes

These are small wires surrounded by electrodes, which are implanted within the brain itself through small skin pokes. The electrodes are able to record brain activity along the entire length of the implanted wire. They have the advantage of recording activity from structures deeper in the brain.

Electrodes Combination

In a number of instances, it may be beneficial to implant a combination of subdural and depth electrodes.

Stereoelectroencephalography (SEEG)

Increasingly common, invasive monitoring may be done using SEEG. Here, multiple depth electrodes are implanted in a specific pattern individualized to the patient. The three-dimensional space which is covered by the depth electrodes is designed to encompass the seizure focus.

Functional Mapping

This is usually performed in patients with implanted subdural electrodes while they are in the EMU. After a sufficient number of seizures are recorded, brief electrical stimulation is provided through each electrode separately to determine the normal function of the part of the brain underneath that electrode. It is a painless procedure. The purpose is to map out critically important areas of the brain such as those necessary for motor, sensory, and language functions, and to determine if there is any overlap with the seizure-generating regions. This allows tailoring of surgical resections to minimize the risk of major neurological deficits after surgery.

Neurosurgical Procedures

Brain surgery (or neurosurgery) requires certain criteria to be met and tests to be done to assess suitability. It involves resection, disconnection, stereotactic radiosurgery, or implantation of neuromodulation devices. Within these categories, there are multiple options depending on the clinical scenario.

Surgical Resection

Surgical resection (the removal of abnormal tissue) for epilepsy may fall into the following broad categories:

The Montreal Procedure: In this procedure, after administration of a local anesthetic, the surgeon removes part of the skull to expose the brain tissue and, by the use of probes, the conscious patient describes to the surgeon his/her feelings so that the surgeon can identify the exact location of seizure activity. The surgeon then proceeds to the removal of brain tissue in this location reducing the side effects of surgery.

Lesionectomy: A lesion is a generic term for brain abnormalities that show up on imaging. Some types of lesions — such as cavernous malformations (blood vessel abnormalities) and tumors — are prone to cause seizures. When the pre-operative testing indicates that these lesions are the cause of the epilepsy, they can be removed surgically.

Lobectomy: Each hemisphere, or half of the brain, is divided into four main lobes — 'frontal', 'temporal', 'parietal', and 'occipital'. Seizures may arise within any of these lobes. A lobectomy is an operation to remove a lobe of the brain. Removal of one of the temporal lobes — called a 'temporal lobectomy' — is the most common type of epilepsy surgery performed. Other types of lobectomies may rely on more specialized testing and surgery to prove a lack of vital function (such as speech, memory, vision, motor function).

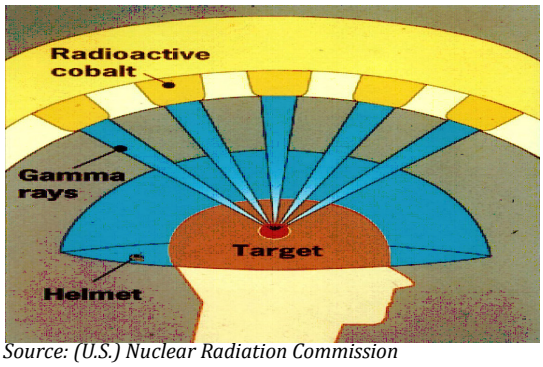
Multilobar Resection: A multilobar resection involves the removal of parts or all of two or more lobes of the brain. It is reserved for more widespread abnormalities causing seizures, providing that no vital functions are in those regions.

Hemispherectomy: The brain is divided into a left and a right hemisphere. In rare instances, children may have severe, uncontrollable, and devastating seizures that can be associated with weakness on one side of the body. This may occur with a large amount of damage or injury to one of the hemispheres. The removal or disconnection of a hemisphere, a hemispherectomy, may be curative. There are many subtypes of this surgery, the two main divisions being anatomic and functional hemispherectomy:

- **Anatomic:** It involves removing the entire half of the brain that is injured and is generating the debilitating seizures. This includes the four lobes of the hemisphere — frontal, temporal, parietal and occipital.
- **Functional:** It involves separating the abnormal hemisphere from the normal one by disconnecting fibers that communicate between the two. Often, some portions of the abnormal brain are surgically removed in order to perform this disconnection. This is, very often, surgically curative.

Surgical Disconnections

These surgeries involve cutting and dividing fiber bundles that connect portions of the brain. The rationale is to separate the area of the brain generating the seizures from the normal brain (Figures 3 and 4).



Source: (U.S.) Nuclear Radiation Commission

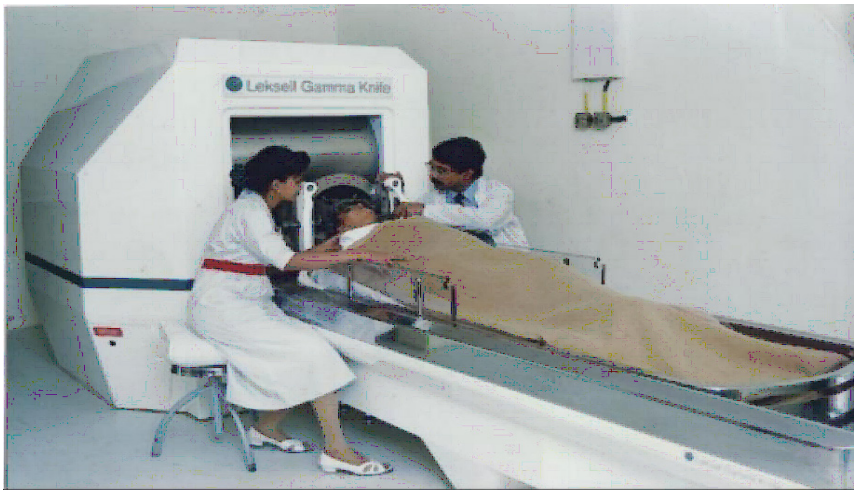
http://www.nrc.gov/images/reading-rm/photo-gallery/20071114-040.jpg

Figure 3: *Graphic of the Leskell gamma knife*

They include:

• **Corpus Callosotomy:** The corpus callosum is one of the main fiber bundles that connect the two hemispheres. It's cutting-off in whole or in part is a palliative procedure against debilitating generalized seizures or falling-type seizures that start on one side of the brain and quickly spread to the other.

• **Multiple Subpial Transections (MST):** This procedure may be performed when the seizures are deemed to be arising from an area of the brain that cannot be safely removed. A small wire is placed into the brain to perform transections at multiple points in a given region so as to arrest seizures by disconnecting the cross-communication of neurons.



Source: Wikipedia - Dr. B. K. Misra performing Stereotactic Gamma Knife Radiosurgery

Figure 4: *A doctor performing gamma knife radiosurgery*

Stereotactic Radiosurgery (SRS)

Radiosurgery is the destruction of precisely selected areas of tissue using ionizing radiation rather than excision with a blade. It was originally defined by the Swedish neurosurgeon Lars Leksell as "*a single high dose fraction of radiation, stereotactically directed to an intracranial region of interest*" (Figure 3). It is performed by a multidisciplinary team of neurosurgeons, radiation oncologists, and

medical physicists who operate and maintain highly sophisticated, highly precise, and complex instruments, including the Gamma Knife unit (commercialized under the brand name Cyberknife). (Figure 4). Significant clinical judgment must be used with this technique. In SRS, a focused beam of radiation is delivered to a specific target area. One of the most common forms, 'gamma knife radiosurgery' (GKRS) uses gamma-rays to target the area to be treated.

In epilepsy, SRS is generally reserved for small, deep-seated lesions that are visible on MR imaging. The highly precise irradiation of targets within the brain is planned using information from medical images that are obtained via CT and MRI. Issues of importance are the indications for treatment, the total radiation dose delivered, the fractionation schedule, and the conformity of the treatment plan.

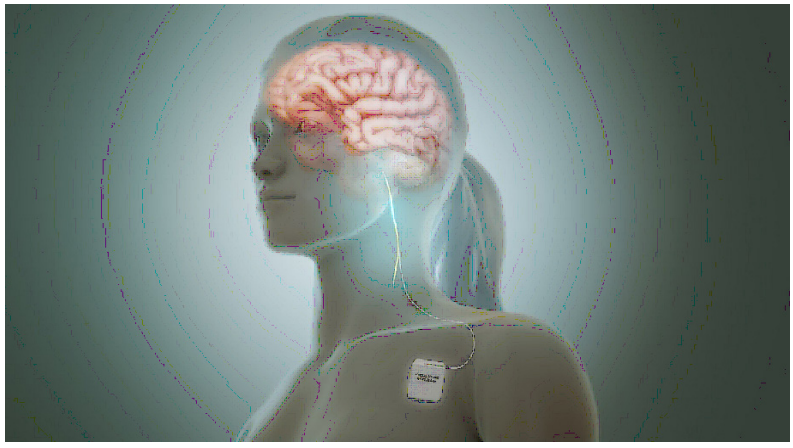
The device aims gamma radiation through a target point in the patient's brain. The patient wears a specialized helmet that is surgically fixed to the skull, so that the brain remains stationary at the target point of the gamma rays. GKRS is able to accurately focus many beams of gamma radiation on one or more areas that cause epileptic seizures. Unfortunately, the outcome may not be evident until months after the treatment.

Neurostimulation Procedures

There are currently two FDA-approved devices that modulate the nervous system for the treatment of epilepsy that is not controlled with antiepileptic medications: vagus nerve stimulation (VNS) and responsive neurostimulation (RNS). The goal is to improve seizure control. Both devices are considered palliative in that the goal is improved seizure control, and rarely do patients become seizure free. [For a comprehensive treatment of peripheral and deep brain stimulation, refer to Fymat' (2019, 2020).

Vagus Nerve Stimulation (VNS)

An important advance in epilepsy treatment was the development of the VNS technique, especially for patients experiencing serious adverse effects of antiepileptic drugs. The vagus is the tenth cranial nerve, arising from the medulla and carrying both afferent and efferent fibers. The afferent vagal fibers connect to the nucleus of the solitary tract, which in turn projects connections to other locations in the central nervous system (Figure 4).



Reference: Manu5 - http://www.scientificanimations.com/wiki-images/

Figure 4: *Vagus nerve stimulation*

VNS is an option for those who are not candidates for other types of surgery. It is an outpatient procedure that requires two separate incisions. It involves the surgical implantation of a stimulator – a programmable 'pulse generator' (called neurocybernetic prosthesis NCP) in the chest cavity. Generally, the left vagus nerve is stimulated at the mid-cervical region rather than the right because the right plays a role in cardiac function such that stimulating it could have negative cardiac effects. The electrodes positioned around the left vagus nerve and a generator placed below the collar bone in the upper chest region. The stimulating electrodes carry the electrical

signals from the generator, sending regular, mild electrical stimulations through this nerve to help calm down the irregular electrical brain activity that leads to seizures. Subsequently, a programmer (from outside the skin) can be used by the epileptologist to change the intensity, duration, and frequency of stimulation to optimize seizure control. VNS decreases seizure frequency by at least half in 40%-50% of patients, but rarely eliminates all seizures.

"Wearable" devices are being tested and developed that involve transcutaneous stimulation and do not require surgery.

Frequent side effects of this stimulation include coughing and shortness of breath. Other adverse effects include cardiac arrest, bradycardia, voice alteration and hoarseness, cough, shortness of breath, pain, a tingling sensation, nausea, and headache. Difficulty swallowing has also been reported as common as well as sleepiness. As of 1997, in randomized controlled trials for epilepsy conducted in the U.S., one-third of the subjects had an increase in seizures, with 17% having greater than a 25% increase and some having 100% increase or greater.

Responsive Neurostimulation (RNS)

RNS is a treatment for adults with partial-onset seizures having one or two seizure onset-zones, whose seizures have not been controlled with two or more ASM/Ds. The associated device is designed to prevent epileptic seizures. The surgery is generally reserved for patients who are not candidates for surgical resection, since the RNS improves seizure control but rarely stops seizures from occurring. It involves placing a neurostimulator in the skull and connecting it to two electrodes placed either on the surface or into the brain, in or around the area deemed to be the likely onset region for the seizure. The device monitors brain activity in order to detect abnormal patterns, and in response delivers electrical pulses in an attempt to prevent seizures. It is trained by the epileptologist to detect the electrical signature of the seizure onset and to then deliver an impulse which can stop the seizure. Data collected by the neurostimulator can by uploaded by the patient with the use of a hand-held wand to a secure web-based application, which can be accessed by the epileptologist (Figure 5).

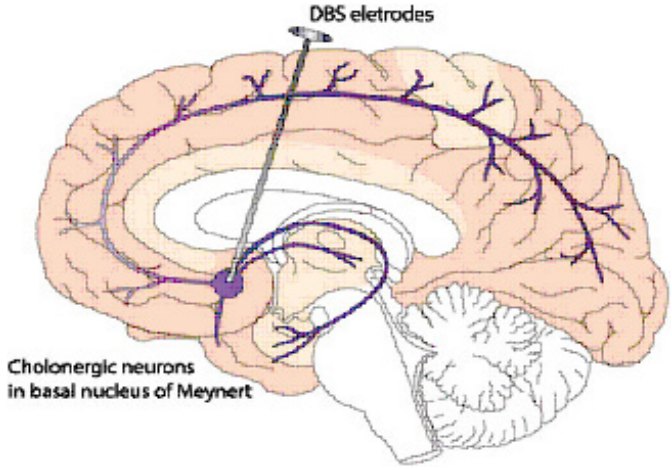


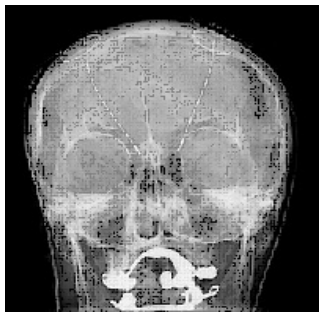
Figure 5: *Pictorial showing an inserted deep brain stimulation electrode*

The RNS System was approved by the (U.S.) FDA in 2013. One such device, the NeuroPace RNS, was approved in 2014. As of March 2017, over 1,000 patients have been implanted with it. Improved technology and testing have now made it possible to identify more accurately the epileptogenic regions (i.e., where seizures originate in the brain). Further, advances in surgery have made operative management safer for all forms of surgery for epilepsy.

Deep Brain Stimulation (DBS)

DBS therapy is a surgical treatment which aims to reduce seizures not controlled with medication, and where surgery to treat the cause of seizures is not possible. With growing evidence for its safety and results suggesting earlier intervention may be beneficial,

researchers further examined its use for targeting other brain areas pertaining to epilepsy. Further innovations are emerging with advances in neuroscience and technology. For example, while traditional DBS delivers constant stimulation, newer adaptive devices can self-tune stimulation in response to certain features of a person's brain activity or behavior. For example, one such closed-loop device is approved for the treatment of medically-refractory epilepsy. Nonetheless, questions remain about exactly how DBS works, and new directions are likely to emerge through research on the mechanisms that underlie its benefits (Figure 6).



(Bright white areas around the maxilla and the mandibles represent metal dentures that are unrelated to the DBS device)

Figure 6: *DBS-probes are shown in an X-ray of the skull*

Benefits and Risks of DBS

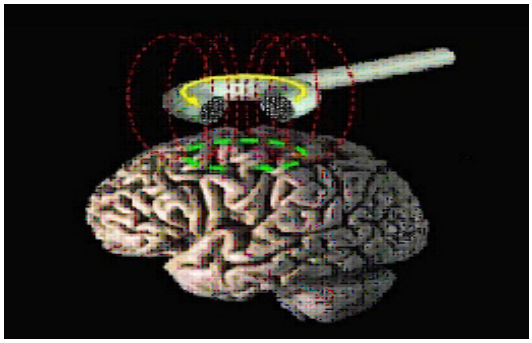
DBS is a minimally-invasive surgical procedure that involves minimal permanent surgical changes to the brain. There is a low chance the placement of the stimulator may cause bleeding or infection in the brain. Nonetheless, it carries some associated risk. Complications may include bleeding and swelling of brain tissue, headaches, seizures, and temporary pain following the surgery. Such complications may result from mechanical stress from the device but are generally reversible. Also, the hardware may erode or break down with use, requiring surgery to replace parts of the device.

Prognosis Following the Procedure

DBS for epilepsy may reduce the number of seizures over time. However, it changes the brain firing pattern and does not slow the progression of the neurodegeneration.

Repetitive Transcranial Magnetic Stimulation (rTMS)

Approximately one-third of patients with epilepsy remain with pharmacologically intractable seizures. rTMS is an emerging therapeutic modality for seizure suppression. Despite being considered a safe technique, it carries the risk of inducing seizures, among other milder adverse events, and thus, its safety in the population with epilepsy should be continuously assessed. The similarity between the safety profiles of rTMS applied to the population with epilepsy and to individuals without epilepsy supports further investigation of rTMS as a therapy for seizure suppression (Figure 7).



Source: Eric Wassermann

Figure 7: *Illustrating transcranial magnetic stimulation*

Table 2 provides a comparison of transcranial magnetic stimulation techniques.

Modality	Types	Effects	Indications	Contra-indications	Adverse effects	Benefits
TMS/ rTMS Single-pulse / repetitive Transcranial Magnetic Stimulation	o Single-pulse. o Multiple pulses. o Reaches shallow depths (<6 cm). o Modified coils reach deeper.	Increase/ decrease of neuronal activity depending on higher/lower frequency.	Diagnostic neurology. Progressive neurologic insult. Psychiatry. Connections of cerebellum to other brain areas. NEUROLOGY: Activity/function of specific brain circuits. Connection CNS primary cortex and PNS. AD. ALS. Epilepsy. MS. PD. Persistent vegetative state, Schizophrenia. Speech-related dis-ability. Traumatic brain injury. Tinnitus. PSYCHIATRY: Addiction. Anxiety panic. Autism. PTSD. Substance abuse. OCD. Resistant major de-pressive disorder.		SHORT-TERM: Current induction in implanted devices (pacemakers) or defibrillators. Cognitive changes. Discomfort. Fainting (uncommon). Hearing loss. Hypomania. Seizures (extremely rare). Working memory (impaired).	Diagnostic & therapeutic potential in Neurology and Psychiatry.
MST Magnetic Sei-zure Therapy	Induces seizures		Treatment-resistant depression. OCD. Schizophrenia.			
PEMFT/ lfMS/ TTF Pulsed E M - F i e l d Therapy/ Low-Field Magnetic Stimulation/ Tumor Treating Fields	Electromagnetic & low-fields		Delayed & non-union fractures. Depression. Glioblastomas. Knee osteoarthritis. Pain (post-operative).			

Source: A.L. Fymat (2019)

Table 2: *Comparison of transcranial magnetic stimulation techniques*

Laser Interstitial Thermal Therapy (LITT)

This new technique involving LITT technology was developed in Israel in or about 2018 by Dr. Daniel Hyatt, Dr. Orna Eisenstein, and Prof. Dafna Ben-Shabat. Using a device called Visualase, the technique allows for real-time monitoring of the brain-ablated area. The procedure is performed in two stages. In the first stage of the operating room, a small optic fiber is inserted carefully using a stereotactic navigation system through a small hole in the skull about 4 mm. in diameter. Then, the optical fiber is connected to the Visualase system, while an MRI scanner monitors real-time brain temperature maps and closely monitors the size of the ablated tissue. This preserves adjacent brain regions that can be responsible for critical functions.

Gene Therapy and Immunotherapy

Although most patients respond to medication, approximately 20%–30% do not improve with or fail to tolerate anti-seizure medications. Surgery to remove the epileptogenic zone can be offered only in a small minority of them, but is not feasible if the seizures arise from brain areas that are essential for language, vision, movement or other functions. As a result, many people with epilepsy are left without any treatment options to consider. There is, thus, a strong need for the development of innovative methods for treating epilepsy such as gene therapy and immunotherapy.

Gene Therapy (GT)

In recent years, GT in human disease has expanded rapidly with the development of safer and more effective viral vectors. It presents a novel approach to the treatment of epilepsy. Studies in animal models have demonstrated that over-expression of inhibitory peptides can modify seizure threshold, prevent the development of epilepsy, and modify established epilepsy. More recently, there has been a flurry of studies using "optogenetics" in which light-activated channels expressed in neurons can transiently change neuronal excitability on exposure to light, thereby enabling the development of closed loop systems to detect and stop seizure activity. Likewise and alternatively, "chemogenetics" does not require light delivery to the brain but relies on expressing a mutated receptor in the seizure focus that can be activated by an exogenous drug.

Principle and Methods

GT relies on viral or non-viral vectors to deliver DNA or RNA to target brain areas where seizures arise in order to prevent the development of epilepsy or to reduce the frequency and/or severity of seizures. It can be accomplished by several methods that are being studied for some forms of epilepsy, having delivered promising results in early stage clinical trials for other neurological disorders such as Parkinson's disease (PD), GT has raised the hope that it may become a treatment for intractable epilepsy.

Through the use of viral vector gene transfer with the purpose of delivering DNA or RNA to the epileptogenic zone, several neuropeptides, ion channels, and neurotransmitter receptors have shown potential as transgenes for epilepsy treatment. Among such vectors are retroviruses, adenoviruses, and adeno-associated virus vectors (AAVV), which have the following important properties: High and efficient transduction, ease of production in high volumes; wide range of hosts; and extended gene expression. Lentiviral vectors have also shown promise.

The two major classes of methods are: Viral methods, which use recombinant viruses (sometimes called biological nanoparticles or viral vectors); and non-viral methods, which use naked DNA or DNA-complexes.

Viral Approaches in Preclinical Development

Seizures that characterize epilepsy typically result from the excessive and synchronous discharges of excitatory neurons. The logical (and perhaps naive) goal for GT treatment would therefore be to *reduce excitation* or *enhance inhibition*. This excitation/inhibition rebalancing assumes that it is a linear process, which, in actuality, is not. The neuropeptide transgenes being researched are:

- **Adenosine**: An inhibitory nucleoside that doubles up as a neuromodulator, it aids in the modulation of brain function. Further, it has anti-inflammatory properties, in addition to neuroprotective and anti-epileptic properties. The most prevalent theory is

that, upon brain injury, there is an increased expression of the adenosine kinase (ADK), which increases the metabolic rate for adenosine nucleosides. Seizures are triggered due to the decrease in these nucleosides that possess anti-epileptic properties and ADK over-expression, potentially resulting in the development of epileptogenesis. While ADK over-expression leads to increased susceptibility to seizures, Adenosine can counteract and moderate this effect, thereby preventing seizures. Adenosine is an ideal target for the development of anti-epileptic gene therapies.

- **Gamma Aminobutyric Acid (GABA).**
- **Galanin:** Found primarily within the central nervous system (CNS), Galanin has neuroprotective and inhibitory properties, and decreases the number and duration of induced seizures. It increases the stimulation threshold required to induce seizures, and suppresses the release of glutamate that would increase susceptibility to seizure activity. Galanin can be utilized to significantly moderate and reduce seizure activity and limit seizure cell death.
- **Neuropeptide-Y:** Found in the autonomous nervous system (ANS), It increases the seizure threshold, arrests disease progression, and reduces seizure duration. After examining its effects on behavioral and physiological responses, it was discovered that it had no effect on learning or memory.
- **Potassium channels:** Kv1.1, a voltage-gated potassium channel, is widely expressed in the brain and peripheral nerves. It thus plays a role in controlling the excitability of neurons and the amount of neurotransmitters released from axon terminals. Successful GT using lentiviral delivery of KCNA1 has been reported in a rodent model of focal motor cortex epilepsy. It is also effective in other models of epilepsy.
- **Somatostatin:** Somatostatin is a neuropeptide and neuromodulator that plays a role in the regulation of hormones as well as aids in sleep and motor activity. Potentially as an anti-seizure drug, it decreases the average duration of seizures. The premise for this drug's use is that by over-expressing it in specific cells, and increasing the GABAergic tone, it is possible to restore balance between inhibition and excitation.
- **Optogenetics:** A potential obstacle to the clinical translation of GT is that viral vector-mediated manipulation of the genetic make-up of neurons is irreversible. An alternative approach is to use tools for on-demand suppression of neuronal and circuit excitability. The first such approach was to use optogenetics. Several laboratories have shown that the inhibitory light-sensitive protein Halorhodopsin can suppress seizure-like discharges in vitro as well as epileptic activity in vivo. A drawback of this approach is that light needs to be delivered to the area of the brain expressing the opsin. This can be achieved with laser-coupled fiber-optics or light-emitting diodes, but these are invasive.
- **Chemogenetics:** An alternative approach for on-demand control of circuit excitability that does not require light delivery to the brain is to use chemogenetics. It relies on expressing a mutated receptor in the seizure focus that can be activated by an exogenous drug. G-protein coupled receptors mutated in this way are called Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). When activated by the drug Clozapine N-oxide, seizures are suppressed without any detectable side effects. Olanzapine has been identified as a full and potent such activator.
- A mouse model of Dravet's syndrome (DS) has been treated using a variant of CRISPR that relies on a guide RNA and a dead Cas9 (dCas9) protein.

Non-Viral Approaches

'Transfection'' is the process of deliberately introducing naked or purified nucleic acids into eukaryotic cells. "Magnetofection" is a transfection method that uses magnetic fields to concentrate particles containing viral vectors to target cells in the body. It has been adapted to a variety of vectors, including nucleic acids, non-viral transfection systems, and viruses. The method offers several advantages including high transfection efficiency and biocompatibility. It is done through the use of super paramagnetic iron oxide nanoparticles (SPION) coated with polyethylenimine. Iron oxide nanoparticles (ION) are ideal for biomedical applications in the body due to their biodegradable, cationic, and non-toxic properties; they are further FDA-approved.

Clinical Research

There are several challenges to the clinical translation of gene therapy, which can be detrimental to patient safety, namely: Possible

immune responses to the viral vectors and transgenes; possibility of insertional mutagenesis; and scaling up from the volume needed for animal trials to that needed for effective human transfection, although it has been overcome in other diseases.

Application in *Status Epilepticus*

Because of both the delay in gene expression following transfection and also the necessity of using focal transfection, there is a limited number of situations in which GT can be used in status epilepticus. One such condition is *epilepsia partialis continua* (EPC). Walker., *et al*. (2013) have shown that they can "cure" the condition. Recent evidence suggests that gene therapy targeting subcortical regions can modify generalized or more diffuse epilepsies, indicating that the range of situations in *status epilepticus* in which GT could be used will expand.

Future Implications

The use of gene therapy in treating neurological disorders such as epilepsy has presented itself as an increasingly viable area of ongoing research with the primary targets being somatostatin, galanin, neuropeptide, potassium channels, optogenetics and chemogenetics. As the field of GT continues to grow and show promising results for the treatment of epilepsy among other diseases, additional research needs to be done to ensure patient safety, develop alternative methods for DNA delivery, and find feasible methods for scaling up delivery volumes.

Immunotherapy (IT)

The innate immune response exists to protect the central nervous system (CNS) from insult and, ordinarily, the process is halted by removal of the injurious stimuli. However, as a result of incompletely understood processes, this important biological switch-off mechanism may become compromised, resulting in persistent microglial activation and cytotoxicity. In this way, the inflammatory response may well contribute to the development of recurrent seizures and, furthermore, may be implicated in a person's response to anti-seizure medications. Thus, targeting brain inflammation may represent a novel therapeutic strategy for epilepsy. The inflammatory pathways are targeted by add-on immunomodulatory drug interventions. The objective is to provide an additional therapy in focal epilepsy syndromes for adults (aged over 16 years).

Intravenous Immunoglobulin

The objective is to assess the role of immunomodulatory interventions (treatments that target the immune system) in reducing seizure frequency or the safety of these agents in infants and adults with focal epilepsy syndromes. The primary outcomes of all available clinical trials were 50% or greater reduction in seizure frequency and seizure freedom. Secondary outcomes included serious and commonly occurring adverse effects, allergy, withdrawal, and quality of life assessment.

In one study including both children and adults, the effect of intravenous immunoglobulin (IVIg) as add-on therapy for the treatment of epilepsy was not significantly different from placebo for the primary outcomes (seizure freedom or 50% or greater reduction in seizure frequency). Further, no secondary outcomes (adverse effects, allergies) were demonstrated. This treatment may be effective in reducing seizure frequency in some patients with epilepsy but more trials are necessary before any definite conclusions and recommendations can be made.

In conclusion, it is not possible at this time to draw any conclusions about the role of immunomodulatory interventions in reducing seizure frequency or the safety of these agents in adults with epilepsy. Further randomized controlled trials are needed.

Complementary and Alternative Therapies (CAT)

During the last two decades a series of CATs have emerged in the treatment of epilepsy. These are: Chiropractic therapy; holistic therapies: herbal medicine (utilizing St. John's Wort, evening primrose oil); homeopathy; and relaxation therapies (aromatherapy, massage, and reflexology). Other therapies include: Acupuncture; Ayurvedic medicine; lifestyle modification and exercise (proposed as

possibly useful for preventing seizures with some data to support this claim); melatonin; traditional Chinese medicine (herbal remedies plus acupuncture); traditional and psychological therapies (autogenic training, neurofeedback, and music therapy); use of *Cannabidiol* and medical marijuana; vitamins; and yoga.

Although some of these therapies seem to have an effect, most of them are considered as complementary therapies needing more studies in order to establish their therapeutic effect and their usefulness in everyday clinical practice. However, fasting and diet have proven to be helpful.

Diet Therapy

The foundational principle, application, use(s), benefit(s) and side effect(s) of five main proposed diets are summarized (in alphabetical order) in Table 3 in as far as this information is known or has been reported in the open literature. Only the benefits concerning epilepsy have been considered although other benefits may accrue for some of these diets.

Diet	Principle	Application	Use(s)	Neurological benefit(s)	Side effect(s)
1. Atkins' classical (AD)	o Similar to the classical ketogenic diet for adults. o The claimed "metabolic advantage" is false.	o Whole unprocessed food with low glycemic index. o Low carb, high fat diet. o No limit on calories & proteins.	For weight loss (questionable).	Reduction of epileptic seizures in adults (some evidence).	Increased heart disease.
2. Atkins' Modified (MAD)	Less strict regimen than the original Atkins' diet.	Ketogenic ratio of 1:1.	o Not for weight loss. o No initial fast. o No hospital stay. o No intensive dietitian support.	Reduction of epileptic seizures in adults (some evidence).	Increased heart disease.
3. Ketogenic classical	o To burn fats not carbs.	o High fat, adequate protein, low carbs. o Ketogenic ratio 4:1 (fats-to- combined carbs and proteins).	o Refractory pediatric epilepsy (no longer used). o Adult epilepsy with less strict diet (similar to modified Atkins'). o Other NDDs. o Requires vitamins & minerals supplementation.	o Neuroprotective. o Disease-modifying.	o Constipation. o High cholesterol. o Growth slowing. o Acidosis. o Possible kidney stones.
4. LGIT Ketogenic variant	o Stable blood glucose level may be one of the mechanisms of action. o Low glycemic index carbs.	o ~60% of calories from fat. o Allows more carbs than the classic ketogenic or MAD. o Carbs of low glycemic index.	o No precise weighting of food. o Initiated and maintained at outpatient clinics. o No intensive dietitian support .	For children on ketogenic diet: o Neuroprotective. o Disease-modifying.	o Constipation. o High cholesterol. o Growth slowing. o Acidosis. o Possible kidney stones.
5. MCT Ketogenic variant	o Ketogenic ratio of 1:1.	o 50% calories from a form of coconut oil). o 50% less overall fat than classical ketogenic.		o Neuroprotective. o Disease-modifying.	o Constipation. o High cholesterol. o Growth slowing. o Acidosis. o Possible kidney stones.

Table 3: *Main diets, their particulars, benefits, and side effects for epilepsy*

Key: **GI**=Glycemic index; **LGIT**= Low Glycemic Index Treatment; **MAD**=Modified Atkins Diet; **MCTs**= Medium Chain Triglycerides

Source: Fymat (2019)

Diet therapy may be utilized in some patients with specific forms of epilepsy. The most common diets are the ketogenic diet and the modified Atkins' diet. Both diets have been shown to reduce seizures in approximately half the patients who have been identified as appropriate candidates. These are mainly children with refractory epilepsy who are not surgical candidates.

Ketogenic Diet (KD)

The classic ketogenic diet (CKD) is a mainstream dietary therapy that was developed to reproduce the success and remove the limitations of the non-mainstream use of fasting to treat epilepsy. It is a special high-fat, adequate protein, and low carbohydrate diet that forces the body to burn fats rather than carbohydrates. It provides just enough protein for body growth and repair but sufficient calories to maintain the correct weight for age and height. If there are little carbohydrates in the diet, the liver converts fats into fatty acids and ketones (acetoacetate, beta-hydroxybutyrate, acetone), which pass into the brain and replace glucose as an energy source. An elevated level of ketone bodies in the blood (a state known as *ketosis*) leads to a reduction in the frequency of epileptic seizures. The ketogenic ratio by weight is 4:1 of fat to combined proteins and carbohydrates. This is achieved by excluding high-carbohydrate foods such as starchy fruits and vegetables, bread, pasta, grains, and sugar while increasing the consumption of foods high in fat such as nuts, cream, and butter. There are several variants of the ketogenic diet which at times have been employed in combination with the classic one.

In pediatric medicine, the diet is used primarily to treat difficult-to-control (refractory) epilepsy in children. Around half of children and young people with epilepsy who have tried some form of this diet saw the number of seizures drop by at least half, and the effect persisted even after discontinuing the diet. Some evidence indicates that adults with epilepsy may also benefit from the diet and that a less strict regimen, such as a modified Atkins' diet (MAD), is similarly effective. It may also have other positive effects. However, because of its side effects (stomach and intestinal problems in ~ 30% of people, constipation, risk of developing kidney stones, and long-term concerns about heart disease) and the advent and availability of anticonvulsants, this diet is considered beneficial or recommended in epilepsy.

The KD is a reasonable option for those who have epilepsy that is not improved with medications and for whom surgery is not an option. Less radical diets are easier to tolerate and may be effective. It is unclear why this diet works and further research is necessary. (Note: In people with celiac disease or non-celiac gluten-free sensitivity and occipital calcifications, a gluten-free diet may decrease the frequency of seizures.)

Although popular in the 1920s and '30s, CKD was largely abandoned in favor of new anticonvulsant drugs. Most individuals with epilepsy can successfully control their seizures with medication. However, 25%–30% fail to achieve such control despite trying a number of different drugs. For this group, and for children in particular, the diet has once again found a role in epilepsy management.

Nonetheless, the KD or some of its variants continue to be under investigation for the treatment of a wide variety of neurological disorders other than epilepsy. Thus, clinical trials and studies in animal models suggest that ketogenic diets provide neuroprotective and disease-modifying benefits for several pediatric and adult neurodegenerative disorders. Possible therapeutic uses for the KD have been studied for many additional neurological disorders, some of which include: Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), autism, brain cancer, headache, neurotrauma, pain, Parkinson's disease (PD), and sleep disorders.

Medium-Chain Triglyceride (MCT) Therapies

Foods containing MCTs provide the fuel necessary for the mitochondria (the energy factories) in brain cells to make adenosine triphosphate (ATP), the actual fuel that allows brain cells to carry on with their tasks. They also convert to ketones in the liver, those tiny molecules of organic fuel that have co-existed with humanity since its beginnings and have indeed contributed to its very survival. The (U.S.) Food & Drug Administration (FDA) recognizes ketones as generally safe. Unfortunately, infection and inflammation can slow down

the metabolism of ketones so that, depending on their physical constitution and general health, some people may respond only partly or not all to a ketone therapy. Setbacks may also happen during therapy.

MCTs are found principally in coconut and palm kernel oils although in much smaller quantities than in laboratory-produced ketone esters. Thus, while a reprieve may be anticipated from a coconut oil- based diet, the benefits will not be as pronounced as with ketone esters.

Classical (CAD) and Modified Atkins' Diet (MAD)

The classical Atkins' diet (CAD) is similar in principle to the ketogenic diet. It is a low-carbohydrate fad diet marketed with questionable claims that carbohydrate restriction is critical to weight loss. There is no good evidence of its effectiveness in achieving durable weight loss, however, it may increase the risk of heart disease. There is weak evidence that it is more effective than behavioral counseling for weight loss at 6-12 months and the effect size is smaller over longer periods. There is some evidence that adults with epilepsy may experience seizure reduction derived from therapeutic ketogenic diets, and that a less strict regimen, such as a modified Atkins' diet (MAD), is similarly effective.

Low Glycemic Index Treatment (LGIT)

The LGIT diet attempts to achieve the stable blood glucose levels seen in children on the classic KD while using a much less restrictive regimen. The underlying hypothesis is that stable blood glucose may be one of the mechanisms of action involved in the ketogenic diet, which occurs because the absorption of the limited carbohydrates is slowed by the high-fat content. Although it is also a high-fat diet (with approximately 60% calories from fat), LGIT allows more carbohydrate than either CKD or MAD (~ 40–60 g per day). However, the types of carbohydrates consumed are restricted to those that have a low glycemic index (lower than 50). The purpose is to avoid the spikings in blood glucose.

Prognosis

While epilepsy cannot be cured, for some people the seizures can be controlled with medication, diet, devices, and/or surgery. Most seizures do not cause brain damage, but ongoing uncontrolled seizures may cause brain damage. It is not uncommon for people with epilepsy, especially children, to develop behavioral and emotional problems in conjunction with seizures.

Issues may also arise as a result of the stigma attached to having epilepsy, which can lead to embarrassment and frustration or bullying, teasing, or avoidance in school and other social settings. For many people with epilepsy, the risk of seizures restricts their independence (some States refuse drivers' licenses to people with epilepsy) and recreational activities.

Epilepsy can be a life-threatening condition. Some people with epilepsy are at special risk for abnormally prolonged seizures or sudden unexplained death in epilepsy.

Conclusions

Epilepsy is a long-term or even a lifetime condition that cannot generally be 'cured'. It can be a life-threatening condition. Some people with epilepsy are at special risk for abnormally prolonged seizures or sudden unexplained death. It is not uncommon for people with epilepsy, especially children, to develop behavioral and emotional problems in conjunction with seizures. Issues may also arise as a result of the stigma attached to having epilepsy.

Numerous anti-seizure medications have been introduced over the past decades. They are usually the first-line treatment for epilepsy and are selected based on the type of seizure one has as well as the patient's other pertinent medical history. The aim of treatment is 'optimal therapy', meaning taking the fewest types of anti-seizure medications at the lowest dose in order to get the best seizure control possible with the fewest side effects. If optimal therapy cannot be found with one particular medication, there are usually several others that can be tried, alone or in combination. Initial treatment is usually a 'monotherapy'. If the seizures are not controlled

with a single medication, a combination of medications may be taken (called 'polytherapy'). Some people continue to have seizures despite taking anti-seizure medications. In this case they may continue to take them to reduce their seizures as much as possible and consider trying other types of treatment. Four of the available anti-seizure medications (*Carbamazepine, Gabapentin, Phenobarbitol*, and *Valproate*) cause an increased risk of birth defect while two others (*Lamotrigine* and *Levetiracetam*) have the lowest such risk.

If medication does not stop all seizures, or only stops some of them, other types of treatment (neurostimulation, neurosurgery, gene therapy, immunotherapy, and complementary and alternative treatments) might be considered instead of, or alongside, anti-seizure medications.

Approximately 70% of epileptic patients have well-controlled seizures with medications. The remaining 30% are considered medically-resistant and, for them, surgery provides the best chance of complete control of their seizures. However, not all patients with refractory epilepsy are suitable candidates for surgery and must undergo pre-surgical evaluation. Brain surgery (or neurosurgery) requires certain criteria to be met and tests to be done to assess suitability. It involves resections or removal of abnormal tissue (Montreal procedure; lesionectomy; lobectomy; multilobar resection; and anatomic or functional hemispherectomy); disconnections (corpus callosotomy; multiple subpial transections); and stereotactic radiosurgery (gamma knife). Another emerging therapeutic modality for seizure suppression is repetitive transcranial magnetic stimulation. However, despite being considered a safe technique, it carries the risk of inducing seizures, among other milder adverse events, and thus, its safety in the population with epilepsy should be continuously assessed.

A series of complementary or alternative therapies have emerged in the treatment of epilepsy: acupuncture; autogenic training: Ayurvedic medicine; Cannabidiol and medical marijuana; chiropractic; fasting; herbal remedies; holistic; homeopathy; lifestyle modification(s) and exercise; Melatonin; relaxation; traditional Chinese medicine; traditional and psychological; music; neurofeedback; vitamins; and yoga. Although some of these therapies seem to have an effect, most of them are considered as complementary therapies in need of more studies in order to establish their therapeutic effect and usefulness. The foundational principle, application, use(s), benefit(s) and side effect(s) of six main proposed diets have been summarized: Atkins' (original, modified), ketogenic (classical, modified), low glycemic index, and medium chain triglycerides. The ketogenic diet is a reasonable option in those who have epilepsy that is not improved with medications and for whom surgery is not an option. How it works remains a mystery. It is indicated as an adjunctive (additional) treatment in children and young people with drug-resistant epilepsy. Two less restrictive dietary variants—the low glycemic index treatment and the modified Atkins' diet—are more appropriate for adolescents and adults, mainly due to better adherence. It is not a benign, holistic, or all-natural treatment. As with any serious medical therapy, it may result in complications, although these are generally less severe and less frequent than with anticonvulsant medication or surgery. Foods containing medium-chain triglycerides provide the fuel necessary for the mitochondria in brain cells to make adenosine triphosphate, the actual fuel that allows brain cells to carry on with their tasks. They are generally considered as safe. Unfortunately, infection and inflammation can slow down the metabolism of ketones so that some people may respond only partly or not all to a ketone therapy. Setbacks may also happen during therapy. The low glycemic index treatment achieves stable blood glucose as one of its mechanism(s) of action, achieving the same result while using a much less restrictive regimen.

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