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Review Article

Neuromodulation techniques in medically refractory epilepsy: A comprehensive assessment

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ABSTRACT

Introduction: The aim of this research is to explore the efficacy and safety of neurostimulation techniques, particularly responsive neurostimulation, in treating medically refractory epilepsy. The study reviews relevant literature, discusses the mechanisms of action, and presents evidence of reduced seizure frequency and improved quality of life in patients receiving neurostimulation.

Materials and Methods: To evaluate invasive Neuromodulation's efficiency for medically refractory epilepsy, we searched databases like Google Scholar, Medline, and Elsevier using keywords 'Neuromodulation and epilepsy'. Numerous relevant results emerged. We conducted rapid abstract reviews to identify key articles, cross-referencing for valuable references, ensuring a comprehensive analysis of pertinent research.

Conclusion: Neuromodulation techniques, particularly VNS, DBS, and RNS, offer promising therapeutic options for medically refractory epilepsy. Ongoing research and clinical trials are vital for refining these treatments, adapting them for diverse populations, and enhancing outcomes. The potential to improve patients' quality of life through innovative approaches is encouraging, driving further progress in neuromodulation.

1. Introduction

Epilepsy is one of the primary disorders of the brain and accounts for 1% of the global burden of diseases.[1] According to International League Against Epilepsy, an epileptic seizure is caused by to abnormally excessive or hyper-synchronous neuronal activity in the brain and results in the transient occurrence of signs and symptoms.

A person is diagnosed with epilepsy if he/she has two recurrent seizures unprovoked by any systemic or neurological abuse (not caused by reversible medical conditions like low blood sugar or alcohol withdrawal). A seizure provoked by reversible medical conditions doesn't fall under the definition of epilepsy as it is of short duration.[2]

Looking back into history, epilepsy and it's treatment roots date back at least 4 millennia to the ancient civilization of the middle east. Several databases have suggested that the use of invasive Neuromodulation is quite safe and effective in the treatment of medically Refractive epilepsy. It has shown promising results in reducing the frequency of partial-onset seizures acutely, showed improving seizure reduction over time, was well tolerated, and was acceptably safe. Other Neuromodulation technique as Vagus nerve stimulation (VNS) and deep brain stimulation is also effective. Also, there are several approved medicine for the treatment of epilepsy but in case of medical resistance epilepsy or non-responsive to medical treatment.

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A need for looking for alternative safe treatments have arisen. Because it was impossible to review all the published data of the same as the history of Neuromodulation has dated back to the 19^{th} century. There were numerous published articles in the different medical database such as PubMed, Google Scholar, Medline, Elsevier etc. We have selected articles and significantly Cross-reference of importance was selected. Here we have tried to focus on the Neuromodulation technique used in the treatment of epilepsy briefly and has discussed Responsive Neurostimulation in details.

2. Materials and Methods

To answer the above arises question regarding the efficiency and efficacy of invasive Neuromodulation in the treatment of medically refractive epilepsy. We have searched several databases mostly published online like Google scholar, Midline, Elsevier etc. using the keyword 'Neuromodulation and epilepsy, Responsive Neuromodulation. We found more than thousands of search results closely related to Aim but practically it was impossible to review all of them. A quick reading of the abstract of conducted and on the basics of researchers perception. Articles of significantly importance was selected. Further, valuable reference was cross-referred.

3. Discussion

After the advancement and development of the EEG machine. The International League Against Epilepsy (ILAE) published an international classification of elliptic seizure in 1981[3] Since several modifications and revision were made in different years in 19985,1989 and 2010.[4,5] The recent modification was announced by ILAE in 2017 for both epilepsy and seizure, which has been adapted widely for its classification and diagnosis.[6]Tables 1 and 2.

It has been postulated that genetic deformities or defect and mutation either acquired or congenital that lead to alterations in the balance between the inhibitory (γ-aminobutyric acid (GABA)) and the excitatory (glutamate) neurotransmission.[12] The discovered genes involved cause epilepsies to encode both voltage-gated and ligand-gated ion channel subunits. In general, seizures are more susceptible in the immature brain than a mature brain due to developmental changes such as synaptic pruning, density changes of neurotransmitter receptors, changes in receptor activity such as GABAA (excitatory in immature neurons due to modified Cl- gradient and inhibitory in a mature neuron).[13] Several genes (and gene mutations) were identified in the last decade which affects the ion channels and is believed to be the cause of certain idiopathic epilepsies.[7,8] Table 3

Acquired epilepsy is caused due to extraneous mechanisms (severe brain and/or birth trauma, stroke, lesions, infections) or unknown mechanisms (brain tumours, brain development malformations) which abuse the central nervous system.[14,15] These mechanisms induce epileptogenesis – events which turn a normal neuronal network into an epileptic (hyperexcitable) network. Epileptogenesis is a series of events which starts with cortical seizures. The cortical seizures cause neuronal damage and this injury leads to rewiring of neuronal networks and increases excitability which further increases susceptibility to further seizures.[16] New granule cells are also formed in epileptogenesis which results in: a) Sprouting of mossy fiber axons from the granule cells and results in aberrant integration into the already present hippocampal circuitry.[17–19] B) Sprouting of hilar basal dendrites from the newborn granule cells which receive mossy fiber synapses in the hilus and further alters the hippocampal circuit.[20] C) Migration of newborn granule cells into the hilus which results in abnormal morphology of the granule cell layer.[21] The three new changes alter hippocampal physiology and introduce epileptogenic circuits and epileptic activity.[22] Acquired epilepsies have perinatal and postnatal acquired factors and may or may not have a genetic component.[23] Acquired epilepsies can also be a result of an altered ion channel function such as transcriptional channelopathies. Receptor density after a small seizure and age dependence of such changes are also implicated in one literature.[24]

Many drugs has been approved in treatment of epilepsy and effective in reducing the onset of seizure, hence, decision regarding treatment and management should be taken wisely. In the case of the regular onset of seizure or patients with previously identified epilepsy example, juvenile myoclonic epilepsy treatment becomes straight forward.[25] Evidence has suggested that around 10 % of cases remain undefined and failed to receive the first line of treatment. Also, in the misdiagnosed case around 15% receive epileptic treatment although, they are not epileptic.[26] So, we do believe that any treatment any management plans or treatment modules should not be taken likely and after a confirmed diagnosis, the only initiative should be taken. Several treatment procedures have been approved and are being practised widely across the global like Anti-epileptic drugs, Surgery, Neuromodulation etc.[27–33]

Anti-epileptic drugs or a combination of various anti-epileptic drugs (AED) are the first line of treatment and can help in decreasing the frequency and intensity of seizures. The clinical objective is the selection of a treatment which provides the best match for the characteristics of a particular patient and also ensuring a high probability of achieving seizure freedom without causing serious side effects. Medications are chosen based on the type of epilepsy, frequency of seizures, age, etc.[27,28] Side effects include tiredness, dizziness, weight gain or loss, memory problems, poor coordination, depression, etc. The patient

Table 1: Genes associated with idiopathic epilepsies(adapted from).[7,8]

Idiopathic epilepsy	Associated genes
Ligand-gated channelopathies	
Idiopathic generalized epilepsy with GEFS+	GABA receptor subunit gene: GABRG2
Juvenile myoclonic epilepsy	GABA receptor subunit gene: GABRA1
Autosomal-dominant nocturnal frontal lobe epilepsy	Nicotinic ACh receptor subunit genes: CHRNA4, CHRNB2
Voltage-gated channelopathies	
Severe myoclonic epilepsy of infancy	Na+ channel gene: SCN1A
Generalized epilepsy with febrile seizures plus (GEFS+)	Na+ channel genes: SCN1B, SCN1A
Benign familial neonatal–infantile seizures (BFNIS)	Na+ channel gene: SCN2A
Benign familial neonatal seizures (BFNS)	K+ channel genes: KCNQ2, KCNQ3
Autosomal-dominant partial epilepsy with auditory features	K+ channel subunit: LGI1
Juvenile absence epilepsy (JAE) Juvenile myoclonic epilepsy (JME) Epilepsy with grand mal upon awakening	Cl- channel gene: CLCN2A
Temporal lobe epilepsy (TLE)	K+ channel gene: KCDN2
Generalized epilepsy with paroxysmal dyskinesia (GEPD)	K+ channel gene: KCNMA1
Non-ion channel genes	
Several other complex epilepsies	Monogenic, audiogenic seizure susceptibility 1 homolog (MASS1), Bromodomain – containing 2 (BRD2), malic enzyme 2, NAD+ - dependent, mitochondrial (ME2), EF-hand domain containing 1 (EFHC1)

Table 2: Adapted from[9–11]

Seizure classification of 2017, Types of seizure; According to International League Against Epilepsy (ILAE0).				
Focal onset	**Aware**	**Motor onset**	**Automatisms**	
		Motor onset	Atonic	
			Clonic	Focal to bilateral
			Epileptic spasms	tonic-clonic
			Hyperkinetic	
			Myoclonic	
			Tonic	
		Nonmotor onset	Autonomic	
			Behavior arrest	
	Impaired awareness		Cognitive	
			Emotional	
			Sensory	
Generalized onset		Motor	Tonic-clonic	
			Clonic	
			Tonic	
			Myoclonic	
			Myoclonic- tonic-clonic	
			Myoclonic-atonic	
			Epileptic spasms	
			Typical	
		Nonmotor (Absence)	Atypical	
			Myoclonic	
			Eyelid myoclonia	
Unknown onset				

Table 3: Adapted from {64,65,66}

Levels of diagnosis and epilepsy classification of 2017 ILAE classification of the epilepsies:			
First level	**Second level**	**Third level**	**Etiologies**
Focal onset seizures	Focal epilepsies	Epilepsy syndromes	Structural Genetic Infectious Metabolic Immune Unknown
Generalized onset seizures	Generalized epilepsie Combined generalized and focal epilepsies		
Unknown onset seizures	Unknown epilepsies		

that has been subjected to medication but remain ineffective or has become non-responsive to drugs in case of drugs-resistance epilepsy, such candidate may be considered or can undergo surgical intervention.[34]

Generally, the goals of epilepsy surgery include a) Removing the area of the brain responsible for seizures. b) Disrupting nerve pathways that become hyperactive and synchronize during a seizure. The type of surgery performed also depends on the type of epilepsy and the area of the brain they start from.

1. Resection – Resection involves removing a section(lobe) of the brain where the seizure starts. Temporal lobectomy is the most common example of surgery as it is the most common seizure focus type in adults and teens. Extratemporal resection is a surgery where the tissue surrounding the temporal lobe is removed to alleviate symptoms of epilepsy.
2. Lesionectomy – This is a type of surgery performed to remove damaged tissues (neoplastic lesions) in the brain. Common examples include the removal of primary brain neoplasms, vascular lesions, and removal of inflammatory and infectious lesions.
3. Corpus callosotomy – Also known as split-brain surgery and involves disconnection between the two hemispheres of the brain which prevents the spread of seizures from one hemisphere to the other. Performed in patients which extreme forms of uncontrollable epilepsy.

Neuromodulation devices are indicated in the treatment of medically refractory epilepsy (seizures keep coming back even after treating with at least two AEDs) where patients are also not candidates of surgery. Techniques include vagal nerve stimulation, deep brain stimulation of the anterior nucleus of the thalamus, trigeminal nerve stimulation, responsive neurostimulation system.

In Vagal nerve stimulation – Electrodes are implanted around the left vagus nerve and the generator is implanted subcutaneously in the left sub-clavicular region. Open-loop control device with one exception where the stimulation is increased in case of increased heart rate. Efficacy is stated as 35% at 1 year and 44% at 3 years.[35] Adverse events include hoarseness and cough, vocal cord paralysis, infection.[35] It was originally reported in 19^{th} centuries that Vagus nerve stimulation could results in alleviated symptom of epilepsy. Corning, first postulated it and believes that seizures were as a outcome of excess blood flow to the Brain. Human trials were not performed till then. A century later in 1997 Food and drugs authority of USA approved for use in Human.[29] VNS consists of a stimulating electrode, implanted, around the left vagus nerve and a waveform generator typically implanted in the sub clavicle region. Several published literature suggests the efficiency of VNS but 1^{st} clinical trials were reported in the early 1990s.[42.43] It was also concluded that future clinical trials are necessary for the best outcome and efficiency of it's uses in the treatment of epilepsy.

A recently published meta-analysis literature in 2011, indicated that the overall reduction in seizures frequently was around 45%.[32] In comparison between children and patients, it was suggested that VNS stimulation is more beneficial to children. The author also stated that efficiency is directly proportional to the duration of exposure. Here in case 36% shows reduce in frequency when exposed to duration of 3-12 months. Interestingly, on another hand side, 51% reported a decrease in frequency when exposed for a duration longer than 12 months, suggesting VNS functions in part through long-term modification of neural circuits as opposed to acute suppression of seizure activity.[32]

Now, in case comparison between stimulating parameters between high vs low, it was found that high stimulation was more effective than low.[32] Cochrane review also suggests and supported the same.[33] some literature also suggested that children are more benefited compare to adult patients.[36] It was also controversial in determining "when to initiate " the VNS. Early or later stages. Some studies have shown that the initial insult of epilepsy can cause damage to seizures and neural Circuit dysfunction. Hence, it is suggestive to start VNS in the initial or early phase. Long term change in neural Circuit physiology

determines its efficiency.[37] Research on the people of different aetiology, races and groups should be performed for a better understanding of universal data and evidence. Future more, future research and controlled clinical trials is always mandatory in determining the best outcome and it's effectiveness. We believe that in future in the case of medically resistant epilepsy VNS could be a boon to doctors and also to patients in decreasing the episode of seizures and maintaining a normal healthy lifestyle.

In Deep brain stimulation of the anterior nucleus of the thalamus – Open-loop device with bilateral depth electrodes implanted in the anterior nucleus of the thalamus and the generator is implanted I the left sub-clavicular region. Efficacy stated at 41% at 1 year and 69% at 5 years.[38] Adverse effects include implant site pain and infection, paraesthesia.[38]

In Trigeminal nerve stimulation – Open-loop device which uses transdermal electrodes to stimulate supraorbital branches of the trigeminal nerve. Efficacy stated at 27.4% at 6 months and 34.8 at 12 months.[39] Adverse events include skin irritation, headache, and anxiety.[39]

Responsive neurostimulation is Indicated in refractory partial-onset seizures with up to two identified seizure foci. A closed-loop device with two depth or subdural strip electrodes is implanted in or over the seizure foci with the stimulator implanted within the skull in a pocket. Stimulation is only delivered when epileptiform activity is detected. Efficacy stated at 44% at 1 year and 65.7% at 6 years.[40] Adverse events include implant site infection and haemorrhage.[40]

The RNS System is a closed loop neuromodulation device used in the treatment of medically refractory partial onset seizures and off label in some generalized seizures. The device continuously monitors electrocorticographic brain activity and delivers therapeutic stimulation when seizure activity is detected which can be set by the physician. The device also supports telemetry and the setting and stored data can be retrieved. The physician uses a patient device management system (PDMS) to visualize the downloaded data from the device and can decide if he/she wants to tweak the detection and stimulation settings. The PDMS also has advance features such as the simulation function which can be used by the physician to test detection algorithms prior to deploying the configuration to the device.[41]

The RNS system consists of a neurostimulator which is implanted by making a pocket in the cranium. It supports two depth, or two cortical strip leads or a combination of the both. Dimension of the device are 60 * 2.7 * 7.5 mm.[41]

The neurostimulator has four configurable amplifiers which can be tweaked to monitor different electrocorticographic activity. The device can also store eight 90s recordings of ECoG activity which can also be configured around detection algorithms, amplifier saturation, scheduled activity and magnet swiping.[41]

A total of four (4) biomarker pattern detectors can be configured. The detection algorithms include a half-wave/bandpass detector, a line length detector and an area under curve (AUC) detector. The half-wave or bandpass detector detects increase in power in a specific frequency range and LFP spikes. The line length detector detects increase in line length in a specific sliding window and compares it to a longer-term baseline length. The line length detector is also sensitive to frequency and amplitude increase or decrease. The area under curve detector compares the area of a short sliding window and a longer-term baseline area and is also sensitive to amplitude and frequency increase or decrease. These detecting algorithms detect abnormal epileptic waveform including seizure onset and interictal discharges which include oscillation in all bands of brain waves and LFP spikes.[41]

The neurostimulator can stimulate in any combination of the eight (8) electrodes and the case. The stimulation pattern includes variable voltage variable pulse width, bipolar or monopolar stimulation and is associated with the volume of tissue activated by each stimulation. For example in temporal lobe epilepsy adjacent positive and negative contacts (bipolar) are used for both the leads (+-+-) while for epilepsy focus in neocortex monopolar contacts are used between the leads (++++ and —-) or both the leads can be monopolar while the case acts as the opposite polarity (cathodal or anodal). Each burst consists of two (2) stimulations which can be detection specific. Five therapies of two bursts can be used.

The device has data telemetry capabilities and can also store 8 different time stamped 90 seconds recordings. The device communicates with a wand which is connected with a computer for easy storage, retrieval and transfer of recordings.[41]

The battery installed is a 1114 mAh lithium ion battery with longevity estimate of 8 years with medium (100 minutes) usage per day.[41]

3.1. Mechanism of action

Simulation induced modulation in patients with the responsive neurostimulation system has two main effects: direct and indirect. Direct effects are contributed by events during stimulation or in the immediate post-stimulation interval and are classified as ictal inhibition and frequency modulation of the ongoing seizure activity.[42–44] Indirect effects are contributed by events which occur long before or after the stimulation and include spontaneous seizure inhibition, modulation of seizure frequency, seizure fragmentation (Electrographic Seizure Pattern (ESP)* temporal progression interruption), and modulation of seizure duration.[45]

Long term effectiveness of RNS seizure modulation depends greatly on stimulation-induced modulation of the

seizure generating network (SGN), induced long term plasticity which decreases seizure frequency, and network desynchronization of SGN.

*Electrographic Seizure Pattern (ESP) – The point in an ECOG recording after which the activity is no longer interictal and is followed by paroxysmal discharge of seizure pattern and features such as rhythmical spiking, spike-waves, electro-decremental and/or rhythmical evolving theta, delta, alpha frequency patterns.[46,47]

3.2. Inhibition of ESPs

Direct – The applied stimulation pulse terminates the progression of the ictal activity. This effect is attributed to the direct effect of RNS and has been termed as direct inhibition.[48]

3.3. Frequency modulation of ESPs

Direct – Frequency modulation in terms of attenuation of baseline frequency and generation of higher than baseline frequency with time is also seen as an immediate effect after the application of stimulation pulse.

Indirect – Band transformation such as from alpha (8-12 Hz) to theta (6-10 Hz) and beta (13-20 Hz) or delta – alpha (3-12 Hz) to a very wide band (2-50 Hz) which are independent of the stimulation pulses applied.[45]

3.4. Attenuation of ESPs

Indirect – Spontaneous discontinuation of ESP progression in the absence of a stimulation pulse.

3.5. Seizure fragmentation

Indirect – Fragmentation of ESPs is also classified as an indirect effect of stimulation and results in interruption by normal background activity during ongoing ictal activity.

3.6. ESP duration modulation

An Increase or decrease of ESP duration which is independent of the ictal pattern duration is also attributed as an indirect effect of RNS.

Direct inhibition leads to activation of local postsynaptic potentials which in turn create extracellular fields. These extracellular fields oppose the gradient created by epileptogenic circuits and reduce the hyper-synchronization in an excitatory population.[49] Whereas, given the time indirect modulation creates a barrier of extracellular electrical fields which separates the epileptogenic populations and isolates the region. Over time the neuronal population is separated from the epileptic core and thus the frequency, baseline amplitude and power of further seizures are reduced.[50,51]

3.7. Neuromodulation in a network disorder

Epileptic seizures are caused due to abnormally excessive or hyper-synchronous neuronal activity in the brain and results in the transient occurrence of signs and symptoms but there is an increasing belief that epilepsy is a network disorder, is highly distributed and dynamic. The network theory of epilepsy[52] states that the dominant factor in epilepsy is anomalous networks and hyper-synchrony between the anomalous networks.[52–56]

Cortical and subcortical areas of the brain are connected anatomically and functionally and form various brain networks. The most primitive network consists of two nodes connected by two pathways.[57] The anomaly can rise in either a node or a pathway or a node together with a pathway. There can also be a case where the nodes and the pathways are not anomalous, but the entire network is anomalous as a whole. Since nodes and pathways causing the epileptic network are not known, or why they are anomalous or the extent of the anomaly, predicting the SGN is a difficult task.

The use of a closed-loop device as a brain-computer interface (BCI) to monitor, detect and stimulate the seizure focus is a novel system but the network theory of epilepsy poses challenges such as dynamics and spatial scale for the system. The monitored network might not be defined at the time the device was installed and might present itself with time. The non-uniformity of response from all the nodes in the network to stimulation also possesses further challenges.

Intriguing evidence has suggested that electrical stimulation, specially timed out to the onset of epileptic form activity could be an effective therapeutic strategy. In 2004, Kossoff et al. In there study they successfully implanted the RNS system in 50 patients and found that in 4 patients RNS in the cortex was effective in reducing seizure frequency and duration. After this literature, many pivotal clinical trials were initiated. Looking back in history, we found that 'Direct electrical stimulation in aborting seizures completely "this idea or hypothesis is recorded in the 1950s[43] also some preclinical data from the 1980s suggested that closed-loop feedback stimulus, could be useful in harnessing therapeutic values.[44]

Morrel et al. In 2011 published a multicentre, double-blind randomized controlled trial, suggesting that RNS gives promising results in decreasing the frequency of seizures and also it don't degrade the quality of life or mood swings. Psychological parameters like mood and Qol was found to be normal.[58]

In this study, a total of 191 adults suffering from medically intractable partial epilepsy was selected and for a period of 12 weeks, 50% of the population were exposed to stimulation were as other 50% of the population were kept unstimulated/Sham group(placebo). One month after the implantation, stimulation was initiated and interesting it was found that seizures were significantly reduced (-

37.9) of the population (N=97) receiving stimulation. On the other side, or compared to the sham group (N=94) decrees in the seizures were reported only in 17.3%. Interestingly, seizure frequency revealed a transient reduction in seizures of about 25%. Thereafter, the seizure rates continued to decrease in the stimulation-treated patients, whereas the non-treated patients gradually approached their pre-implant seizure frequency. By the final month of the blinded period (5 months after implant), patients treated with responsive stimulation had a significantly larger seizure frequency reduction (41.5%) than the sham stimulated patients (9.4%; GEE estimate, $p = 0.008$)).[58]

At the end of the 12 week, a subsequent 84- week open labelled period were all patients received responsive stimulation and there seizures rates continue decreases. The median percent reduction in seizures in the OLP was 44% at 1 year and 53% at 2 years, which represents a progressive and significant improvement with time ($p < 0.0001$)), 60–66% at years 3–6 (Bergey et al., 2015), and 75% at year 9 (Nair and Morrell, 2018). Author did not stated any significant difference in adverse effects between the two groups (active stimulation and sham stimulation) All the neuropsychological behaviour and mood were normal. This study also suggested Responsive stimulation to the seizure focus reduced the frequency of partial-onset seizures acutely, showed improving seizure reduction overtime was well tolerated and was acceptably safe. (Hecket all 2014).[58–61] Implanted device-related side effects or adverse effects were seen 3.6% reported infection at the implanted site were as 2.6% and 3.7 % reported lead damage and lead revision respectively. Haemorrhage and infection rates were found to be similar to other invasive Neuromodulation devices.[62] Kokoszka MA et al. Bercu MM et al. In their studies suggest the efficacy of RNS in paediatric patients is restricted as of now.[9,11,63,64]

4. Conclusion

The use of neurostimulation in the treatment of epilepsy is gaining popularity in several past decades. The choice of the device should be made on the preference of the operator and patients. In the case of drugs resistance epilepsy or area where surgery is contraindicated. Vagus nerves stimulation and responsive neurostimulation can be used as a boon in reducing seizure rate and treatment of epilepsy if used with precautions and safety. Data has supported this argument and we also believe that neurostimulation technique is out of reach for general population as this is limited to multi-specialty and Tier 1 cities. Special advanced skilled is required for gaining benefit and avoiding side effects. Developing countries like India need further advance infrastructure and skilled professionals. Aside from this people should also be aware regarding it's beneficial out come. Theirs has been may superstitions prevailing in India population and people's psychology. Moreover, Neurostimulation is effective in reducing seizure reoccurrence/rate. This fact cannot be denied. Our primary ethics for any treatment is based on "positive outcome vs adverse effects' and if positive effect surpasses negative outcome, generally, the physician proceeds with the treatment. Similarly, in our study, we have found that with minimal adverse effects, neurostimulation has huge potential for a positive outcome. Several published data has supported our finding and believe.

Although multiple research has been published describing neurostimulation effectiveness in epilepsy but still further, clinical controlled trials in a large number of population with different demographic status and races are always mandatory.

5. Source of Funding

None.

6. Conflicts of Interest

There are no conflicts of interest.

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