DEPARTAMENTO DE MEDICINA

Vagus Nerve Stimulation en Epilepsia Fármaco-Resistente: Eficacia y Tolerancia / Vagus Nerve Stimulation in Medically-Resistant Epilepsy: Efficacy and Tolerance

TESIS DOCTORAL

Ana Suller Marti, MD, MSc

Programa de Doctorado 3139 Medicina – Mención Internacional

Línea de Investigación: Neurología

Curso Académico 2020/2021

Director: Dr. José Miguel Láinez Andrés

A mis padres & Sean,

por todo su apoyo incondicional.

AGRADECIMIENTOS

El presente trabajo ha sido posible gracias al apoyo intelectual y moral de muchas personas a largo de todos estos años. Porque al final es llegar y aquí estoy. Muchas gracias a todos, sin vosotros este trabajo no hubiera sido posible.

A José Ángel Mauri Llerda por enseñarme lo fascinante que es la epilepsia y motivarme a seguir aprendiendo e investigando en este apasionante campo.

A José Miguel Láinez Andrés por su incondicional apoyo en mis decisiones y facilitándome mis progresos.

A Jorge G. Burneo de las Casas por enseñarme mucho de epilepsia, de investigación y como profesional. Definitivamente, él es una persona que ha marcado mi camino en el mundo de la epilepsia.

A Sean, porque su ayuda ha sido clave para estar donde estoy. Por su extrema paciencia, por apoyarme día tras día, y motivarme a seguir adelante. Sin ti difícilmente hoy estaría aquí.

A mi madre y a mi padre, por apoyarme en cada paso y hacerme levantar cuando todo paracía imposible. A mi hermano, por su don de padre. A mi cuñada y sobrinos, porque todo vuestro amor ha hecho que fuera más fácil llegar donde estoy.

A mis queridos Linda y Kevin, gracias por toda esa constante ayuda y paciencia depositada en mí.

A mis queridos departamentos de Neurología del Hospital Clínico Zaragoza (en especial Elena Bellosta y Sonia Santos), del Hospital Clínico de Valencia (Anna Martín y Francisco Gascón) y al Clinical Neurological Sciences London Ontario (Michelle-Lee Jones, Seyed Mirsattari, David Steven y Andrea Andrade), por apoyarme y demostrarme de lo que soy capaz.

A todos mis amigos con los que he tenido el placer de compartir momentos, incluyendo Andrea Martin, Paloma Isach, Marian Martinez, Ana C. Wing, Cecilia Kramer, Gabriel Osvaldo, Victoria Mayoral, Maryam Nouri, Tresha Antaya y muchos más que no

voy a poder nombrar. Gracias por todos esos mensajes de apoyo que me han hecho seguir hacia adelante.

Finalmente, a todos los pacientes que sufren epilepsia y que luchan cada día con la incertidumbre. Para mí, ellos son una fuente de inspiración y de motivación para seguir aprendiendo día a día para poderles mejorar un poquito sus vidas.

I have been impressed with the urgency of doing.
Knowing is not enough; we must apply.
Being willing is not enough; we must do.
Leonardo da Vinci

El éxito no es definitivo,
el fracaso no es fatídico.
Lo que cuenta es el valor para continuar.
Winston Churchill

INDEX

ACRONYMS

ATN	Anterior Nucleus of the Thalamus
ATN-DBS	Anterior Nucleus of the Thalami Stimulation
ASD	Antiseizure Drug(s)
ASM	Antiseizure Medication
CNS	Central Nervous System
CBF	Cerebral Blood Flow
CSF	Cerebrospinal Fluid
CAE	Childhood Absence Epilepsy
COPD	Chronic Obstructive Pulmonary Disease
CT	Computerized Tomography
DHEW	Department of Health, Education and Welfare
DBS	Deep Brain Stimulation
DCS	Direct Cortical Stimulation
EEG	Electroencephalography
EMU	Epilepsy Monitoring Unit
ERDMC	Epilepsy-realated direct medical costs
EZ	Epileptogenic Zone
EC	European Commission
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma Aminobutyric Acid
GGE	Genetic Generalized Epilepsy
GLUT	Glucose Transporter
HRQOL	Health-Related Quality of Life
HFS	High Frequency Stimulation
HVA	Homovanillic Acid
ID	Intellectual Disabilities
IGE	Idiopathic Generalized Epilepsy
SPECT	Interictal and ictal Single Photon Emission Computed Tomography
ILAE	International League Against Epilepsy
IQR	Interquartile range
ECoG	Intraoperative Electro-Corticography
LGS	Lennoux-Gastaut Syndrome
LC	Locus Coeruleus
LFS	Low Frequency Stimulation
MRI	Magnetic Resonance Imaging
MEG	Magnetoencephalography
MCT	Medium-Chain Triglyceride
NA	Noradrenaline
NC	Nucleus Coeruleus
NTS	Nucleus Tractus Solitarius

OSA	Obstructive Sleep Apnea
OR	Odds Ratio
py	patients per year
PTE	Positive Transfer Effect
PET	Positron Emission Tomography
PMA	Premarket approval application
PNES	Psychogenetic Non-Epileptic Seizures
PG	Pulse Generator
QOL	Quality of Life
RNS	Responsive Neurostimulation
SE	Status Epilepticus
SEEG	Stereoencephalography
SUDEP	Sudden Unexpected Death in Epilepsy
SGE	Symptomatic generalized epilepsy
T	Tesla
TNS	Trigeminal Nerve Stimulation
VNS	Vagus Nerve Stimulation

1. INTRODUCTION

1.1. EPILEPSY: EPIDEMIOLOGY, MANAGEMENT AND MEDICALLY RESISTANT EPILEPSY.

Epilepsy is a frequent neurological disease characterized by the tendency to have recurrent seizures and by the neurobiological, cognitive, psychological and social consequence of this condition (1). The International League Against Epilepsy (ILAE) created a practical definition of epilepsy, which is more useful than the previous definition. The new definition defines epilepsy as cases with two or more seizures in more than twenty-four hours. The actual worldwide accepted definition follows the subsequent statements: 1. At least two unprovoked (or reflex) seizures occurring >24 h apart. 2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years. 3. Diagnosis of an epilepsy syndrome (2).

Epilepsy affects approximately 1% of the population (3), especially prevalent in the infant and elderly populations (4,5). A study published by Simpää et al. showed that the epilepsy incidence in children was decreasing between 1986 and 2002. However, the incidence rate is increasing in the elderly population (6). Concerning this incidence increment, Besocke et al, published research highlighting notable growth in epilepsy rates as populations gets older. Between the ages of 40-45 the incidence is 40 cases per 10^5 habitants, between the ages of 60-65 the incidence is 80 cases per 10^5, and in cases older than 80 years-old the incidence is 140 cases per 10^5 (7).

Epilepsy is a disease in which the seizures are an expression of the condition. Epileptic seizures are ephemeral signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain (3). The seizures are the result of an imbalance between inhibitory and excitatory influences (8). In some cases the seizures are caused by a loss of inhibition and in other cases an increase of excitation. The International League Against Epilepsy (ILAE) in 1993 made an important distinction dividing the seizures as a provoked or unprovoked seizure (9). A provoked seizure is when there is an acute condition that

can cause seizures, and if the cause is corrected the risk of seizures disappears. The second type, unprovoked seizures, is when no clear condition causes them. Another important distinction is non-epileptic seizures or psychogenic non-epileptic seizures (PNES). In this case, the patient presents with symptoms or an event that may be similar to a seizure however the episode does not originate from a misbalance of brain excitability.

Recently the ILAE updated the epilepsy etiology classification to make it clearer. The etiology was divided into: structural, genetic, infection, metabolic, immune and unknown (10). An important feature of seizures is the way it presents without distinction of the epilepsy etiology. The symptoms and signs associated with a seizure are called seizure semiology and it is related to the brain region where the abnormal discharge originated. The seizures are classified according to the first symptom-signs at onset, considering focal, generalized or unknown (11). It is described as a focal seizure when the seizure originates within networks limited to one hemisphere. In the case of generalized seizures, they arise within rapidly engaging bilaterally distributed networks (12). In **figure 1** there is the classification of the type of seizures. The seizure type informs which type of epilepsy the patient has. If the patient just has focal onset seizures, the epilepsy type will be focal. But the focal onset seizure can progress to a bilateral tonic-clonic with the evolution of the seizure, however investigating the onset of the seizure is an important step toward to defining the epilepsy type. In the case of generalized seizures, the patient has generalized epilepsy, and the cases that are unknown at the onset, are classified as unknown. In cases with unknown epilepsy it is recommended to admit the individual to an Epilepsy Monitoring Unit (EMU) to investigate the type of epilepsy, especially if they don't respond to antiseizure drugs (ASD). It is important to keep in mind that not all patients fall into one category or seizure type. A mix of two types of seizures is not uncommon.

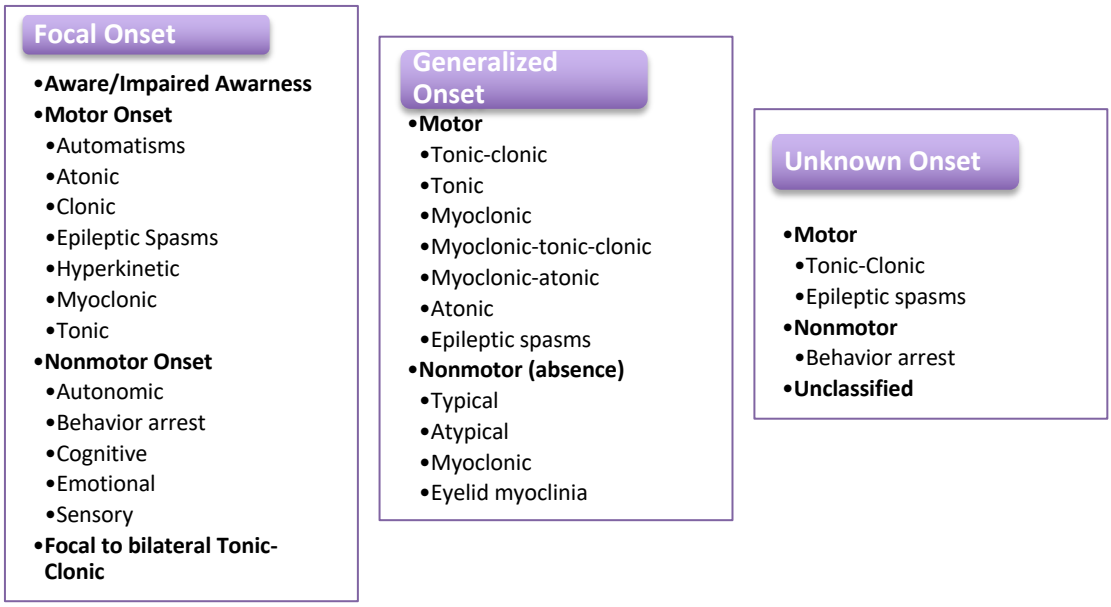


Figure 1. Type of seizure classification using the updated version of the ILAE (2017) (11).

The first step to diagnose epilepsy is the clinical suspicion. It can be an "event" compatible with a clinical seizure. For that reason, in the clinic a complete and detailed anamnesis is required with information about risk factors for seizures (specifically perinatal problems, febrile seizures, meningitis-encephalitis, traumatism, toxics and family history of seizures). Another important piece of information will come from the description of the signs and symptoms that the patient experiences at the beginning of the seizure, as well as during and after the seizure (known as semiology). Frequently, the patients are not able to describe what happened during seizures, for that reason an external observer, who may be a relative, friend, co-worker, teacher, etc., can provide a description of the details. All patients should be asked about their mood, sleep problems and memory. Concerning the seizures, it is important to ask the age of onset, the frequency, the duration, when seizures occur (sleeping, awake, working-school, etc.), if there is any specific trigger or if they relate the seizure to something. The neurological examination is normal in many cases, and it can be a clue about the etiology or localization of the epileptogenic zone (EZ). Finally, it is necessary to think about seizure mimic disorder to avoid the wrong epilepsy diagnosis, and the associated features of ASM, side effects,

stigma, personal limitations (loss of driving license, job, etc.) and find the accurate diagnosis.

If the history is compatible with epilepsy, the next step is to try to find the cause of the epilepsy. To that end, we should order complementary studies. The first one is the EEG, using the International 10-20 system (13). The interictal epileptiform discharges (IED) presence is highly correlated with the diagnosis of epilepsy (14). This test is specific, showing abnormalities suggesting epilepsy in around 2% of the healthy population (0.1-6.6%) (14, 15, 16, 17, 18). However, in just 50% of the routine-EEGs the patient will show IED. With two EEGs the prevalence of IED will increase to 85%, with similar results in a single sleep recording, and 90% with four EEGs (19). When reviewing these numbers, it is necessary to accept that if the clinical suspicion is high, even if the EEG is normal, epilepsy diagnosis can be done. The next important investigation is neuroimaging. The Magnetic Resonance (MR) is preferred, with thin slices, especially in the temporal regions, including coronal sequences with T2 and FLAIR (less than 3 mm) and T1 (1mm) (20).

Epilepsy is a chronic disease that requires to be treated in order to avoid further seizures. In the market there are currently more than 21 ASM. In the last twenty years the number of ASM has increased substantially. There are eight ASM from the second generation and six from the third generation (Please see the **table 1**) (1, 21, 22, 23). All of the ASM have side effects, although the new generations have a better profile, especially concerning long-term side effects. The ASM prescribed needs to have the best profile for the patients, taking into consideration the possible side effects, the pharmacokinetics, the comorbidities, other special conditions, such as women of childbearing age and elderly patients, and always use the minimum effective dose (24).

Mechanism of Action	1st ASM Generation	2nd ASM Generation	3rd ASM Generation
Sodium Chanel Inhibition	**CBZ, PHT** (ETX, VPA, BZD, PB)	**LMT, OXC**, TPM, ZNS (GBP, FLB)	**RFM, LCM, ESL**
Calcium-L Chanel Inhibition	CBZ	TPM, FLB	
Calcium-N, P/Q Chanel Inhibition	(BZD, PB, PHT)	**GBP, PGB**, LTG, OXC, ZNS, (LEV)	
Calcium-T Thalamic Chanel Inhibition	**ETX**, (VPA)	**ZNS**	
Potassium Chanel Activation	(CBZ, ETX)	OXC, TPM	**RTG**
GABAergic facilitation	**BZD, PB**, VPA, (PHT)	**VGB, TGB**, GBP, FLB, TPM, (LEV, ZNS)	Estiripentol
Glutamatergic inhibition	PB, CBZ, VPA, (PHT)	TPM, FLB, LTG, GBP, OXC, PGB, VGB, (LEV)	Perampanel
SV2A -related		LEV	Bivaracetam

Table 1. Classification of antiseizure medications by mechanism of action and generation type. Bold: Main mechanism of action. Non-Bold: Secondary mechanism of action; Brackets: possible mechanism of action or in high ASM concentrations. ASM: Antiseizure drugs; BVR: bivaracetam; BZD: benzodiazepine; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; RTG: retigabine; TPM: topiramate; VPA: valproic acid; VGB: Vigabatrin; ZNS: zonisamide (359).

The optimal management is with one ASM and at the lowest effective dose. Around 49% of the patients will become seizure free after the first ASM. Up to 37% will respond to the second ASM and with each additional ASM 3-5% of patients have control over their seizures (25).

Around 20-30% of focal epilepsy and 5-10% of generalized epilepsy will not respond to any ASM (26). It is considered medically resistant epilepsy (MRE) when the patient does not become seizure free after ASM trail of at least two ASM, which have been used for enough time, with appropriate indication and sufficient doses to see improvement. One is considered seizure free when the seizure free period is three times longer than the longest period without seizures (27).

Patients with epilepsy have a higher risk of chronic conditions (28, 29), lower quality of life (evaluated by QOL) and lower health-related quality of life (evaluated by HRQOL) (30, 31). An important mention needs to be made concerning the psychiatric comorbidities. It has been shown that the lifetime prevalence of psychiatric comorbidities, including major depressive disorder, bipolar disorder, dysthymia or cyclothymia, is 34.2% compared with 19.6% in the general population. If we make specific mention of major depression disorder, the prevalence is 24.4% and the lifetime prevalence is 17.7% (32). There are some publications that refer to the bidirectional relation between epilepsy and psychiatric disorders, showing that epileptic patients have a higher risk of developing depressive disorders and patients with primary depressive disorder have a higher risk of developing epilepsy than the general population (33-38). The frequency of suicide and suicide attempts are greater than in the general population. The estimated risk of suicide and suicide attempts in patients with epilepsy is 5-14.3% and 6-25 times higher in people with temporal lobe epilepsy, compared to the general population (39-40). As a consequence, all these problems that the patients with epilepsy must face could complicate social situations. In general, these patients have a tendency to sway toward lower incomes (30, 41, 42, 43), obtain lower educational achievement, are less likely to have full-time employment or to be currently working (28, 41, 42) and receive high levels of stigmatization (44, 45).

The population with MRE is characterized by frequent and uncontrolled seizures, without responding to ASM. Taking into consideration the limitations of the general epileptic

population, individuals with less seizure control have, a higher risk of domestic accidents, traumatism, hemorrhages, fractures, status epilepticus, higher doses of ASM resulting in more side effects, worse cognitive function, more frequent mood problems, sudden unexpected death in epilepsy (SUDEP), and many other issues. The increased morbidities lead to frequent visits to emergency rooms, frequent visits to the clinics, frequent visits to the family physicians, decreased quality of life of patients, hospitalizations, and increased health costs (30, 31). Seizure control tries to offer a better quality of life with limited complications from the disease and the treatment (46, 47).

Another important fact of MRE is the persistence of seizures and pathophysiological changes in brain areas where the EZ and seizure propagations occur. There are some studies that show, in some cases, persistent electrographic seizure activity (electrographic seizures and the continuous state as electrographic status epilepticus) is able to trigger seizures in other areas surrounding the EZ and also in other distant parts such as the homotopic contralateral secondary site, with a positive transfer effect (PTE) (48, 49, 50).

For these reasons, patients with MRE need to be considered for other therapeutic options in addition to solely ASM. In the past, other options, such as epilepsy surgery, were considered for some epileptic patients, if the patient experienced MRE for many years (51). However, more recent approaches suggest the opposite. As soon as the patient is diagnosed with MRE, the patient should be referred to a Comprehensive Epilepsy Centre (52). The patient with MRE needs to be referred to an Epilepsy Centre and be evaluated by an epileptologist. One of the first things that is required is to admit the patient to an Epilepsy Monitoring Unit (EMU) to characterize the type of seizures, define if the patient has focal, generalized or both, identify the zone of onset of the seizures (epileptogenic zone, EZ) and in some cases the real seizure frequency. During that admission the patient will be monitored with video-EEG telemetry using the International 10-20 system for several days or even weeks, until all the information required is obtained (13). During that time the aim is to obtain information from patient's EEG while the patient is awake,

resting, asleep, as well to capture seizures. In some cases, a reduction of the ASM is needed to obtain seizures.

When considering a MRE patient as a possible candidate for epilepsy surgery, the patient needs to agree with the surgical option. If the patient agrees, the epileptologist will pursue the investigations. There are certain tests that may obtain additional information for the final decision of whether the MRE patient is a good candidate for surgery. The complementary examinations are Positron Emission Tomography (PET), interictal and ictal Single Photon Emission Computed Tomography (SPECT), neuropsychology evaluation (used to find any deficits or localization-lateralization abnormalities especially in visual and verbal memory, speech problem or motor function), higher resolution MRI (3T or even 7T), functional MRI (fMRI) and Magnetoencephalography (MEG) (53). The MRE cases need to be presented in a multidisciplinary epilepsy meeting with epilepsy surgeons, epileptologists, neurophysiologists, neuropsychologists and neuroradiologists to make the best decision, which leads to the best outcome for the patients. Even after all these tests and evaluations, sometimes there is not enough information to support a definitive EZ, which should be resected. If there is not enough information to delimitate the EZ, the next step in the epilepsy management is to implant invasive electrodes, if the patient agrees to that strategy. During the meeting previously described, the team needs to formulate a hypothesis of where the seizures originated. There are different strategies for the invasive evaluation; it could be intraoperative (intraoperative electro-corticography (ECoG)) or extraoperative. The most common extraoperative modalities are strips, subdural electrodes and stereoencephalography (SEEG) (54). After the implantation, in the case of the extraoperative implantation of invasive electrodes, the patient will be admitted to the EMU to try to capture seizures, localize the EZ and confirm the hypothesis. Another useful tool to use with the invasive electrodes is the direct cortical stimulation (DCS). With the DCS it is possible to localize eloquent areas and confirm the hypothesis of where the seizures originate (55, 56).

Once all this information is obtained, it will be discussed again in a multidisciplinary epilepsy meeting to decide if the patient can undergo an epilepsy resection safely. The most relevant insight to consider when making the decision is if the team was able to identify or localize an EZ and the EZ doesn't overlap with eloquent areas. If the EZ is localized in a safe resective area, the decision is expected to be in favour of an epilepsy resection. These resections could be temporal lobectomies, lesionectomies, tumorectomies, etc. With the resection surgery, the chances of being seizure free after the surgery are the highest when compared to the other options that can be offered to treat MRE. Ten years after surgery 65% of patients will remain seizure free and 20% of patients will have improved seizure control (57, 58).

Unfortunately, many cases have bilateral or multiple epileptogenic foci, have the EZ overlapping with eloquent areas, or have an unidentifiable EZ (49). Approximately 4.5% of all the patients with epilepsy and 0.03% of the population could potentially undergo epilepsy surgery (60). Those cases with MRE require other treatment options in addition to solely ASM. The other therapeutic options are palliative surgeries, neuromodulation, cannabinoids, ketogenic diet and trials of experimental antiseizure medications (61). Examples of palliatives surgeries are hemispherectomies and corpus callosotomies (partial or complete). However, the complications of these types of surgeries are higher when the candidates are not young, and the outcome may not change the frequency and/or intensity of the seizures. In the case of the ketogenic diet there are different versions of ketone's ratio (Modified Atkins Diet, Low Glycemic Index Therapy, Medium-chain triglyceride (MCT) diet). Some specific conditions may benefit the patient more than others. For example, myoclonic atonic epilepsy, Dravet syndrome, epilepsies with myoclonic seizures, infantile spasm and some metabolic conditions such as Glucose transporter GLUT-1 deficiency have shown better results (62). There are important contraindications to consider before starting the ketogenic diet, including fatty acid oxidation defects, existing coronary artery or cerebrovascular disease, early family history of strokes or heart disease, recurrent pancreatitis, undiagnosed hepatitis, porphyria,

severe reflux, familial hyperlipidemia, cardiomyopathy and history of renal calculi (63). A 50% seizure reduction is achievable utilizing the ketogenic diet, 32% utilizing the classic diet and 30% utilizing the modified Atkins diet (62, 63). The ketogenic diet is more commonly used in the paediatric population.

1.2. NEUROMODULATION

1.2.1. CONCEPT OF NEUROMODULATION AND BACKGROUND.

Neuromodulation is the process or technology that applies electrical currents, in varying parameters, by means of implanted electrodes to achieve functional activation or inhibition of specific neuronal groups, pathways, or networks (64).

The aim of the neuromodulation is to reduce the seizure frequency, prevent secondary generalization, and minimize risks associated with intractable epilepsy. However, it is less likely to provide seizure freedom compared to epilepsy surgery (65).

The neuromodulation is not a new strategy to treat diseases. However, in the last century it has significantly increased in interest and it has been used to develop new devices and tools for seizure control (66). The first reports of neuromodulation date from the first century AD, the Roman physician Scribonius Largus treated headaches by applying electric torpedo fish to the head. Pedanius Dioscorides, another Roman physician, in 76 AD applied electric torpedo fish to treat patients with epilepsy (67).

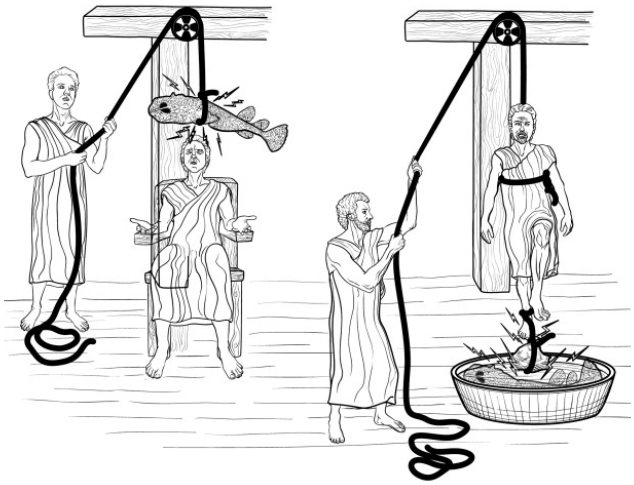


Figure 2. Representation of how the roman physicians, Scribonius Largus and Pedanius Dioscorides, applied torpedo fish on patients with headache/seizures. (Obtained from https://images.app.goo.gl/nQfReSXjCcjBDFVt9).

Many centuries later, in 1791 Luigi Galvani realized the stimulatory effect of electricity on animal tissue (68). In the first part of the nineteenth century Luigi Rolando and Pierre Flourens starting to use electrical stimulation to localize animal brain functions (69, 70). In 1870 Eduard Hitzig and Gustav Fritsch demonstrated that some parts of the animal brain surface produce a response to electrical stimulation (71). This led to the introduction of artificial electrical stimulation on humans by Robert Bartholow (1874), William Richard Gowers (1881), Victor Horsley (1884), Charles Sherrington (1893) and Harvey Cushing (1909) (72-76).

Over several decades, in the twentieth century, Wilder Penfield, Herbert Jasper, and his colleagues made the most important contribution to the effect of artificial electrical stimulation on the human brain, by correlating brain area stimulation with specific responses (77).

Another important finding was that low frequency stimulation caused an increase of the cortical synchrony with pro-epileptic properties. On the other side, the use of high-frequency cortical stimulation must have antiepileptic effects (78, 79).

1.2.2. DEVICES OF NEUROMODULATION

There are different devices with different mechanisms of action; all of them share neuromodulation properties. The most commonly used devices in epilepsy are: Vagus Nerve Stimulation (VNS), Anterior Nucleus of the Thalami Stimulation (ATN-DBS or simply DBS), Responsive Neurostimulation (RNS), and Trigeminal Nerve Stimulation (TNS) (80).

Neuromodulation devices can be classified depending on several features. For example, if the anatomical structure that is stimulated is located inside or outside the central nervous system (CNS). The DBS and RNS stimulates the CNS, and in the VNS and TNS stimulates outside of the CNS. If we classify the devices based on the method of stimulation, RNS is defined by closed loop stimulation, and DBS, VNS and TNS is defined by open loop stimulation (47). However, the VNS model 106SR acts as a closed loop (81). See **figure 3.**

To describe how the most important devices works, it is necessary to describe each one individually. We will focus on VNS, DBS and RNS. The VNS is going to be extensively described in the point 1.2.2.3.

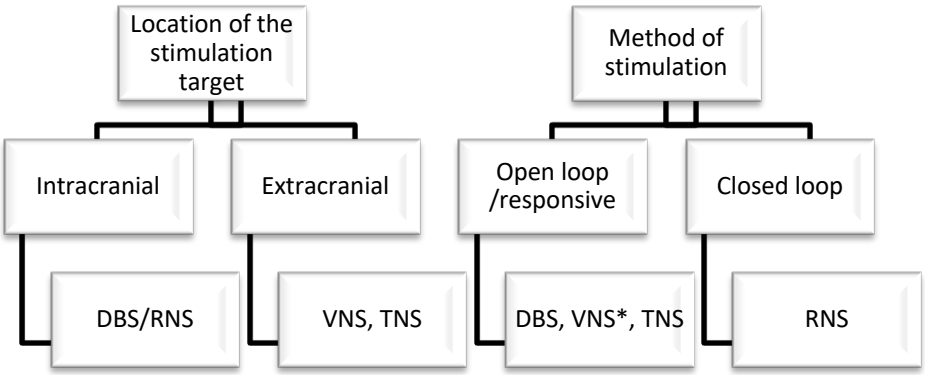


Figure 3. Classification of neuromodulation devices by location of the stimulation target and method of stimulation. DBS: Deep Brain Stimulation; VNS: Vagus Nerve Stimulation; RNS: Responsive NeuroStimulation; TNS: Trigeminal NeuroStimulation. * VNS with the pulse generator 106SR.

1.2.2.1 DEEP BRAIN STIMULATION (DBS)

The DBS has the therapeutic target over the anterior nucleus (AN). The AN belongs to the circuit of Papez, that it is a relay station between amygdala, hippocampus, fornix, mammillary body, cingulate gyrus. It is involved in the seizure propagation. Initial research studies demonstrate that the stimulation or lesioning of the AN pathways had antiepileptic properties experimentally, as well, the application of electrical stimulation over the AN was able to stop the seizures (82, 83, 84). Cooper and Upton in 1985 presented the first report of AN-DBS for the treatment of refractory *complex partial seizures* (82). Studies with the combination of EEG and functional neuroimaging showed the involvement of AN in the initiation and propagation of generalized seizures (85). The use of high lesioning or high-frequency stimulation of AN causes an increment of seizure threshold and a reduction of the epileptic activities (86).

The DBS has a generator, which creates an impulse. The generator is located in the left subclavicular region, as a subcutaneous implantation, and two depth electrodes implanted in both AN of the thalamus (see **figure 4**). This device was approved for the management of medically resistant epilepsy in Europe by the European Commission (EC) in 2010, in Canada in 2012 and in US by the Food and Drug Administration (FDA) recently in May 2018.

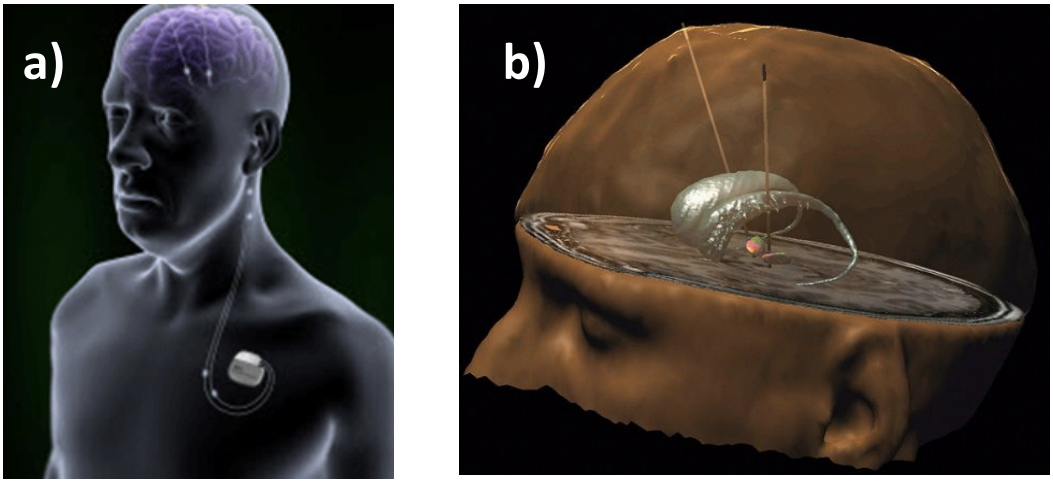


Figure 4.a. Representation of the DBS-AN implantation, with the pulse generator and two depth electrodes implanted in both anterior nuclei of the thalamus. (Obtained from https://www.alzforum.org/news/series/deep-brain-stimulation-surgical-relief-parkinsons-and-beyond) **4.b**. More detailed illustration concerning the localization of the electrodes of the DBS-AN. (Obtained from: www.toledoblade.com/Medical/2008/11/14/Brain-pacemaker-may-hold-promise/stories/feed/index.rss).

Regarding the efficacy of the DBS, the most important trial was published in 2015, the SANTE trial. It included 110 patients. There were two groups at the onset of the prospective study, both were implanted with DBS, however the control group did not have their DBS turned on and the other group did have their DBS was turned on after the implantation. The seizure reduction was 15% in the control and 40% in the second group. In the open label of the study, a seizure reduction of 41% in the first year and 69% after five years was found. The side effects detected during the trial were memory loss related with the alteration of the Papez circuit, vocal cord paralysis and local infection (87).

1.2.2.2. RESPONSIVE NEUROSTIMULATION (RNS)

Penfield and colleagues directed cortical stimulation in different structures as cerebellum, hippocampus, AN of the thalamus and the cortex. They recognized the therapeutic properties of electrical stimulation to supress the epileptiform discharges in humans (88, 89). From this research the RNS was developed.

The RNS is a device in which generator-software is implanted in the skull. One or two depth electrodes with one to four contacts on each electrode are implanted into specific areas related to the EZ (see **figure 5**). The software is able to detect seizures and responds with electrical brief pulses of stimulation to interrupt those patterns and stop the seizures. The stimulation parameters are adjustable in frequency and amplitude. This device also has the storage function, informing the course or response to the device. The

RNS was approved in 2013 by the FDA as adjunctive therapy in patients older than eighteen with focal onset refractory epilepsy.

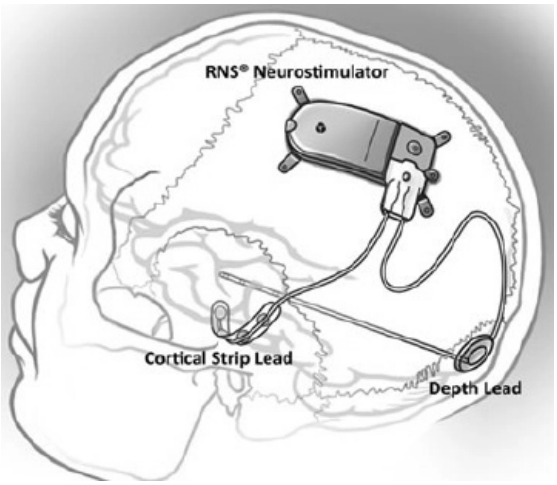


Figure 5. Scheme of the Responsive Neurostimulation (RNS) device, including the software and the depth electrodes. (Obtained from https://www.researchgate.net/figure/A-Illustration-of-the-RNS-System-with-the-neurostimulator-implanted-in-the-skull-and_fig2_333229286).

The first trial using RNS was published in 2011. A total of 191 patients were included in the study with medically resistant focal epilepsy. All of them were implanted with the RNS. For the first twelve weeks, in one group the devices was not turned on (control group) and the other group it was turned on. During this time, the efficacy and safety of the devices were evaluated. During the first 3 months the seizure reduction was 9.4% in the control group and 41.5% in the other. In the open label for the following forty-eight weeks, in both groups the device was turned on. In the first year the achieved seizure reduction was 50 % or more in 44% of patients and in the second year the achieved seizure reduction was 50 % or more in 55% of patients. The most common adverse effect detected was pain in the site of the implantation (15.7%), headache (10.5%) and dysesthesias (6.3%), without a statistical difference between both groups. The complications found were intracranial haemorrhage (4.7%) and implant/incision site infection (5.25%) (90).

1.2.2.3. VAGUS NERVE STIMULATION

1.2.2.3.1 CONCEPT

Vagus Nerve Stimulation is a neuromodulation device that triggers a chronic intermittent electrical stimulation of the left vagus nerve, delivered by a programmable pulse generator implanted in the left upper part of the chest.

The VNS was approved by the EC in 1994 and in the US in 1997 for the treatment of medically resistant focal onset seizures in patients twelve years old or older, and also generalized by EC. In 2017, the VNS was approved by the FDA to be implanted in patients older than four years old.

1.2.2.3.2. ANATOMICAL CHARACTERISTICS

The *vagus nerve* (X cranial nerve) is considered the longest nerve of the cranial nerves. It Latin name is originated from the Latin root and means “wandering”. This is related to its long path from the brain steam to arrive to the thorax and abdomen arriving to the colon. The vagus nerve originates from several filaments in the medulla, between the inferior olive and the inferior cerebellar peduncle, just below the glossopharyngeal nerve (IX cranial nerve). All the nerve filaments gather (together) in the subarachnoid space and leave the cranial cavity through the jugular foramen (91). After that, it descends through the carotid sheath, located between the carotid artery and the internal jugular vein. Interestingly at this point the left and right vagus nerve is different. The right vagus nerve leaves the root of the neck and enters to the thorax anteriorly to the right subclavian artery. Once in the thorax, the nerve’s path goes medial to the arch of the azygous vein and after posterior to the root of the right lung. Its branches are distributed to the pulmonary, esophageal and cardiac plexus. In contrast, the left vagus nerve trajectory (path) is located in the left side of the aortic arch and posterior to the root of the left lung.

After that, the nerve gives branches to the thorax plexus. Another distinguishing feature is the cardiac innervation (91). The right vagus nerve innervates the sinoatrial node and the left the atrioventricular node (92). This is an important physiological consideration, the vagus nerve stimulator is implanted in the left side, and not the right, because the left vagus nerve has most of the parasympathetic branches for the ventricles and the right vagus nerve has most of the parasympathetic branches for the atrial region (93). The stimulation of the right vagus nerve produces more deceleration compared to the left vagus nerve stimulation (94). See **figure 6.**

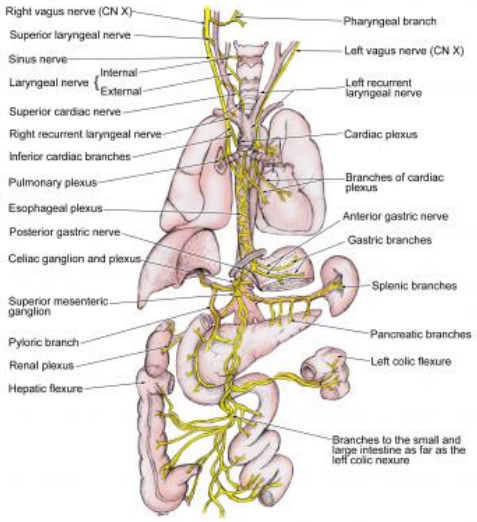


Figure 6. Vagus nerve (left and right) and its branches.
(Obtained from https://www.anatomynote.com/human-anatomy/nerves-system/vagus-nerve-innervation-in-the-human-body-diagram/).

The vagus nerve is a parasympathetic mixed nerve, containing approximately 80% afferent sensory fibers and 20% efferent fibers (95, 96). The afferent fibers bring viscerosensory information from the receptors in the abdominal viscera, esophagus, heart, aortic arch, lungs, bronchia, thachea and larynx (91). Other afferent fibers carry somatic sensation (gathered from an small area of the skin and near the external ear) and taste (from the receptors in the periepiglttal pharynx) (97). The neurons of the afferent fibers are located in the jugular ganglion and nodose ganglion, just below the jugular foramen (98). Mostly of these afferent fibers make synapses to the dorsal nucleus in the brain stem, including nucleus tractus solitarius (NTS), spinal trigeminal nucleus, medial reticular formation, area postrema, dorsal motor nucleus of the vagus nerve and ambiguus nucleus (99, 100, 101). The NTS is a relay station and sends information to both cerebral hemispheres, amygdala, hypothalamus, thalamus, parabrachial nucleus, locus

coeruleus and accumbens (96, 97, 102). Using those pathways, the NTS can have a direct influence over the activity of the extrapyramidal system, ascending visceral fibers and autonomic central system (103, 104). Also, it connects to the amygdala allowing it to modulate access to the amygdalo-hippocampal complex and entorhinal cortex of the limbic system and can potentially control epileptic seizures (105).

The parasympathetic efferent fibers of the vagus nerve arise from the dorsal motor nucleus of cranial nerve X and ambiguus nucleus. These efferent fibers make synapsis with the parasympathetic ganglion near the organ's targets, like pharyngeal and laryngeal muscles and most of the thoraco-abdominal viscera arriving to the splenic flexure (98).

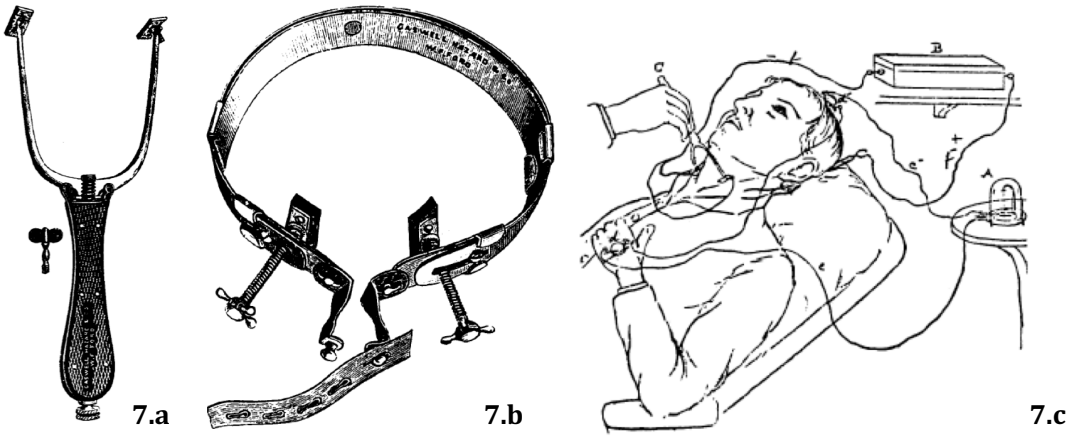
1.2.2.3.3. HISTORICAL BACKGROUND

The history of vagus nerve stimulation is in close relation with the development of neuromodulation, with some specific facts regarding the VNS that need to be highlighted.

During the eighteenth century, Parry was the first person to observe facial flushing, carotid bounding, and cranial pulse during seizures and headaches. He stated that seizures and headaches are related to excessive cerebral blood flow (CBF), which he called "venous hyperaemia" (106). This theory led him to conduct several experiments using manual compression of the carotid artery, decreasing CBF and decrement in the heart rate, decreasing the cardiac output and the cerebral flow, and causing the suppression of seizures and headaches (107, 108, 109).

The American neurologist James L. Corning realized that manual carotid compression during seizures was problematic due to the violent contraction of the cervical muscles during an epileptic seizure (106). For that reason, in 1880 he developed a small two-prolonged, fork-like instrument and applied it to the carotid, which produced a temporal compression of the carotid as an abortive treatment for seizures (110, 111, 112, 113).

That instrument was called the "carotid fork" (**figure 7.a**). The side effects detected were mydriasis, ptosis, drowsiness, dizziness, confusion, syncope and facial pallor (114). Dr. Corning later developed an adjustable belt-like instrument to encircle the neck (the "carotid truss") as an epilepsy prophylactic preventive device to produce more prolong compression for hours or even days (**figure 7.b**) (110, 111). Dr. Corning stated the stimulation of the vagus nerve produces a decrease in seizure frequency. In 1883, he combined the carotid compression devices with another device, similar to a vacuum, applied to the lower body, to cause cardiac output decrement, and decreasing cerebral blood flow (110, 115). Just one year after, he combined the carotid compression and electric transcutaneous stimulation of the vagus nerve to develop the first prototype of the actual VNS (**figure 7.c**) (112).



7.a **7.b** **7.c**

Figure 7: **7.a)** Corning "Carotid fork" used by Corning to apply the electrical stimulation over the vagus nerve (82). **7.b)** Corning "carotid truss" as a seizure preventive device (82,84). **7.c)** How the stimulation was applied to the patients (115). (Obtained from: **7.a)** and **7.b)** www.sciencedirect.com/topics/nursing-and-health-professions/digital-compression; and **7.c)** n.neurology.org/content/58/3/452).

Dr. Corning was aware of the possible complications related to the therapy, especially the excess of compression. He described the importance of accurate control of the strength

of the current and the degree of pressure to avoid dizziness and syncope (116). Corning stated that VNS was a promising therapy and may prove of value in the treatment of epilepsy, but he had a limited experience of its' efficacy in epileptic patients. He was lacking the number of patients treated with that device needed to establish efficacy (117).

Although Corning claimed a dramatic benefit from the VNS, the results of this device in epileptic patients were not producing consistent positive results. Corning's VNS treatment was not well received; his ideas and prototypes were forgotten in the late 19th century and were not rediscovered for many years (106, 118).

At the beginning of the twentieth century there were several experimental studies using animals to evaluate the possible utility of the stimulation of the vagal nerve to treat epilepsy. It was not until 1938 that the stimulation of the vagus nerve was taken seriously as a potential treatment for epilepsy. This was a consequence of a study that showed the stimulation of the central portion of the vagus nerve in cats caused an increment of electrical potentials at the orbital surface of the frontal lobe (119).

Several years later, in 1951 Dell and Olson stated that the stimulation of the vagus nerve produced a slow wave in both the amygdala and rhinal sulcus as well as caused desynchronization in the EEG (120, 121). Experiments with cats showed the complete elimination or significant reduction in the spontaneous cortical spindles using repetitive central vagal nerve stimulation (122). The ability of EEG synchronization or desynchronization to apply repetitive VNS was also demonstrated by Chase et al. in 1960 (123, 124).

The next step in the evolution of the actual VNS was Zabara in 1985, when he hypothesized, in animal experiments, that seizures cause hypersynchronization of the brain activity and this hypersynchronization could be prevented by activation of specific afferent neurons. For that reason, he used vagus nerve stimulation to prevent or control

the motor and autonomic components of seizures in seizures induced chemically (125, 126, 127, 128).

It was in 1988 when the first vagus nerve stimulation was implanted in humans for the treatment of medically-resistant epilepsy, which was conducted by Penry et al. (129). Afterwards, there were worldwide clinical studies to evaluate the efficacy and safeness of the VNS treatment system (the NeuroCybernetic Prosthesis) for the treatment of medically resistant epilepsy, especially by the Cyberonics (58, 62, 130, 131, 132, 133, 134, 135, 136).

The European Community approved the VNS for seizure prevention and control in 1994. Three years later, in 1997, the US Food and Drug Administration approved the VNS as an adjunctive therapy in adults and adolescents over 12 years of age with focal onset (previous classification was partial onset) seizures with medically resistant epilepsy for reducing the frequency of seizures.

1.2.2.3.4. MECHANISM OF ACTION

There are many studies demonstrating the efficacy of the VNS, however there is not a clear explanation of how the mechanism of action is able to decrease the seizure frequency in patients with MRE. There are several hypotheses that attempt to explain this.

Taking into consideration the anatomy and the ramifications of the vagus nerve, the efficacy of the VNS could be related to the afferents fibers that reach the brain and the indirect effect through the efferent fibers (137). The principal projection of the VNS is the NTS, an important release station of the vagus nerve. Other important release stations of the vagus nerve are ambiguus nucleus, spinal trigeminal nucleus, pontine reticular formation, area postrema, dorsal motor nucleus of the vagus nerve, and cuneatus nucleus

(99, 100, 101). From these nucleuses, the vagus nerve connects with the limbic system, hypothalamus, thalamus, and insular cortex. The NTS has projections that arrive to the encephalic nucleuses, locus coeruleus (LC), raphe nuclei, reticular formation, and other brainstem nuclei (121, 138, 139,140). The LC is related to the release of norepinephrine and the nuclei raphe with the release of serotonin. These neurotransmitters modulate the epileptic seizures' threshold through several factors, including the release of gamma acid butyric by the interneurons. Using vagus nerve stimulation, the levels of noradrenaline (NA) and serotonin increase in the LC and raphe nuclei. These changes in the concentration of neurotransmitters are considered a critical element in the seizure-suppressing effect of the VNS (141, 142). Krahl et al. used cats with a chronic and acute lesion in the locus cerelous and applied VNS therapy. It was not effective and stated that the seizure suppression efficacy of the VNS was related to the NA release (143). Similarly, the NTS also has projections to the amygdala, particularly the basolateral amygdala. As the mechanism involved with LC and efficacy of the seizure control, the VNS triggers an incremental release of the NA in the amygdala.

Another nuclei that has been related to the VNS mechanism of action is the reticular activating system. McLachlan et al. in 1993, used stimulation of vagus nerve in rats, to show that VNS decreased the cortical epileptiform activity indirectly by influencing the reticular activating system (144). The study discovered, through EEG findings, that the only part of the seizures affected by the VNS were in the chronic phase (144). The interictal spike frequency reduction was 33% during the first twenty seconds of stimulation ($p < 0.001$) and the reduction of the seizure duration was 30.2 +/- 15.7 s to 5.0 +/- 1.8 s ($p < 0.01$) (144). See **figure 8.**

Several studies using neuroimaging showed bilateral blood flow alteration while the VNS was active. Herny et al, conducted studies using PET to evaluate the change in the brain blood flow, especially in the right thalamus, bilateral posterior temporal cortex, left putamen nucleus and left cerebellum hemispheres (98, 145). There is a decrement in the

blood flow bilaterally in the amygdala, hippocampus and cingulate gyrus. There is an increment in the in the blood flow bilaterally in the thalamus, hypothalamus, and insular cortex (146). Herny et al. stated that the bilateral increment of blood flow in the thalamus was correlated with seizure frequency reduction (147). In similar studies using SPECT, Van Laere et al. showed a hypoperfusion during the initial states of the vagus nerve stimulation in the left thalamus, parahippocampas circumvolution and right hippocampus. The VNS causes a hyperperfusion in the left thalamus during the chronic state (148). Changes in the amygdala and the right hippocampus after a chronic VNS stimulation were predictive of the clinical efficacy (148, 149). Even if it is not the case that some of the seizure spread and propagation are in those regions, this mechanism of action does not completely explain how the VNS works to reduce the seizures.

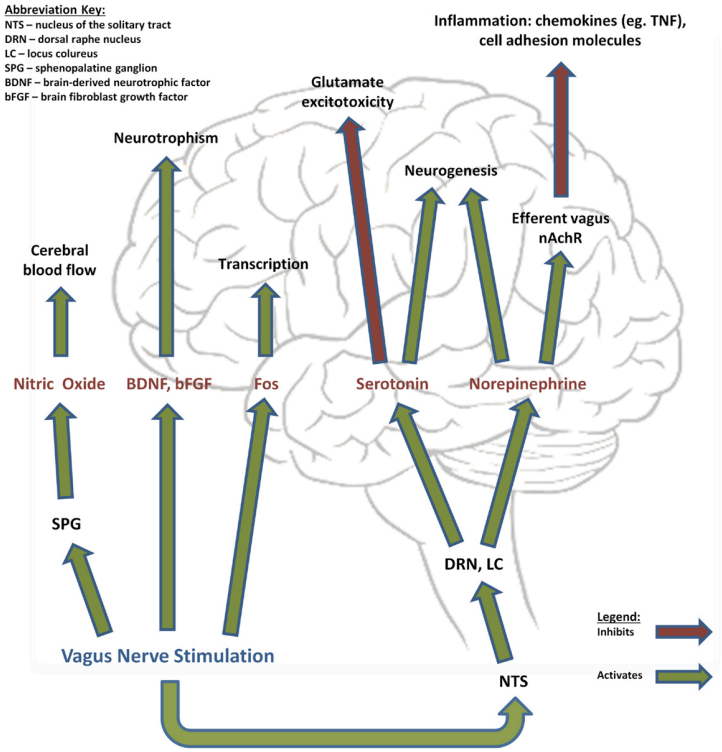


Figure 8. Different mechanism of actions related to the efficacy of VNS. (Obtained from https://www.frontiersin.org/articles/10.3389/fneur.2014.00107/full).

The neurotransmitters are an important factor in the epileptogenesis. Previously, it has been described as an increment in the NA in the amygdala, secondary to the probable effect of the NA release by the LC or/and by the NTS (141, 142). It is also noticed that

patients with VNS have an increment of the Gamma Ammino-Butiric-Acid (GABA) in the cerebrospinal fluid (CSF) and higher density of receptors GABA-A in the hippocampus, compared to the control group (150). The studies of Ben-Menachem et al. and Hammond et al. found higher levels of homovanillic acid (HVA), 5-hydroxyindoleacetic acid, phosphoethanolamine, ethanolamine, serotonin and GABA and lower levels of aspartate (151, 152). However, only the phosphoethanolamine was statistically significant in the seizure control. The phosphoethanolamine is a precursor of the phospholipid membrane. Milby et al. suggested that an incremental in phosphoethanolamine in patients with good responses to the VNS was related to an incremental of the neuronal membrane replacement, membrane stabilization and, neuronal protection effect (153). Another study showed that only the HVA in CSF increases significantly after the use of VNS (154).

Interest in immunology and neuroscience has grown over the years. In the peripheral tissues there are neuronal guidance proteins that contribute to the local control of the leukocytes' migrations and inflammation (155, 156, 157). Neutrin-1 is one the neuronal proteins that regulate the resolution of the acute inflammation (158). Mirakaj et al. proved that the vagus nerve regulates the netrin-1 and pro-resolving lipid mediators in a bidirectional fashion to stimulate the resolution of the inflammation (121). VNS will increment the production of the proinflammatory citokines. In the immune system there is a reflex circuit called, "inflammatory reflex", which signals travel through the vagus nerve to inhibit the monocyte and macrophage production of tumour necrosis factor (TNF), IL-6 and other cytokines (159, 160). Animal models of stimulation of the vagus nerve trigger the production of acetylcholine in the spleen and other tissues through the stimulation of the choline acetyltransferase-positive T cells (161). The union of the acetylcholine to the α-7 nicotinic acetylcholine receptors (α7nAChR) triggers the production of cytokines by monocytes, macrophages and stromal cells (159, 162, 154). The electrical stimulation of the vagus nerve enhances the inflammatory reflex signalling and reduces the cytokine production. This finding suggests that the VNS is able to attenuate disease severity in experimental models of endotoxemia, sepsis, colitis and

preclinical animal models of inflammatory syndromes (159, 163, 164, 165, 166).

In some animal models using high frequency and intensity stimulation of the vagus nerve caused desynchorinization of the brain rhythms (153, 167). However, these results haven't been seen in the EEG of humans (168, 169). There are also no studies that demonstrate a reduction in the interictal paroxystic activity in epileptic patients (124, 125, 144, 170, 171).

1.2.2.3.5. TECHNICAL ASPECTS

1.2.2.3.5.1 PARTS OF THE VNS

The vagus nerve stimulator is a device implanted in the left vagus nerve. The VNS has different components. The five components are: the pulse generator or stimulator, the VNS lead, the computer, the programming wand and the magnet. The first two elements are implanted in the patient and the rest are external components of the device.

1. One of the most important part of the VNS is the **Pulse Generator or Stimulator (PG).** It is implanted under the skin on the left side of the chest. The PG is the size of a Canadian two-dollar coin or a two euro coin. The PG uses a lithium carbon monoflouride battery and is housed in a hermetically sealed titanium case, with a similar structure to pacemakers. The generator contains a program that is calibrated from the external devices using radiofrequency signs (!). The PG has a number of programmable settings including pulse width, magnet-activated output current, output current, magnet-activated ON time, signal frequency, magnet-activated pulse width, signal ON time and signal OFF time. The PG is in charge of sending signals through the electrodes of the lead to the brain by way of the left vagus nerve. Another feature of the PG is its' capability to supply information

about its' operating characteristics, such as parameter settings, lead impedance and history of magnet use to the software when it is interrogated.

The generator is the part that is the most evolved, from its size to the programs that it uses for the stimulation. There are a total of eight different PGs. The most important change over the years is the reduction of the size until Model 103. After that its' size increased again.

VNS Therapy® System Model 100 Generator
VNS Therapy® Pulse Model 101 Generator
VNS Therapy® Pulse Model 102 Generator
VNS Therapy® Pulse Duo Model 102R Generator
VNS Therapy® Demipulse®, Model 103 Generator
VNS Therapy® Demipulse® Duo, Model 104 Generator
VNS Therapy® Aspire HC®, Model 105 Generator
VNS Therapy® Aspire SR®, Model 106 Generator
VNS Therapy® SenTiva

The models 102, 103 and 104 had a double pin to connect to the lead. Newer models are back to single pin. Model 100 and 101 are no longer available. The PG-VNS models are:

The technology of the PG has been similar for years, however with the model 106SR there was a significant change. This model has a special feature, AutoStim (Automatic Stimulation Mode or AutoStim) as well as the Magnet and Normal Modes. The AutoStim is a verify heartbeat detection system. The increment of the heart rate is a common finding in patients with epilepsy, specifically with focal epilepsy, occurring in approximately two thirds of cases (172). For that reason, technology was developed that uses tachycardia as a trigger to deliver the stimulation. The AutoStim has onboard heartbeat sensing technology that is able to detect and monitor the heart rate change above baseline from 20 to 70%,

although 30-40% is more commonly used. When we use the 20% increased heart rate, the system is more sensitive but not specific. On the other side, if the AutoStim is programmed to detect 70%, it is going to be really specific, but it can miss many increments in the heart rate. The detection algorithm establishes a baseline heart rate over a period of approximately five minutes and a near-term (foreground) heart rate for comparison (81, 173). In real time, the AutoStim keeps comparing the average heart rate (previous five minutes) with actual heart rate average in the lapse of time of 5 seconds. If the current heart rate exceeds the background heart rate by the threshold programmed by the clinician (20-40%), the VNS is going to provide an extra stimulation. With this extra stimulation, the system is able to replace and reprogram the next programed stimulation towards the left in 30-45 seconds, avoiding receiving two stimulations (AutoStim and the programmable to close in time). The parameters of that extra stimulation are set by the physician and can be different than the standard stimulation or the one provided by the magnet.

The US, Canada and Europe approved a new device, Model 1000-SenTiva. This device incorporated new technology from the previous SR106 model. The external tools that use this device are wireless, making it easy to change parameters. Another interesting feature of this device is that the titration schedule can be programmed during the visit with the neurologist, avoiding the need to come to clinic as regularly (no longer needing to come every 15 days to 1 month). It incorporates software that allows it to have two independent sets of parameters, one for day and one for night, to customize and deliver based on each patient's needs. This is particularly important for the patients that have only nocturnal or daytime seizures. Model 1000-Sensitiva is also MRI compatible (1.5 and 3 Tesla). In addition, the device is able to collect and log events including the patients' body position and heart rate changes (bradycardia and tachycardia) depending of the parameters set by the physician. See **table 2** and **figure 9**.

Generator Model Name	101	101	102 Pulse	102 Pulse Duo	103 Demi-pulse^{R}	104 Demipulse^{R} Duo	105 Aspire HC	106 AspireS R	SenTiva
Lead compatibility	Single pin	Single pin	Single pin	Dual pin	Single pin	Dual pin	Single pin	Single pin	Single pin
Manufactured since	1997	2000	2002	2003	2007	2007	2011	2015	2019
Thickness	13.2 mm	10.3 mm	7 mm	7 mm	7 mm	7 mm	7 mm	7 mm	6.9 mm
Volume	31 cc	26 cc	14 cc	16 cc	8 cc	10 cc	14 cc	14 cc	8 cc
Weight		38 g	25 g	27 g	16 g	18 g	25 g	25 g	16 g
Battery Capacity			3,3V 1.7 Amp-hour	3,3V 1.7 Amp-hour	3,3V 1 Amp-hour	3,3V 1 Amp-hour	3,3V 1.7 Amp-hour	3,3V 1.7 Amp-hour	3,3V 1 Amp-hour
Magnet	+	+	+	+	+	+	+	+	+
System	Open Loop	Open Loop	Open Loop	Open Loop	Open Loop	Open Loop	Open Loop	Close Loop	Close Loop
AutoStim	-	-	-	-	-	-	-	+	+
Price ($)	9200	10950	15975	15975	18000	18000		30000	30000

Table 2. This table illustrates the differences in technical characteristics between PGs.

Figure 9. Image of the shape of the VNS devices.

Some patients implanted with VNS will move to another city and won't know the PG model and the model of PG is not registered in the clinical notes. It is possible to identify the PG model using x-ray. **Figure 10** shows the appearances of the different PG units.

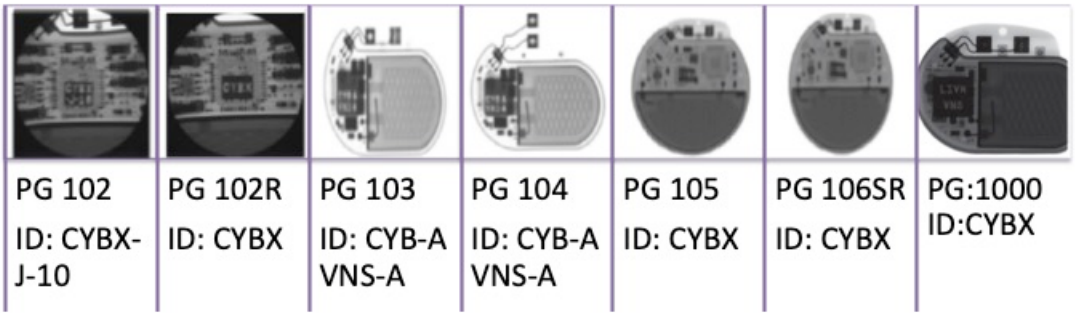


Figure 10. Different appearances of the PG using x-ray. (Obtained from: file:///Users/sean2/Downloads/VNS%20Therapy%20System%20Physician's%20Manual%20(Non-US).PDF and http://www.neurosurgeryresident.net/E.%20Epilepsy%20and%20Seizures/E23.%20VNS.pdf).

2. The second component is the electrode wires, the **leads**, which are attached directly to the left vagus nerve. The bipolar electrical lead connects the vagus nerve to the generator or PG. The lead is made up of the pin that connects on one side to the generator and the helices that contain the stimulation electrodes and anchor tether on the other end. The stimulation electrodes have two terminals made from platinum. The stimulation electrodes are attached to a silicon helicoidally structure with three helical coils one electrode positive (cathode) and one electrode negative (anode). The anchor belongs to the terminal part of the electrode and allows the fixation of the electrode to the vagus nerve. There are thin cables going over the helicoid on the distal side. These thin cables allow the manipulation of these filaments without damaging the platinum contacts.

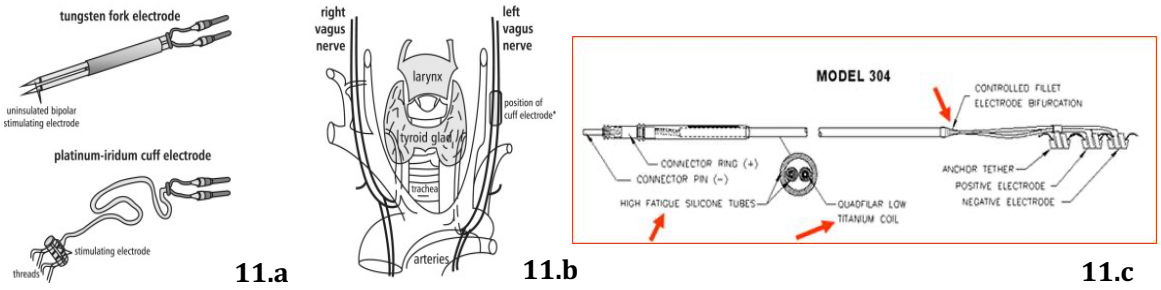


Figure 11: **11.a.**: Representation electrodes. **11.b.**: Electrodes representation and position of the electrode in the vagal nerve. **11.c.**: Representation of VNS lead model 304. (Obtained from: https://www.sciencedirect.com/science/article/abs/pii/S0361923018301412).

The lead is implanted just under the skin, under the clavicle, on the left side of the chest. The proximal part contacts with the PG. In models 100, 101, 102, 103, HC105 and SR106 there is a single connection. However, models 102R and 104 had two cables to connect to the PG.

There are several lead models: 300, 302, 303 and 304. The currently available lead models have two different sizes based on helical inner diameter, the sizes are 2.0 mm or 3.0 mm. However, the Model 300 is not distributed anymore and 302 is not available in all the countries. See **table 3.**

Lead Model	300	302	303	304
Insulation	Silicone	Silicone	Silicone	Silicone
Length	43 cm	43 cm	43 cm	43 cm
Resistance	120 to 180 ohms, pin to electrode	180-250 Ohms, pin to electrode	180-250 Ohms, pin to electrode	120-250 Ohms, pin to electrode
Conductor Material	Platinum	Platinum iridium	Platinum iridium	Platinum iridium

Table 3. Characteristics of each lead model.

3. The third part of the external component of the VNS is a **telemetric wand**. It is a hand-held device that transmits the information of the programming from the computer to the PG. It is shaped like the palm of your hand to be able to cover all

of the PG in order to obtain or send the information. This device allows one to activate, program and interrogate the pulse generator.

12.a **12.b**

Figure 12: 12.a): VNS telemetric wand and the cable (old model-a-). **12.b)**: Programming wand (M2000) and programmer (M3000) (Models Aspire106SR and SenTiva). (Obtained from: **12.a)** www.medicalexpo.com/prod/cyberonics/product-84639-544485.html; 12.b) www.medgadget.com/2017/10/livanovas-new-sentiva-neurostimulator-epilepsy-fda-approved.html).

4. The fourth part is the **VNS therapy software**. This software program permits communication between the implanted PG and the computer. In the old model, the wand was connected to using a cable to receive or send the information. The newest wand model is wireless. The computer has three or more monitors to display the software program's different parameters in different modes of stimulation. The programmed parameters and operational status can be interrogated using the wand. It is possible to change several parameters at once. Also, it is required to verify the new parameters. The software version used is the current VNS Therapy is 16.1.9i.

5. The VNS has an external device that can trigger an extra stimulation, outside of the programmed settings. It is called the **magnet** (see **figure 13**). There are two magnets used with VNS therapy, one is a watch-style and the other is a pager-

style. When the magnet is passed for a couple of seconds over the surface of the PG, the magnet is able to close the electric circuit of the PG by its' magnetic field and cause a stimulation. The magnet has several utilities, most importantly it aborts the seizures when the patient has an epileptic aura. It is in that moment when the magnet needs to be swiped over the region of the PG, to try to stop or decrease the severity of the seizures. The other possibility is when the parents or caregivers realize that the patient is going or starting to have a seizure, then they use the magnet to avoid secondary generalization (174, 175, 176). In some cases, the postictal period can be shorter or less severe. Other features of the device are to check that the device is working properly and to check it has the ability to provide stimulation. The excessive or continuous use of the magnet (> 8 hours) can cause overuse of the device during the working cycle and reduce the duration of the battery.

Picture 13. Imagine of a magnet used for manual stimulation. (Obtained from: www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Vagus-Nerve-Stimulation).

1.2.2.3.6. INDICATIONS AND CONTRAIDICATIONS

The VNS was approved in Europe as a coadjutant treatment for the reduction of seizures in patients with medically resistant epilepsy, with focal onset seizures (with or without bilateral tonic clonic seizures) or in patients with medically resistant generalized epilepsy. In the US, it was approved as coadjutant treatment for focal medically resistant epilepsy in patients older than 4 years old.

VNS was approved by the FDA in July 2005 for the treatment of chronic recurrent depression in patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. However, this VNS indication is not of our interest in this study.

The VNS cannot be implanted in everyone who meets the indications. They must not have any of the contraindications. The absolute contraindications are: history of left cervical vagotomy or severe cardiac arrhythmia (177).

There are relative limitations that can be discussed in each case. For example, the diagnosis of a neurological or systemic progressive condition, active gastric ulcer, severe insulin-dependent diabetes, severe asthma, people who use their voice professionally (130, 136, 178). Severe cases of chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA) can cause worsening of the respiratory function or increase of the apnoea index, requiring a lower frequency of stimulation or a longer time off (179, 180). Previous neck surgery can increase the surgical risk of the implantation (181). The MRI can be conducted for patients with VNS, if the device is turned off previous to the neuroimaging and turned on after the neuroimaging. In cases of MRI of 7 Tesla, which are only available in some centers for research, there is no safety data regarding neuroimaging if the patients were implanted with VNS. However, in cases with no cerebral MRI, it should be avoided, specifically the thoracic or cervical MRI, due to the fact that the magnetic current generated by the MRI can hit the VNS electrodes and damage the surrounding tissues.

There is limited information on the use of VNS during pregnancy. Less than 40 patients worldwide have been described using VNS for epilepsy while they were pregnant. It seems that the VNS is safe to use during pregnancy, however more studies need to be done, including a significant increase in the number of patients studied (182, 183, 184, 185).

When a patient is implanted with VNS, the diathermy needs to be avoided. Using short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy is not allowed. However, the diagnostic ultrasound does not have any use limitation in patients with VNS. Another thing that can affect the therapy with VNS is the external defibrillator and electric cardioversion, which may damage the circuits of the PG. The manufacturer recommends using lower amounts of energy and placing the defibrillation pads as far as possible from the PG and electrodes (186). However, the most important thing is the life of the patients over the preservation of the normal function of the device. It is better to start as soon as possible, rather than take longer to try to find the perfect spot for the VNS.

In patients with VNS who undergo any type of surgery, the utilization of electrocauterization or radiofrequency ablation causes an increase of the hit in the area of the PG or electrodes, which may lesioning of the surrounding soft tissues (187). In the same way, the lithotripsy using extracorporeal shock wave can damage the PG. All of VNS's stimulation modes should be turned off during the treatment and turned on after the treatment is completed (186).

Finally, the VNS is not affected by the use of any type of radiofrequency antenna, microwave, phones, security systems at the airports or other electric devices. It is recommended the patients bring a card-document stating that a VNS is implanted when they are traveling by plane or outside the area of residency, to prove to the authority's the device is implanted.

1.2.2.3.7. IMPLANTATION

VNS implantation requires general anaesthesia and it takes one to two hours. The patient needs to be in a supine position on the table and the head goes on a foam headrest,

slightly extended, and turned to the right, with or without a roll under the scapula to help extend the neck. After the preoperative antibiotics are given and the neck and chest are prepped, the surgery begins. The neck incision should be done in the left lateral cervical region, located in the anteromedial aspect of the sternocleidomastoid muscle, in the level of the cricothyroid interval (C5/C6), using the cutaneous fold. This region is recommended because it is possible to access the vagus nerve distally to its' superior and inferior cardiac branches. The incision should be four centimeters long and could be done horizontally or vertically, but horizontally is recommended for esthetic reasons.

After the skin incision, the dissection continues through the subcutaneous tissue, exposing the platysma muscle following its' fibers that are vertically divided. The vagus nerve will get exposed laterally to the sternocleidomastoid and omohyoid muscle, and medially the trachea and larynx, exposing the deep cervical fascia, which is opened (188). When the sternocleidomastoid muscle is retracted laterally, the neurovascular bundle, which is constituted by the left carotid artery medially and the internal jugular vein laterally, is seen. The vagus nerve is usually located between these two vascular structures. Once the vagus nerve is identified, approximately three centimeters of it should be exposed. It should be isolated using vessel loop and mobilized from the vascular structures to avoid the damage of the nerve (177). It is recommended to keep some connective tissue around the nerve, to protect and keep the vascularization of the nerve.

The electrode implantation of the VNS needs to be completed distally to the superior laryngeal nerve and the cardiac branch of the cervical nerve, avoiding complication during the stimulation, which could result in tension sensation or pain in the throat or bradychardia or asystole (189). The recurrent laryngeal nerve runs with the vagus nerve, and for that reason it can be affected during the stimulation, producing vibratory sensation in the left vocal cord or hoarseness for a while (190, 191). The anode, cathode and tethering coil electrodes are implanted, from proximal to distal order, wrapping them around the vagus nerve in the longitudinal axis. The electrodes need to contact the nerve

without compressing it (177). After that, an accessory loop of the cables is created and secured to the cervical fascia with silicon ties (91).

The next step is to create a pocket for the PG. An incision in the left anterior axillary line and subclavicular region will be cut, to make a deep subcutaneous pocket. This will be localized between the fat tissue and the superficial fascia of the pectoralis major, under the clavicle. The pocket needs to be big enough to contain the PG.

After the pocket is ready, it is necessary to create a tunnel from the cervical region to the subcutaneous pocket and then connect the cable to the PG. Afterwards, the PG is located inside the pocket and secured to the fascia with a prolene suture. The cable is fixed with attachment clips to the fascia, loop the cable to avoid tension in the electrode and to allow neck movements without causing mechanical tension in the system. The cervical incision is closed with subcuticular stitch with an absorbable suture and the subcutaneous tissue is also closed with absorbable sutures (91).

In the patient paediatric implanted with VNS, especially those with intellectual disabilities, it is recommended to create the pocket under the pectoral muscle, submuscular level, to avoid any manipulation from the skin, self harm and harm to the device (192). There is another type of incision, used for a single cervical incision. The retraction of the superior part of the incision will expose the vagus nerve, and the distal part will be used to create the subclavicular pocket for the PG (193).

The devices can be turned on with a low current if there are no complications. The patient will recover from surgery and anesthesia in the recovery room. If he/she feels fine and is an adult, they can go home. In the case of the paediatric group, the patient will remain in the hospital for at least 24 hours before being discharged. Prophylactic antibiotic treatment previous to the surgery and continuing for several days after surgery to avoid any infection of the surgical area is recommended (194). Concerning ASM, the patient will

continue with the same medication prescribed previous to the intervention.

Battery replacement or PG replacement can be done under local anesthesia. However, many centres use general anesthesia to avoid any seizures or other events during surgery.

1.2.2.3.8. PARAMETERS

The VNS effect is delivered through a series of pulses from the pulse generator to the left cervical vagus nerve. There are different stimulation modes, which are normal mode, magnet mode and the new model of VNS has AutoStim. Each one of these modes has different settings that can be adjusted and modified. The titration of the setting of the stimulation mode is known as dosing. It is necessary to increase the parameter to the recommended setting to obtain the maximum potential benefit from the device's ability to control the seizures. The programming will be completed at least 2 weeks after the implantation and, after that first visit, can be done every two weeks or once a month. However, if the patient has a good tolerance for VNS changes or availability to come to the clinic, the programming can be done in shorter intervals. For example the patient could come to the clinic every week or twice in one day to avoid coming frequently in case the patient leaves far. For that reason, it is important to know the setting of and the possibilities of the VNS.

The settings of the VNS are:

A. Normal Mode of Stimulation:

- **Output current or current.** This is the intensity of the stimulation. It is measured in milliAmperes (mA). The lowest current is 0, but when the VNS is implanted and turned on, the intensity will set to 0.125 mA. The current can be increased from 0.125 (model 106) or 0.25 in previous VNS models, up to the intensity that the clinician considers necessary. The target current recommended is 1.5-2.25 mA, however when significantly higher than that is it is considered safe (up to 3.75 mA)

(105).

- **Signal frequency.** This is the number of pulses per second, expressed in Hertz (Hz). The usual setting is 30 Hz, but decreasing to 25 or 20 Hz may improve some side effects such as pain or coughing. However, this change can cause negative impact on the efficacy. For this reason, it is not the first setting of reprogramming that is used in an attempt to resolve side effects. When the VNS is implanted, the signal frequency is set to 30 Hz and that is the target value.
- **Pulse width.** The pulse width is the duration of each output in the series of pulses comprising the dose of therapy. It is measured in microseconds (µsec). The initial pulse width is 500 µsec, however the patients tolerate 250 µsec and there is no affect to the VNS efficacy (195). The range of this setting goes from 130 to 1000 µsec.
- **Signal on.** The VNS delivers an alternant current of square long pulses, following which there is a time of respite. The duration of time, in seconds (s) that the stimulation is being delivered to the vagus nerve is the Signal On. There is an additional two seconds at the beginning of the stimulation when the device ramps the output current to the programmed value, and also two seconds at the end of the stimulation phase when the output is ramped down to 0 mA. This fact makes the real stimulation four seconds longer than what it is shown on the screen or what is programmed by the physician. The initial setting of the signal on will be 30 s, but there is a range from 7 to 60 s. In some cases, it is recommended to decrease the time on, to measure an increased tolerance. See **figure 14**.
-

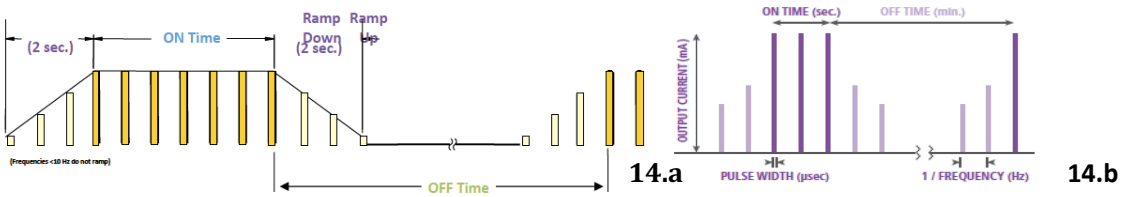


Figure 14. 14.a and 14.b: Representation of VNS parameters of stimulation. (Obtained from: Cameron Finlay, Education Manager & Sr Technical Product Specialist, Neuromodulation Division, LivaNova Canada, Revised 2018).

- **Signal off.** The other part of the stimulation pulse is the time off. It is described/defined as the time from the beginning of the ramp down phase until the end of the ramp up phase for the next bout of stimulation. It includes the last ramp down and the next ramp up phase. It is expressed in minutes (min). The first setting after the implantation will be 5 min, and that is the recommendation. However the signal off has a range that goes from 0.2 to 180 min.

B. Magnet Mode of Stimulation

- Magnet Output Current. The magnet current is the intensity of the current generated by the PG when the magnet is activated. It also goes from 0 to 3.5 mA and the target current is 1.75 to 2 mA. The intensity is higher than the normal mode of stimulation to try to stop or attenuate the seizure. When the VNS is implanted and turned on, the magnet setting is 0.25-0.5 mA. The increment usually is 0.125-0.25 every visit, every 15 days to 1 month.

- Magnet Pulse Width. The pulse width in this mode, as in the normal mode, is the duration of each pulse of stimulation. The duration is from 130 to 1000 μsec, and the standard parameter is 500 μsec.

- **Magnet On Time**. The magnet on time is the time that the stimulation will be on. The standard setting is 60 seconds, but it goes from 7 to 60 seconds.

C. AutoStim Mode of Stimulation.

- AutoStim Output Current. The intensity of the current goes from 0 to 3.5 mA. After implantation the setting will be 0.375-0.125 mA. In every visit the current will be increased by 0.125-0.25 dependent upon patient tolerance.

- AutoStim Pulse width. It is most often set at 500 μsec but has the same range as the normal mode pulse width.

- AutoStim On Time. Time on in the normal mode is 60 seconds but the range of stimulation can be set from 7 to 60 seconds.

- **AutoStim Threshold.** The threshold is the percentage (%) in the change in heart rate required to activate AutoStim current. The range goes from 20% to 70%. After the implantation the standard threshold is 30%. If the threshold is set at 20% it is going to be very sensitive, but this can cause many false positives and frequent stimulation. However, on the other side, the 70% threshold is very specific, and can have many false negatives and miss many changes in the heart rate that can be caused by seizure activity.

- **AutoStim Heartbeat Detection**. This refers of the sensitivity of tachycardia detection. It can be on or off. It goes from 1 to 5. It is based on presurgical surface assessment. If it is unknown, it is recommended to start at 1 and increase until there is an accurate heartbeat detection.

Once the parameters are described, it is important to learn about the steps to adjust the settings. These steps are going to be repeated in each visit in which the parameters need to be adjusted. See **table 4**.

Parameters	Unit	Range	Starting Value	Target Value
Output Current	Milliamps (mA)	0.0-3.5	0.25	1.5-1.75
Signal Frequency	Hertz (Hz)	1-30	30	30
Pulse Width	Microseconds (µsec)	130-1000	500	500
Signal On-Time	Seconds (sec)	7-60	30	30
Signal Off-Time	Minutes (mm)	0.2-180	5	5
Magnet Output Current	Milliamps (mA)	0.0-3.5	0.5 (Normal+0.25)	1.75-2.0
Magnet Pulse Widht	Microseconds (µsec)	130-1000	500	500
Magnet On-Time	Seconds (sec)	7-60	60	60

Table 4. Summary of the recommended parameters.

In the first step we need to interrogate the PG. The software-tablet-computer needs to be turned on. Once we are in the main menu or parameters screen menu of the device, we will select “interrogate device” and then “Start Interrogation”. At that time the

telemetric wand will be put over the skin region of the PG, 0.5-1 cm away from skin, avoiding touching the skin. It will take a couple of seconds and when it is ready it will make a sound. If it was a successful interrogation, the programming software automatically displays the parameter screen. If the transmission won't go through, the screen will display a warning message or a message that states that it is necessary to re-interrogate the device. The parameter screen displays the operating parameters of the PG in the normal mode, magnet, AutoStim and tachycardia detection, as well as the model, serial number, battery status (101-106) and patient information. After we review the current parameters, dependent upon those numbers and the patient seizure management and side effects, the device can be programmed. The battery status in the PG model 101 and 102(R) has one battery status (near end of service, Near EOS) and the following models (103-106) have intensified follow-up indicator (IFI), near end of service indicator(N EOS) and end of services indicator (EOS).

After we decide which changes are required, we will go to the "parameters screen menu" and then "program patient data". The programmable parameters are split by stimulation mode and are presented on separate tabs. Dependent upon the PG model, there will be various numbers of tabs. On each tab, there is one line for each programmable parameter which contains three types of information: the name of the parameter and the units, the present setting for that particular parameter and the new button, which when tapped, displays the range of possible settings for that parameter. Then we select the new target value and we tap the "program" button. It will jump to another screen with the summary of all the settings of the VNS. It is necessary to review the parameters so that the appropriate changes are made.

If the changes performed are correct, we will select "confirm" in the "parameters confirmation screen". Then it will bring us to the "start programming screen" and we will press "start programming". At that time we will place the programming wand over the PG and again it will make a sound when the programming is completed.

The last necessary step is to interrogate the PG once again, to verify that the new settings are correct. During the interrogation one stimulation is recommended to check the impedance.

The most common change in every visit is the current in the normal mode, magnet and AutoStim, when it is available in the device. The increase of current is called titration. The manufacturer's recommendation is to delay beginning therapy for at least two weeks after implantation. The clinical practice suggests an earlier activation, even in the postoperative moment. Then it will increase every 2 weeks or a month, according to the ability of the patient to get to the clinic, by a total of 0.125 or 0.25 mA. The company recommends implementation as soon as the patient can tolerate, even 0.25 mA, and if the patient tolerates this well, increase another 0.25 mA after five or ten minutes. The current is increased enough to provide the potential to reach the threshold level of the nerve and create the action potential. When low current is applied, only a minority of fibres are within reach of the current. With the increment of current, mores fibers will be reached and the action potentials will be transmitted to the central nervous system. The nerve saturation will be achieved at a higher setting and increasing the output beyond that saturation point doesn't provide additional benefit to the patient. The aim is to arrive to 1.5-2.25 mA and it will takes 6 to 12 visits.

A reduction in seizures is expected with that output. However, in many cases solely increasing the current will not result in the maximal effect of the VNS. When changes are made in other parameters to try to achieve seizure improvement or quality of life improvement, we talk about duty cycle. The most important parameters are the signal on time and signal off time. The time off decreases more often than time on. A mathematical equation was developed to calculate the percentage of time that the stimulation was on and off, to help find what leads to optimal seizure control. Heck et al recommended at least a 22% duty cycle to have a positive impact in the patient (195). After that change

the parameters to the left are modified. Those changes have a negative impact to the longevity of the battery, but it is compensated with clinical benefit for the patients. The patients usually tolerate these changes well. Several years ago, when the time on was increased, it was called fast cycling mode (195). See **figure 15**.

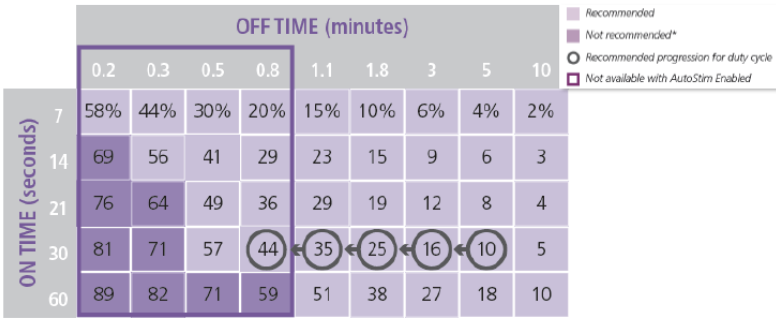


Figure 15. Representation of the Cycling and how it is suggested to increase the efficacy of VNS. . (Obtained from: Cameron Finlay, Education Manager & Sr Technical Product Specialist, Neuromodulation Division, LivaNova Canada, Revised 2018).

Before stating that the VNS is not effective it is necessary to wait at least six months and administer the previously mentioned setting adjustments, it is a long process. The battery lasts for approximately 40 months (23-80 m) (196). To ensure the lack of effectiveness is not caused by the battery being dead, it is required to change the whole PG, keeping the lead attached to the vagus nerve.

In each visit, it is important to evaluate the tolerability of the devices previous and post adjustment of the parameters. By following the possible side effects, it is possible to detect and correct side effects, to improve the tolerability of the VNS in our patients. Many side effects will decrease over time (197, 198). It is necessary to know if the side effects are constant, when the normal mode stimulates the nerve, or if the side effects relate to the other modes (magnet, AutoStim if this is available). Previously, some modifications were described briefly, which may help reduce side effects. The first parameter adjustment that is done to reduce side effects is to decrease the pulse width of the normal mode from 500 to 250 µsec (106,195, 199). This change doesn't have any

impact in the VNS efficacy. If that change doesn't reduce or eliminate the side effects, practitioners will make a change to the signal frequency of the normal mode or the all the modes. The signal frequency will be reduced from 30 Hz to 25 or, if it is necessary, to 20 Hz. If none of the changes have reduced patient complaints, the next step is to reduce output current. In the new model (SR 106) output current can be reduced by 0.125 mA, but in the rest of PG models it can be reduced by 0.25 mA. This adjustment can be done in the magnet mode as well. In cases in which the patient was implanted with Aspire SR106, the AutoStim can be adjusted too. The heartbeat detection can be adjusted in each case and the threshold for AutoStim can be modified. For example, the threshold for AutoStim can be increased by 10% in cases that report "over" stimulation to be more specific in heart frequency change, or reduced by 10% in cases with under stimulation to be more sensitive to all heart rate changes

1.2.2.3.9. LITERATURE REVIEW

1.2.2.3.9.1. HISTORICAL-BEGINNING

Vagus nerve stimulation was approved in 1994 and 1997 in Europe and US respectively. However, the first device was implanted in humans for epilepsy treatment in 1988 by Penry (129). The VNS was developed after the clinical hypothesis of how the stimulation of the vagus nerve could improve seizure control, and after animal models using epileptic cats (122, 200), dogs (125, 126), rats (171) and monkeys (201). In a study conducted by McLachlan, using rats, he tried to quantify the effect of the VNS in induced seizures with penicillin. (171). A reduction of spikes of 33% (from 42 +/- 11 to 28 +/- 11) was found. The abolition or reduction of spikes appeared 1-2 seconds after the stimulus onset, occurred throughout the stimulation period and persisted for a variable duration (from 60 seconds to 3 minutes). Also, it was stated that stimulation of the vagus nerve after 3 seconds of the onset of the seizure was able to reduce the seizure duration from 30.2 +/- 15.7 s to

5.0 +/-1.8 s. The seizure suppression was very prominent in the clonic part, compared to the tonic (171).

After the first VNS implantation by Perny, Terry et al, in 1990, VNS was proposed as a novel treatment for focal onset refractory seizures (202). At the beginning of the 1990's three centres implanted a VNS in patients with a history of focal onset MRE (129, 135, 203). Afterward, the first multicentre study using VNS for MRE was conducted.

Two pilot studies (E01 and E02) investigated 14 patients with focal onset seizures and seizures' refractory to medications. These patients were implanted with a programmable device. The patients were followed up, for the purpose of the study, for 14 and 35 months. There was a 47% reduction in the frequency of seizures (136). After that study was completed, the first randomized, blinded, parallel, controlled study using VNS began (E03). This study included 115 patients. The study looked at the efficacy of low frequency and high frequency stimulation compared to the reduction of seizure rate in medically resistant epilepsy with focal onset seizures (with or without bilateral tonic-clonic) in patients from 12 to 60 years old. The aim of this study was to demonstrate seizure frequency reduction. In the E03, the patients were randomized in high (higher frequency, greater pulse width, and higher duty cycle of stimulation) or low frequency (30 seconds on, shorter pulse width, lower frequency stimulation, 90 minute off period, acting as a placebo-like group) stimulation group when the PG was activated, two weeks after the vagus nerve implantation. ASM was stable during all trials. The first evaluation was 14 weeks after implantation, the high frequency stimulation group had a reduction in seizure frequency of 24.5% and the low frequency stimulation of 6.1%. When they analyzed the frequency of a 50% seizure reduction, the first group achieved a 31% reduction and 13% in the other (placebo) group. After 14 weeks, the open label began. At 12 months there was a 50% response rate in 31% (23-41%). The study divided the response in two groups, adolescents (12-21) and adults (≥22). The adolescents group had a median change in seizure frequency of - 37.3 % (-62.4 to -24.2%) and in the adult group had a median change

in seizure frequency of -30.2% (-38.4% to 21.9%) (130, 204).

The next study was conducted with a population which included paediatric patients (> 2 to 64 years old) with MRE (E04). The study was prospective, open label and 123 patients were included. 2 weeks after implantation of VNS, the PG was activated using high stimulation parameters and the patients included in the study were followed every 3 months for the first year and every 6 months until the end of the study. At 12 months, 50% responder rate was found in 20% (1-72%) in the 4-11 years-old group and 28% (18-41%) responder rate was found in the ≥ 12y-o group. The percentage of seizure change at the end of the study was -24.5% (-39.3% to -0.8%) in the youngest group and -25.9% (-39.2% to +6.3%) in the other (196).

In 1995 another study using randomized, blinded, parallel, controlled was conducted to evaluate the VNS effect. It used VNS with high and low stimulation paradigm to evaluate the seizure rate reduction in patients (12-65 y-o) with focal onset refractory epilepsy (E05). A total of 199 patients were included in the study. It was similar to the E03, using comparable parameters of stimulation: Low frequency stimulation (LFS): 30 seconds of shorter pulse width, lower frequency stimulation, followed by a 180 minute OFF period. High frequency stimulation (HFS): 30 seconds of longer pulse width, higher frequency stimulation followed by a 5 minute OFF period. In the 14 weeks after the implantation the LFS group had 15% seizure reduction and the HFS had a 28% seizure reduction. That difference was statistically significant. After that week, the prospective, open label study, called XE50, began. A total of 28% had a 50% responder rate at 12 months, with seizure reduction of -36.1% in adolescents (12-21 y-o) and -44.3% in adults (≥22) (105, 204, 205).

In the early 2000's, the E06 was started. E-06 Clinical Study (NCT01118455) was a randomized, parallel group, comparative study, which included 39 patients 17 years old or younger with focal MRE. It compared the efficacy of the VNS to antiseizure medication (ASM) to reduce the seizure frequency in children. In the group of ASM, at the time of the

randomization, a new ASM was started. In the VNS group, the device was implanted at the same time as the ASM group began taking medication. At month 12 the VNS groups showed a fifty percent responder rate was found in 21% (6-46%) of the children between the ages of 4-11 and 33% (13-59%) in ≥12. The median percent change of seizure frequency was -2.4 (-27.9% to 70%) in the youngest group and -19.2% (-42.8 to +33.3%) in the other.

Japan developed its' own study in 2010 and it was called Japan Post-Approval Study (JPAS). The total number of patients included in the study was 345 and included patients > 4 years. They were followed for 36 months. The result at 12 months post implantation showed that 47% (28-66%) in the group of 4-11 years old and 56% (48-63%) in ≥ 12, had a 50% responder rate. When considering the median percent of seizure change at 12 m, the results in the 4-11 y-o, 12-21 –y-o and ≥ 22 y-o groups were -38.6% (-75.2% to -16.3%), -50% (-63.3% to -22.2%) and -60% (62.5% to -43.2%) respectively.

All the data obtained from the studies (E03, E04, E05, XE05, E06, PAS) completed for the premarket approval application (PMA) was analysed, to verify the efficacy of the VNS for the treatment of focal onset medically resistant epilepsy. The total number of patients included was 847, of which 805 patients completed the studies. From this number 176 were removed from the analysis due to having only generalized seizures, 2 for no baseline seizures and 6 for missing data. The total for the analysis of 12 months was 582 patients. In the group of 4-11 years old (A) there were 54, and 528 in the ≥ 12 years (B). The analysis of overall studies found that group A had a 50% responder rate in 35% (23-49%), and that group B had a 50% responder rate of 42% (38-47%). When taking into consideration the median change of seizure frequency, group A had a -24.7% (-45.1 to 0%) and B -40.4% (-45.6% to -33.3%) (196, 204, 205). See the summary in **table 5**.

tudy	N	Age (y)	Onset Study	End Study	Type Sz	Reduction Total Sz	50% Sz reduction	Type Study	Follow-up	Reason Study
E01-E02	14	≥ 18	1988	1990	Focal MRE		47%	Prospective, no randomized	14-35 m	Safety
E03	115	12-60	06/90	07/93	Focal MRE	-37.3% (12-21) -30.2% (≥22)	31%	Double blind, parallel, multicenter, prospectively randomized	12	Safety
E04	123	≥ 2	09/91	96/96	MRE Any type	+6.3% (4-11) -24.5% (12-21) -44.3% (≥22)	20% (4-11) 28% (≥ 12)	Open labeled (non-blinded), longitudinal, multicentre	12	Safety
E05	199	12-65	01/95	08/96	Focal MRE	-36.1% (4-11) -44.3% (≥22)	28%	Randomized, blinded, parallel, controlled, longitudinal, prospective, multicentre	12	Safety
XE05	199	12-65	01/95	01/02	Focal MRE	-36.1% (4-11) -44.3% (≥22)	28%	Longitudinal, open labeled (non-blinded), prospective, multicentre	15	Safety
E06	39	≤17	10/04	01/10	MRE any type	-2.4% (4-11) -19.2% (12-21)	21% (4-11) 33% (≥ 12)	Longitudinal, multicentre, parallel, non-blinded	12	Safety
JPAS	345	≥ 4	07/10	12/12	MRE any type	-38.6% (4-11) -50% (12-21) -60% (≥22)	47% (4-11) 56% (≥12)	Longitudinal, multicentre	12	Data source

Table 5. Summary of the VNS premarket studies.

In 1998, the first multicentre study using double-blind, active-control, add-on trial using VNS for focal onset seizures was published (58). During the randomization, one group received LFS (on time 30 seconds, off time 3 hours, pulse width 130 μsec and I-Hz frequency) and the other HFS (on time 30 seconds, off time 5 minutes, 500 μsec and 30 Hz frequency, reaching up to 3.5 mA after 12 weeks since the implantation). The LFS group was considered an active-control group, rather than placebo. The study included 254 patients, 198 were randomized and the analyzed data belonged to 196 patients. After 16 weeks, the LFS had a seizure frequency change of -15.2% (±39.2%) and HFS had a seizure frequency change of -27.9% (±34.3). In the subanalysis, considering seizure reduction ≥ 50%, 15.7% achieved that result in the LFS group and 23.4% in HFS group. Only 2% of the LFS group and 10.6% of the HFS group achieved a ≥ 75% seizure reduction, with a statistically significant difference.

Many of the studies published included a small number of patients or included a short follow up. In 2011, Englot et al. published a metanalysis of 78 clinical studies and 5554 patients. Patients of 1285 physicians from 978 centers in the world (911 US and Canada, and 67 international) were studied. The study showed that the seizure reduction at 0-4 m was 47% compared to 63% at 24-48 m. The response to VNS was 49% in the first four months compared to 63% in the longer follow-up. Seizure freedom was also higher in the prolonged follow up (8.2% compared to 5.1% in the other group). In the first months of follow up the seizure freedom was significantly more likely in generalized seizures at 0-4 and 4-12 m (p= 0.01) but no significant difference was seen at 12 -24 m or 24-48 m (p=0.5) (206). They found ≥ 50% decrease in seizure frequency in 60% of the patients included in the analysis. The response rates and seizure freedom rates increased over time with VNS therapy (206). It realized a multivariate analysis to predict the seizure freedom. It was found if the age of epilepsy onset was > 12 (OR 1.89) and if the patient had generalized seizures (OR 1.39), the patient had a better response. Investigating the response to the treatment, the non-lesional cases had a better profile (OR 1.38) (206).

1.2.2.3.9.2. GENERALIZED EPILESPY AND VNS

The interpretation of this study makes us think that the VNS can work better in patients with generalized epilepsy. It is the group with generalized epilepsy, who frequently have no lesion in the MRI, age of onset is early teenagers and with frequent generalized seizures. There are a few publications that are concerned with the efficacy of the VNS in generalized epilepsy. In 1999, Labar et al completed one of the first publications. He revised the efficacy of the VNS in 24 patients with generalized epilepsy. Looking the efficacy at 1 and 3 months, he compared the symptomatic generalized epilepsy (SGE) group (N=17) with the idiopathic generalized epilepsy (IGE) group (N=7). The median seizure rate reduction was −46% (−85% to +130%), 16 of 24 had > 30% seizure reduction and 11 had > 50% seizure reduction. The subanalysis found that the seizure frequency reduction was higher in the IGE (-60%) compared to SGE (-40%). It also found that the reduction of bilateral tonic clonic was significant in the overall group, as well as the subgroup of patients who were older at the age of seizure onset and were experiencing frequent seizures (196).

Several series of cases were published concerning VNS and efficacy in generalized epilepsy. The number of cases included in each study was limited, but it is important to mention that these studies needed to be conducted to gain a better understanding of VNS in generalized epilepsy. The first one is by Ng et al in 2004 (207). In this study, all patients were implanted with VNS. The study included 165 patients with MRE, and 138 patients with focal MRE (focal), 13 patients with symptomatic generalized epilepsy (SGE) and 14 patients with genetic generalized epilepsy (GGE). It compared the GGE group to the focal and SGE to examine the seizure control with the VNS (180). It found that frequency reduction in each group (F, SGE, GGE) was 58.9%, 57.3% and 72.9% respectively. However, 50% of seizure reduction was achieved in 9.4% (N=13) in F, 7.7% (N=1) in SGE and 35.7% (N=14) in GGE. Another outcome of the study was the group that

experienced a 50% seizure reduction also had an antiseizure drug reduction of. 9.5% (N= 13) in Focal, 7.7% (N=1) in SGE and 35.7% (N=5) in GGE. The follow-up time on average was 21.6 months (207).

Müller et al published another study in 2010, with VNS data from Hungary (205). The total number of patients in the sample was 26 with MRE, but 15 were focal MRE, seven patients with Lennox-Gastaut Syndrome, one with spasm seizures, one with progressive myoclonic epilepsy and two with unclassified cases. A total of 14 patients were followed for at least a year, and the study divided those patients into focal (N=10) and nonfocal (N=4). The study found that the seizure frequency reduction was more pronounced in the nonfocal group, without statistical significance. However, the type of seizure reduction, which had a significant frequency reduction, was the bilateral tonic-clonic (p=0.04) (205).

In patients with generalized epilepsy and MRE there is the possibility of undergoing a corpus callosotomy (anterior (two thirds) or complete). This technic is effective in reducing the frequency and severity of bilateral tonic-clonic, tonic and atonic seizures (208). Seizure reduction in some cases, after that procedure, can be -40 to > 70% (209, 210, 211, 212, 213, 214, 215, 216, 217). However, the risk of complication is not insignificant, and the most common complications are disconnection syndrome and mutism, and generally transient (215, 218). In 2006, Nei et al. published a paper concerning generalized MRE and the response to corpus callosotomy (CC) and Vagal Nerve stimulation. The method was to evaluate seizure frequency response and procedure complications. There were three groups: CC (anterior/complete) (N=53), VNS placement (N=25) and CC and VNS (N=9). When the study compared CC versus VNS, the 50% or more of seizure reduction was found in 79% of the CC group and 40% of the VNS group. In cases with 80% or greater seizure reduction, it occurred in 57% of the CC group and in 20% of the VNS group. These two results had a significant difference. Interestingly, the study subdivided by type of seizures focal and generalized, and the other group was tonic and atonic seizures. In the analysis of generalized and focal, on average a 50%

seizure reduction occurred in 79.5% of the CC group and 50% of the VNS group. In cases with only focal seizures a seizure reduction of 82% in CC and 71% in the VNS were found, and in cases with generalized a seizure reduction of 78% and 29% were found, respectively. 60% of the CC and 33% of the VNS achieved a reduction of 80% or greater (218). In the subtype of seizures tonic/atonic, the seizure reduction ≥ 50 % was found in 77.8% in the CC group and 66.7% in the VNS group. A ≥ 80% reduction was found in 61% of the CC group and 16.7% of the VNS group. In the third group, which had both procedures, four had no changes in seizure frequency or intensity, two had better seizure control and three had approximately an 80% seizure reduction. Those numbers suggest that the CC group or CC and VNS group had better outcomes. However, the frequency of complications was also higher in frequency and severity in those groups, occurring in 21% of the CC group and in only 8% in the VNS group (218).

The evidence-based guidelines concerning VNS for the treatment of epilepsy, reviewed by the subcommittee of the American Academy of Neurology, identified the relevant published studies regarding the topic. It found that there is space for research concerning primary generalized epilepsy refractory to medication, and mentioned a lack of information regarding parameter settings (219).

1.2.2.3.9.3. PAEDIATRIC GROUP

A paediatric population was included in some of the premarket studies mentioned above (E03, E04, E05, XE05, E06 and JPAS). However, the only premarket study that exclusively investigated a paediatric population was the E06. When all these studies are analysed together and samples are classified by ages (4-11 years and ≥ 12), a fifty percent responder rate at 12 months was achieved in 35% (23-49%) of the paediatric population and 42% (38-47%) of adolescents and adult patients. There was also a difference in the median percent change in seizure frequency in these two groups, in young patients there

was a reduction of -24.7% (-45.1% to 0%) and in older patients -40.4% (-45.6% to -33.3%). However, it is important to realize the difference in the sample size, which included only 54 subjects in the paediatric and 528 subjects in the general group. It was stated that difficulties in enrolling children aged 4 to 11 years old existed. For that reason, it was approved in the US only for children > 12 years old.

Even in these results, it is noted that one third of the paediatric epileptic patients do not respond to any ASD (220). The seizures and the ASD side effects can affect cognition, development and quality of life (221). For that reason, the VNS has been used in "off-label" therapy in children younger than 12 years (222). Several studies published have suggested that VNS is effective and safe in patients with MRE younger than 12 years (220, 223, 224, 225, 226. 227). In a multicenter study published in 2014, which included 347 MRE patients <18 years old (228). It found 37.6% of patients were responders 12 months post VNS implantation, from that group 57.3% had generalized seizures and 42.7% focal seizures. The subanalysis of patients younger than 12 years found a 43% responder rate at 12 months post VNS implantation and in the group of Lennox-Gastaut syndrome, 55% were responders (228). Orosz's paper demonstrated a similar effect of VNS in patients younger than 12 and some demonstrated superiority in earlier VNS implantation (227, 229, 230, 231, 232).

The data is limited to evaluating the benefit of early VNS implantation and comparing the outcome to late implantation. An interesting paper recently published included 12 patients, five were younger than 5 years and seven older than 5 (233). The seizure rate reduction was 36.2% in the young group and 36.7% in the other, without showing statistical differences between groups (233). This study supports the efficacy of the VNS to implant patients younger than 5 years-old. However, more data is required to assess the efficacy of VNS implantation in that age group.

1.2.2.3.9.4. QUALITY OF LIFE

Patients with epilepsy have a lower quality of life in different aspects (emotional, social, labour, physical), especially patients with MRE (234, 235, 236). The improvement in quality of life after VNS implantation is another factor to take into consideration when evaluating the effect of VNS in patients with MRE.

More than 40 reports suggest that there is an improvement in quality of life after implantation of the VNS, even when there was no effect in seizure reduction (237, 238, 239). Many of the studies were observations, unblended or abstracts. Dodrill et al. completed a double blind study including 160 patients with MRE focal epilepsy, and divided the sample in patients receiving low stimulation and high stimulation (65). The Quality of Life (QOL) tests were compared before VNS implantation and 12-16 weeks after, and the group with higher stimulation had fewer emotional and physical problems compared to the low stimulation, but there were no clear cognitive changes (65). Other studies found a reduction in the severity of the seizures and found the post-ictal period had better recovery and less hours lost (240).

Similarly, many studies reviewed the effect of the VNS on the quality of life. A European Paediatric study found that 47.7% of the patients at 12 months had a reduction in the intensity of the seizures (228). That study also found that 66.1% of the sample presented an improvement of alertness, one third benefited in areas of concentration, energy, mood, verbal communication, and progress with schoolwork over time, with improvement of the QOL (including memory and development of life skills) over time (228).

In the revision done by the American Academy of Neurology concerning the VNS, it stated that the VNS might have a secondary benefit of mood improvement (219). This mood improvement of the VNS allowed the VNS to be approved for the treatment of severe,

recurrent unipolar and bipolar depression in 2001 in Canada and Europe, and in 2005 in US.

Another important effect of QOL in patients with MRE is the pharmacological treatment. Many of them take several ASD in moderate or high doses. Those combinations can have a synergic effect between them, but it also can cause more side effects. In the literature there are few publications that mention the modifications of each ASD during the follow-ups, but those changes represent an important factor that could affect VNS response. The most common modification that occurs is the increase of ASD or the switch to another ASD. In a study by McLachlan, which looked at ASD doses in patients implanted with VNS, there was a total ASD dose reduction in 43% of patients and an increase in 7% of patients, without any change in the number of ASD (238). A decrease in ASD was also found in the Quabi et al. study, which showed a reduction in 9% of the responders compared to baseline (240, 241, 242). The study, conducted by Kuba et al, found an increment in the number of the ASD (243). There were no changes in the total ASD treatment in the first twelve months of the VNS treatment in the study by Labar et. (244). Similar results were found in the European Paediatric study, referring that the mean number of ASD remained stable from baseline over time but in 50.4% there was at least one concomitant ASD change, and if there was no change it was related to a ≥ 25% decrease in seizure frequency at each analyzed point of time (228).

One of the few studies that monitored changes during follow-ups found that the number of medications remained fairly consistent before and during the follow-up. However, there were frequent changes in doses of ASD in those patients. The most frequent change was an increment in the dose of ASD and the maximal improvement of the VNS was found in patients with more changes in the ASD (245, 246).

In severe epilepsy cases, such as Lennox-Gastaut syndrome (LGS), the use of VNS lead to a 50% seizure frequency reduction in 55% of LGS patients (219). Patients with status

epilepticus (SE), generalized tonic-clonic or LGS have lower quality of life, with significantly higher mortality and morbidity (247, 248). Sierra et al. studied the VNS effect in SE and found that six of their eight patients with history of SE had a significant reduction of the SE over a mean follow-up duration of four years (248). In a similar study, from the ten patients with history of SE in the year prior to the VNS implantation, only three of them experienced SE in the year following VNS activation (250).

1.2.2.3.9.5. OTHER VNS USES

The VNS was approved for depression in 2001 and 2005 in Europe and Canada, and US respectively. Studies involving epileptic patients found that the VNS can produce weight loss. This characteristic of the device opened the door for obesity treatment. Several studies have focused on this effect and VNS implantation has only achieved modest weight loss (251). In a similar way, the parallel beneficial effect of the VNS in migraine reduction was found and multiple series of cases showing this effect are published (252, 253, 254, 255, 256). For that purpose, an external VNS for episodic and chronic migraines was developed (257).

The use of VNS for the treatment of Alzheimer's disease, multiple sclerosis, fibromyalgia and other pain conditions have been also investigated (258, 259). Recently, VNS was studied in the clinical treatment for sepsis and rheumatoid arthritis because it suppresses peripheral inflammation and may be important in modulating neuroinflammation (260).

1.2.2.3.10. COMPLICATIONS, SIDE EFFECTS AND SAFENESS

VNS safety was evaluated in pre-market trials (E03, E04, E05, E06 JPAS). It divided the population (847 patients implanted with VNS) into two groups for safety purposes, 4 to 11 years and 12 to 21 years old. The results after 12 months of follow up did not

differentiate between both groups. Fifty percent of the patients experienced hoarseness, which was the most common side effect associated to the VNS, primarily during the *On* period. Hoarseness varied from severe to barely perceptible depending upon the device's settings.

In the postmarket data, the most common side effects in both groups were: painful stimulation, pain, voice alteration, stimulation not perceived, coughing, dysphagia and migration of the generator. Please see **table 6** for additional information. Concerning complications of the implantation, the most frequent were infection and extrusion of the lead, which are significantly more common in the younger group. The tendency for infection in younger patients suggests the requirement of monitoring the site infection and the need to avoid the manipulation of the surgical site post implantation in those patients.

	4-11 years	12-21 years	Incidence Rate Ratio
Complications Implantation	% total report	% total report	
Infection	6.40%	3.44%	1.53 (1.11)
Extrusion of lead	1.13%	0.26%	3.62 (1.3)
Side Effects Stimulation			
Painful Stimulation	6.25%	10.27	0.50 (0.39)
Pain	4.52%	7.70%	0.48 (0.36)
Voice Alteration	4.97%	6.26%	0.65 (0.48)
Stimulation Not Perceived	2.79%	5.08%	0.45 (0.31-0.66)
Coughing	3.54%	4.52%	0.64 (0.45)
Migration of generator	0.9%	2.46%	0.30 (0.16-0.57)
Dysphagia	1.05%	2.05%	0.42 (0.23)
Cognitive changes	1.20%	1.80%	0.55(0.31)
Erratic stimulation perceived	0.30%	0.77%	0.32 (0.11-0.97)
Continuous stimulation perceived	0.23%	0.67%	0.28 (0.08-0.98)
Syncope	0.08%	0.56%	0.11 (0.01)

Table 6. Summary of the most common complications & side effects described in the literature.

Further literature, makes a distinction between the side effects of complications related to the implantation of the VNS and the side effects related to device stimulation. The complications of the VNS are not common, rated in 2.5-12.5% and increases with time,

related to repeated surgeries for PG replacement and problems with hardware (193, 221, 222, 223, 227, 244, 261, 262, 263, 264, 265). In a 62 month follow-up of 143 patients implanted with VNS, the surgical complications were higher than other studies, 16.8% (266). The most frequently described complication of the implantation is infection. The overall rate of infection goes from 2.6 to 8%. Most of the cases respond to oral antibiotics, but in some cases it is necessary to explant the device (132, 193, 263, 265, 267). The infection rate is higher in the paediatric population as previously described in the premarket studies (219, 265, 268). Less frequent infection occurs during the battery replacement, rated at 1.1% (265). Another not uncommon complication of the implantation is pain at the incision site, impacting up to 30% of the patients in some series, which typically resolves in one or two weeks (269).

Left vocal cord paralysis has been reported in 1-5.6 % of VNS implantations, with complete recovery over time (193, 244, 263, 265, 267, 270, 271). A tendency of vocal cord paralysis when using lead that had 2 mm inner diameter, compared to 3 mm, was reported (272). Lower facial weakness is a rare complication, in only 0.2% in the Révész et al. study (265). It has been associated to high surgical incisions, recommending horizontal skin incisions to minimize the risk (265). Hematoma in the area of the PG implantation occurs In 1.9% of cases, requiring in most cases a conservative treatment (265). In Kahlow and Olivecrona there were three cases of perioperative jugular vein puncture (266), and Elliot et al. found twelve patients with some degree of permanent vagus nerve injury and one case of pneumothorax (221). Other infrequent complications are pain and sensory-related complications, aseptic reaction, cable discomfort, postoperative hoarseness and oversized stimulator pocket (265).

Rare but severe complications of VNS implantation are bradychiaradia and asystole (134, 240, 261, 273, 274). It has been described, that bradychiaradia and the asystole happen in 1 out of every 1000 cases implanted. The cases described occurred in the operating room during the initial device testing and they were controlled with the administration of

adrenaline and/or atropine, in combination with cardiac compressions (261, 275).

Complications related to the lead have been described as occurring in approximately 3.7% (from 0.5 to 20.8%) of all cases, which includes lead fracture/malfunction in 3%, spontaneous VNS turn-on in 0.2%, lead disconnection in 0.2% (265). Most of these complications are related to an older model of leads, especially Model 300, which was more susceptible to breakage and it is no longer available (265).

Cases of side effects related to VNS stimulation are relatively frequent, reported in 68% in some series, and considered mild to moderate in 97.8% (276). The side effects usually happen after VNS adjustments and disappear with time or after adjustment of the stimulation, especially the frequency and the current (190, 193, 277). The most common side effects related to the stimulation are: voice change (6-66%), hoarseness (1.4-64%), cough (7-55%), dyspnea (2-25%), headache (7-30%), neck pain (0.5-22%), throat pain (4.7-22), chest pain (13%), and dysphagia (13-20%) (58, 92, 176, 190,278, 279, 280). An improvement with time is often reported, resolving most side effects after one to two years of continued VNS use (275). In the study of Ben-Menachen et al published in 2015, voice alteration was present in 62% of the patients treated with VNS at 3 months and 20% after 5 years (257). In a similar way, other studies showed that 2 years post implantation the cough decreases from 66% to 5.9% (197).

The previously described side effects are the most common side effects related to the stimulation. There are other side effects reported only in some cases in the literature. Examples of other side effects that have been described are extrapyramidal side-effects (281), late-onset trigeminal pain associated with VNS (282), obstructive sleep apnea (283, 284, 285), psychosis or mania (286), glossopharyngeal tonsillar pain (287), pharyngeal dysesthesias (288), altered Strata valve (Medtronic, Goleta, California) due to magnet use (289). The side effects in the paediatric population are the same as in adults and side effects improve over time (191, 198, 290). In the paediatric population swallowing difficulties have been detected, usually related to patients with severe motor disabilities

(198, 291).

Important mention needs to be made concerning the delayed bradycardia and heart block that is an extremely rare complication related to the stimulation. Delayed bradycardia and heart block have been described in three children and an adult, ages 13, 13, 17 and 47. The arrhythmia occurred 2-9 years after the implantation, which was resolved by turning off the device in two cases (292). The cause of this complication has been related to the manipulation of the vagus nerve, the interaction with ASD, possible microvascular injury and fibrosis, and nerve dysfunction (293).

Twiddler syndrome has been described as an infrequent syndrome in association with the VNS. This was firstly associated with cardiac pacemakers, with flipping on its' long axis and retracting the leads and coiling around the pacemaker boot (294). The VNS in Twiddler syndrome can flip along the long and also the short axis. In the literature, there are only two cases published but it is important to recognize this syndrome in cases of malfunction of the VNS (267, 294). The lead tends to fracture, but it is possible to be recognized by a radiologist. The risk of this syndrome is higher in elderly, obese and children, and is related to the laxity of the subcutaneous tissue (294).

Patients with epilepsy have two to three-fold increased risk of premature death and this risk is highest in patients with refractory epilepsy and those with neurologic and cognitive deficits (296). The SUDEP rate was reported at 0.09-2.3/1000 patients per year (py) and increasing to 9.3/1000 py in epilepsy surgery referrals (296, 297, 298, 299, 300, 301). Annegers' study found that the risk of SUDEP decreased two years after implantation, with 5.5/1000 py during the first two years and 1.7/1000 py thereafter (276). However, more recent study did not find a decrease in the risk of SUDEP after VNS implantation, with SUDEP rate at 3.4/1000 py the first two years and 3.3/1000 py after two years (296). The study did find a significantly higher risk in male patients compared to female (5.3/1000 py compared to 1.3/1000 py). The patients in this study used earlier PG models

and did not include heart rate detection (296). But there is no evidence that patients with VNS have an increased pre-existing elevated risk of SUDEP (296).

Many studies have been published concerning the possible devastating consequences for the fetus and increment of the risk of obstetrical complication of the mother with MRE (302). The ASM can have teratogenic effects to fetus and irreversible consequences for the newborn (181). The information concerning the safety of VNS use during pregnancy is limited. There are less than 40 cases worldwide, with moderate evidence of the safety of the VNS device with some data suggesting a slight increase in the risk of obstetrical complications (182, 183, 184, 303).

1.2.2.3.11. COST-UTILITY ANALYSIS

The VNS was approved in the 1990's around the world. Until January 2016, Livanova Head Office stated that 100,000 patients have been implanted with VNS and 133,000 generators have been implanted worldwide. The implant rates in 2017 in US, UK and Canada showed the following numbers: 27 per 1 million people with Epilepsy, 12 per 1 million people with Epilepsy and 4 per 1 million people with Epilepsy, respectively.

The costs of the VNS devices without including the implantation or clinics, has been increasing from the initial $9,200 USD (10362,45 euros) for the PG model 100, to over $18,000 USD (20274,35 €) for the PG 105 and PG 30000 models, as well as the current Aspire SR106 model. The incremental increases in the prices are related to the technology incorporated in the device and the post implantation service that the company is providing to the physicians, patients and caregivers.

The costs to the epileptic patients are related to both the direct and indirect costs. The direct costs are related to the actual expenditure for the range of treatment (including medications, hospitalizations, follow ups, EEG, neuroimaging, presurgical evaluations,

surgeries, etc.) and rehabilitation services for persons with epilepsy. The indirect costs are considered the costs due to a decrease of output and value, such as those who are working less, relatives missing work to look after patients or premature death due to their disease or complications (304). However, there is also intangible costs, such as pain and suffering, emotional distress, and reduced quality of life (QOL). Even if intangible costs are recognized as an important component of indirect cost and not included in some studies, it should be taken into consideration (305).

The 1975 report from the Department of Health, Education and Welfare (DHEW) estimated the total US costs for epilepsy were $15.96 billion USD (adjusted for inflation to the year 1995) (17976594326,88 €) (306). The report estimated that epilepsy accounted 20% of the total central nervous system diseases costs in 1975, and 85% of the costs were indirect costs (307). Several studies have been published estimating the direct and indirect costs of the epileptic population. Special distinction needs to be made for the general group of epileptic patients and the patients with MRE, it is evident that they will use more resources with an increment of the direct and indirect costs. Halperm et al (2000) showed the difference of the average cost per patient in remission after the initial diagnosis and treatment was $5,786 USD (4888,39 €) less and in persons with MRE was $187,726 USD (211445,75 €) less (308). For patients with MRE, it is estimated that the direct costs are smaller and only represent 40% of the total of the costs (309). Medications contribute more than hospital admissions to the direct costs and the costs of the newer medications are more expensive than the older (310, 311, 234).

Another consideration for patients with MRE is the treatment that they undergo and the cost related to the treatment and the response to the treatment. In 2002, Boon et al. published a paper that included 84 patients with MRE, followed them two years previous to the surgery or therapeutic decision and for two year after the surgery or therapeutic decision (312). In the study, the sample was divided into three groups depending on the treatment, and 29% (N=24) continued politherapy with ASM, 40% (N=35) underwent

epilepsy surgery and 30% (N=25) were implanted with VNS. The study analysed the cost of hospitalizations, clinic visits, antiseizure medications, laboratory tests and epilepsy-related direct medical costs (ERDMC). In the surgical group, epilepsy surgery added $4,000 USD (4505,41 €) to the ERDMC and in the VNS group $10,000 USD (11263,53 €) was added to the ERDMC. The study showed that the cost reduction was statistically significant in the surgical and VNS group compared to pharmacological treatment alone. But when both of these two groups were compared, there were no differences (312).

In the study conducted by Ben-Menachen et al. evaluated the direct health cost of 43 patients implanted with VNS (313). It analysed 18 months before and 18 moths after and quantified the number of unplanned visits to the medical ward, surgery ward, neurology ward, emergency room, and intensive care unit that were attributed to epilepsy, treatment of emergent side effects due to epilepsy treatment, or injuries due to seizures. The costs for all patients before VNS was $211,000 USD (237660,49 €) and costs for all patients after VNS was $30,375 USD (34212,97 €), an average annual cost saving of approximately $3,000 USD (3379,06 €) per patient, irrespective of whether the patient responded to VNS or not. The result of that study showed that the purchase price of the VNS therapy could be absorbed within 2 to 3 years (313). A similar study published recently that included patients with MRE from the age of 12 years old or older, showed similar results (314). The estimated net cost savings using VNS over 5 years (on average) resulted in the reduction in seizure frequency, especially a reduction in hospitalization, and the costs were offset after 1.7 years after implantation (314).

Forbes et al. realized a meta-analysis of randomized controlled trials of VNS, and estimated that six people require implantation in order for one person to experience a 50% reduction in seizure frequency (315). The improvement of epilepsy reduced, on average, £745 (839 €) in health care costs per year. When the study considered needing 6 implantations to have one successful treatment, the baseline model estimated the cost per quality adjusted life year gained £28 849 (32494.2 €). In theoretical cases, where it is

possible to identify and implant a group with a high response rate, an extremely favourable cost per quality adjusted life year value of £4785 (5389.6 €) was found (assuming one out of every three people implanted are responders) (315).

Other study analyzed retrospectively 138 patients who were implanted with VNS and how this device affected the utilization of medical services 12 months before implantation and quarterly rates during 48 months of follow-up (316). The results showed statistically significant reductions in number of emergency department visits, hospitalizations, and hospital lengths of stay beginning in the first quarter after implantation. However, immediately after implantation the average number of outpatient visits was significantly greater than the pre-implant quarterly average, related to setting adjustment. The number of outpatient visits decreased by the fourth quarter of the first year after implantation having on average 12.2% reduction in visits. Similarly, the study found a significant decrease, after patients were implanted, in the average number of days in which patients could not work due of health-related concerns and time spent caring for health problems (316).

The biggest study concerning the economic and medical long-term effects of the VNS was published in 2011 by Helmers et al. (217). A total of 1655 patients were included and there was a pre-VNS period of 6 months and post-VNS period up to 3 years. The total health care costs on average were lower post-VNS than pre-VNS ($18,550 USD vs. $19,945 USD) (20893,85 € vs. 22465,11 €) and VNS is associated with decreased resource utilization and epilepsy-related clinical events (217).

2. OBJECTIVES

The principal objective of this study is to define the seizure response in our patients and evaluate the seizure reduction rates.

The secondary outcomes are:

- Describe the epilepsy characteristics of all types of epilepsy, types of EEG alterations, brain MRI abnormalities, and seizures types of the population who underwent VNS implantation.
- Define the possible predictor factors in the group of responders to the VNS implantation.
- Analysis of VNS' related factors to obtain a better response in patients implanted with the VNS.
- Define other possible benefits of VNS therapy.
- Evaluate the efficacy of VNS in our subpopulation of refractory generalized epilepsy.
- Evaluate the efficacy of VNS in our paediatric population implanted with this device.
- Describe the safeness of VNS, taking into consideration the side effects and the complications.

3. PATIENTS AND METHODS

3.1. PATIENTS SAMPLE

The patients included in this study are patients with medically-resistant epilepsy, following the ILAE definition, were implanted with vagus nerve stimulation (VNS) device at the London Health Science Centre (LHSC) – Western University, and are in the LHSC the Epilepsy Program. The period of inclusion was from 1997, when the VNS was approved in Canada, to July 2018.

3.2. STUDY DESIGN

This was a retrospective, observational and descriptive study that included patients with medically resistant epilepsy who were implanted with VNS at the London Health Science Centre (adults and children) from when the VNS was available in Canada (1997) to July 2018.

The study protocol was approved by the ethics committee at the London Health Science Centre/Western University and followed the Declaration of Helsinki code of ethics.

3.3 INCLUSION CRITERIA

The inclusion criteria was:

- The patients had medically resistant epilepsy.
- The VNS implantation was done to try to control the seizures.
- The patients were not candidates for respective epilepsy surgery, or had a failure to a previous resection.
- They didn't have any other treatment option to try to improve the seizure frequency.
- The patients underwent VNS implantation in London Health Science Centre-Western University, London, Ontario.

- The frequency and/or severity of the seizures cause an impairment of quality of life.
- The patients were followed up in our centre for at least three months after the VNS implantation.

3.4 EXCLUSION CRITERIA

The exclusion criteria was:

- The patients were implanted with a VNS at a centre other than London Health Science Centre – Western University.
- The patients were implanted with a VNS for a different reason than medically resistant epilepsy.
- There was no patient follow up at our centre or the follow up was less than three months since VNS implantation.

3.5. COLLECTING DATA AND VARIABLES

The data collected was concerning patients implanted with VNS for epilepsy management. The data was collected from patient's chart in the paper format and the electronic format (powerchart). The variables collected were divided into pre-implantation and post-implantation variables.

3.5.1. PRE-IMPLANTATION VARIABLES

The patient information concerning patient's characteristics before implantation were:

- Demographic information: age, sex, and hand dominance.
- Epilepsy history: epilepsy onset age, family history of epilepsy, history of status epilepticus.

- Comorbidities: psychiatric, headache, intellectual disabilities, non-epileptic seizures.
- Epilepsy features: type of epilepsy, epilepsy etiology, brain MRI findings, EEG findings, reason not to be a candidate for epilepsy surgery, seizures types, seizure frequency before VNS was implanted (the frequency of seizure pre implantation was defined as the median of the frequency of seizures from 3 to 12 months before implantation).
- Epilepsy management pre-VNS implantation: number of previous ASD before the implantation, number of ASD at the time of VNS implantation, dose of the medication, previous epilepsy surgeries, hospital admissions related to seizures, neuropsychology evaluation, EMU admissions for epilepsy diagnosis, implantation with invasive electrodes for seizure onset zone localization.

3.5.2. POST-IMPLANTATION VARIABLES

The second group of variables are related to seizure outcomes and VNS devices. They were:

- Related with time: age of implantation, years between the onset of the epilepsy and the age of implantation, period of follow up since the VNS implantation, length of VNS battery duration.

- Outcomes: The seizure frequency after the VNS was implanted was the median of the total number of seizures (all types and each type) per month at the time of the last follow-up. In 26 patients the frequency of seizures at 6 months, 1 year and 2 years was analysed. The other outcome was the seizure frequency reduction rate, which was calculated as result of the seizure frequency per month before the implantation minus the seizure frequency per month after the VNS implantation, divided by frequency per month before the VNS implantation, expressed in a percentage. A patient was considered a responder when the seizure frequency reduction rate was 50% or more. Negative results meant that the patient had a reduction in the frequency of seizures from the baseline. Positive results

meant the opposite, an increment of the seizure frequency rate. A 0% seizure frequency rate represented no response after VNS use.

- Other outcomes: reduction of the intensity of seizures, reduction of the duration of seizures, improvement of mood and/or energy, period of seizure freedom, number of hospital admissions after the VNS implantation, subjective improvement after VNS therapy from the patient, relative/caregiver of the patient, or attending epileptologist of the patient.
- VNS settings: the parameters of the normal mode, magnet mode and in some cases autoStim mode, and frequency of different VNS models.
- Adverse events: complications related to VNS implantations and side effects related to the VNS stimulation.

3.6. SUBANALYSIS

In addition to the analysis of all patients, the first subanalysis was completed to analyse the response of the VNS in the paediatric group. The variables analysed were the same as the general and first subanalysis. In this subanalysis, all the patients that followed the inclusion criteria were included. The inclusion criteria was:

- A history of MRE
- Implanted with VNS in our centre (Western University-London Health Science Centre) for epilepsy management
- The frequency and/or severity of the seizures caused an impairment to quality of life
- Age of implantation was 17 years-old or younger.

The second subanalysis completed was concerning the response in patients who had generalized epilepsy and were implanted with VNS. However, the only two groups included were patients with clinical history and electrographic findings compatible with Lennox-Gastaut Syndrome (LGS) and Genetic Generalized Epilepsy (GGE). To select that

group, the inclusion criteria was:

- We considered LGS when there was a history of different types of seizures (including tonic, atonic, generalized tonic-clonic and atypical absences), intellectual disabilities, and generalized slow spikes/spike waves in the EEG.
- The other group was GGE, which included the following syndromes: Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic-Clinic Seizures Alone. The diagnosis of GGE was made with the combination of >2.5 Hz generalized spike-and-wave on EEG recordings and history of absences, myoclonic, atonic, tonic and/or generalized tonic-conic seizures, in otherwise a person with no cognitive impairment (11 reference G. Epilepsy paper)
- A history of MRE.
- Was implanted with VNS in our centre (London Health Science Centre – Western University) for epilepsy management
- The frequency and/or severity of the seizures cause an impairment to quality of life

Cases that did not follow one or more of these conditions were not included in the analysis. The objective was to analyse the VNS response for seizure management in these two groups with generalized epilepsy and to learn about predictor factors of good outcomes, which was defined as a responder. A patient was considered a responder when seizure frequency reduction rate was 50% or more.

The last subanalysis was related to the safeness of the VNS during pregnancy and the outcome of the babies born from the mothers who were receiving VNS therapy during their pregnancy. This part of the subanalysis was a descriptive analysis due to the small number of patients included.

3.7. STATISTICAL ANALYSIS

The statistical analyses of the general group was performed using SAS version 9.4 and the threshold of significance was $p < 0.05$. Continuous variables were summarized using median and interquartile range and the categorical variables using absolute frequencies and percentages.

The VNS efficacy was evaluated using the seizure frequency rate reduction and it was calculated as the result of the seizure frequency per month before the implantation minus the seizure frequency per month after the VNS implantation, divided by frequency per month before the VNS implantation, expressed in a percentage. It was considered a continuous variable and in other analyses as a categorical variable. The continued variable was the absolute number of reduction of seizures (in percentage) comparing before and after VNS implantation. The categorical variable was considered a dichotomy parameter; the ones who had less than a 50% seizure reduction rate were considered non-responders and the ones with a 50% or greater seizure reduction rate, as responders.

In the subanalyses of effectiveness, the effectiveness variable used a continuous variable. To analyze the continuous variables, we used Wilcoxon Signed Rank Test or t-test, depending on if the variables did not follow a normal distribution. We used the Kolmogorov-Smirnov test to verify the normality in the distribution in our variables. When considering categorical variables, Fisher's Exact Test was applied. In the analysis of VNS efficacy over time, we used an ordinary least squares (OLS) linear regression line.

The subanalysis of the paediatric group was completed using SPSS version 22.0. The continuous variables were presented using median and interquartile range. In the bivariate analysis a seizures reduction of 50% or more was considered as an outcome. In the case of categorical variables, a Chi square test was used, and when the number of cases included was less than five, Fisher's Exact Test was used. In the case of continuous variables, normality was tested using Kolmogorov-Smirnov test. In case of normal

distribution, the analysis was completed using Student t-test. When it did not follow a normal distribution a U-Mann-Whitney test was applied. The threshold of significance was $p<0.05$.

In the other subanalysis of the generalized epilepsy group, the descriptive analysis was completed using the same statistical measures as the general group. On this occasion, the sample was smaller and neither group followed a normal distribution. We used the continuous variable Wilcoxon Rank-Sum Test or Mann-Whitney-Wilcoxon test. For categorical variables, Fisher's Exact Test was used. The VNS efficacy over time in the generalized epilepsy group was completed using a simple regression mode.

4. RESULTS

4.1. VNS IN EPILEPSY

4.1.1. PREOPERATIVE VARIABLES

A total of 114 patients were implanted with VNS in our centre with a history of MRE, 56.1% (n=64) of them were men and 43.9% (n=50) were women. The hand dominant was right in 72.8% (n=83), left in 14% (n=16) and 13.2% (n=15) undefined. See **figure 16.**

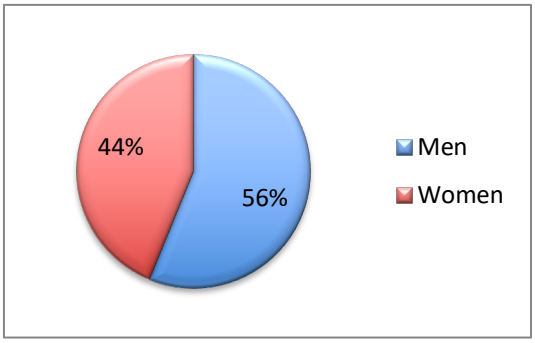


Figure 16. Sex distribution of the sample.

.

The median age of the sample was 35.4 years old (IQR= 28.1-44.0) and the implantation age was 26.5 (IQR= 20-34). The ages and times of the epilepsy duration, expressed in year-old and years, are summarized in the **table 7.**

	Median	IQR	Range
Age of epilepsy onset	7.5	2-14	Birth-56
Age of VNS implantation	26.5	20-34	1.25-59
Age of the sample	35.4	28.1-44.0	1.45-64.1
Total epilepsy duration	22.7	15.6-34.7	0.2-61.7
Duration epilepsy at the time of the implantation	15	9-23.3	0.1-57.5

Table 7. Ages and epilepsy times in the patients of the sample.

The average number of previous trials of antiseizure medication was 5 (IQR= 3-6). The most frequently administered ASD were valproic acid and phenytoin, used in 52.6% (n=60), followed by clobazam in 44.7% (n=51), and carbamazepine and topiramate in 42.1% (n=48) of the cases. The rest of ASD are summarized in the **table 8.**

ASD	Number	%
BVR	0	
CBZ	48	42.1
CLB	51	44.7
CNZ/CZP	14	12.3
ESL	0	
ETX	20	17.5
FLB	2	1.8
GBP	13	11.4
LCS	12	10.5
LMT	45	39.5
LEV	30	26.3
OXC	12	10.5
PER	7	6.1
PB	37	32.5
PHT	60	52.6
PGB	5	4.4
PRM	21	18.4
RFN	6	5.3
TPM	48	42.1
VPA	60	52.6
VGB	14	12.4
ZNS	1	0.9
CBD	4	3.5
Ketogenic	10	8.8

Table 8. Summary of antiseizure medication before VNS implantation. ASM: antiseizure drug; BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol.

At the time of implantation the median number of ASD was 3 (IQR= 2-3). The most commonly used ASD were lamotrigine in 36% (n=41) with a median dose per day of 300 mg (IQR= 200-400), topiramate 33.3% (n=38) as a 225 mg (IQR= 200-381.3), phenytoin 28.9% (n=33) with 300 mg dose (IQR= 200-475) and levetiracetam in 26.5% (n=30) as 2000 mg dose (IQR= 1000-3000). The rest of the data is summarized in the **table 9.**

ASD	N	%	Dose media (mg/24h)	Min	Max	IQR
BVR	2	1.8	125	50	200	50-125
CBZ	23	20.2	1200	800	2800	1000-1600
CLB	28	24.6	20	10	70	10-30
CZP	11	9.6	1.5	1	4	1-2
ESL	2	1.8	800	800	800	
ETX	1	1.8	1500			
FLB	1	0.9	1650			
GBP	3	2.6	2400	300	3000	
LCS	21	18.4	400	300	600	400-450
LMT	41	36	300	50	775	200-400
LEV	30	26.5	2000	500	4000	1000-3000
OXC	9	7.9	1500	300	2300	600-1650
PER	2	1.8	11	10	12	
PB	6	5.3	90	20	180	21.88-135
PHT	33	28.9	300	50	600	200-475
PGB	1	0.9	225			
PRM	13	11.4	500	250	875	312.5-500
RFN	7	6.1	1200	800	2400	800-2100
TPM	38	33.3	225	50	600	200-381.25
VGB	7	6.1	1400	1000	4000	1000-3000
VPA	29	25.4	1000	250	3000	750-1625
ZNS	0					
CBD	2		6.5	4	9	
Ketogenic	0					

Table 9. Summary of the ASM at the time of the time of VNS implantation. ASM: antiseizure drug; BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; N: number; Max: maximum dose; Min: minimum dose; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol.

There was a history of status epilepticus in 38.7% (n=43) (see **figure 17**). 91.9% (n=102) were admitted to the hospital for seizure management at some point and 94.7% (n=108) were admitted to the Epilepsy Monitoring Unit (EMU) for further evaluation or diagnostic purposes. The median days admitted in the EMU were 7 (IQR= 5-11).

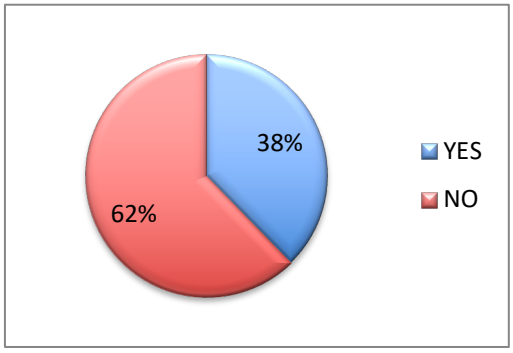
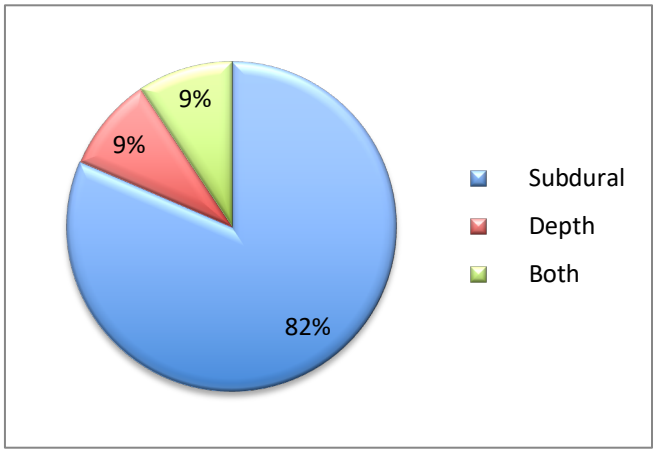


Figure 17. Proportion of the sample with history of status epilepticus.

This refractory epileptic sample underwent presurgical evaluation, 15.8% (n=18) of patients had their neuropsychology evaluation. Invasive electrodes, as a part of the presurgical investigation, were done in 28.1% (n=32). The most common electrodes used were subdural, in 22.8% (n=26) of the total population. See **figure 18.**

Figure 18. Different invasive electrodes used in our patients.



As a refractory epilepsy group, 29.8% (n=34) underwent epilepsy surgery and in 90.9% (n=30) the surgery was done before the VNS implantation. The most common one was corpus callosotomy in 55% (n=21), followed by right temporal lobectomy in 13% (n= 5) and left temporal lobectomy 11% (n=4). The rest of the surgeries are showed in the **figure 19**.

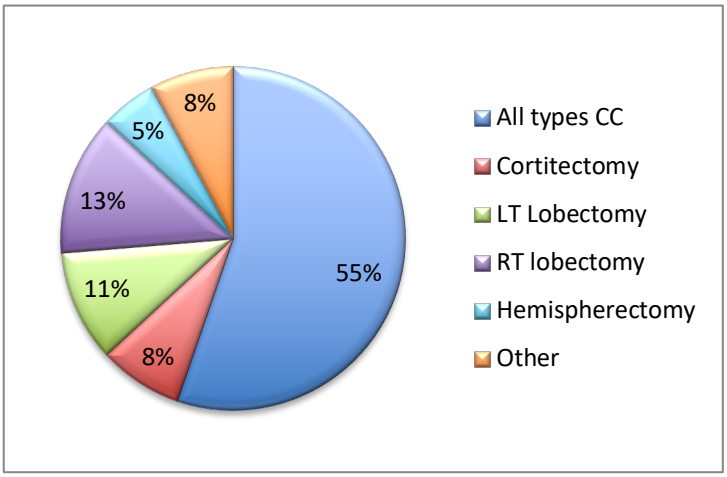
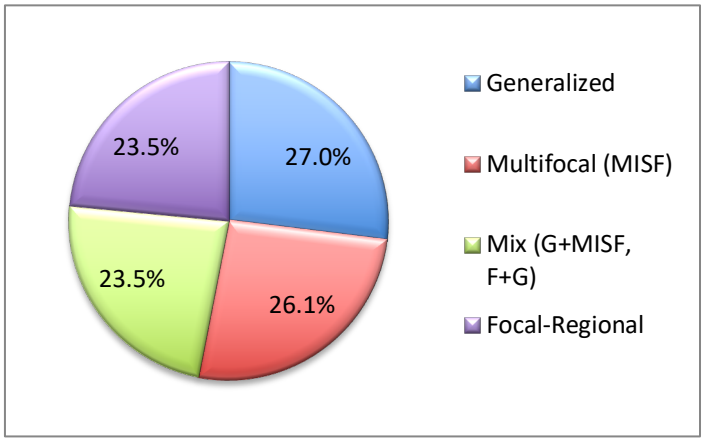


Figure 19. Distribution of the different epilepsy surgeries that patients underwent. CC: Corpus callosotomy; LT: Left temporal; RT: Right temporal.

The type of epilepsy was classified in generalized 27% (n=31), multifocal 26% (n=30), focal-regional 23.5% (n= 27) and mix or combination as generalized and multifocal or focal and generalized in 23.5% (n=27). See **figure 20.**

Figure 20. Different types of epilepsy found in our sample. MISF: multiple independent spike foci; G: Generalized; F: Focal.



The head CT was done in 100% (n=114) and 94.8% (n=109) brain MRI. The most common findings were normal MRI in 32% (n=38), unspecific findings in 23% (n=28), encephalomalacia in 21% (n=18) and malformation of cortical development (MCD) in 11% (n=13). These findings and other MRI findings are shown in the **figure 21**.

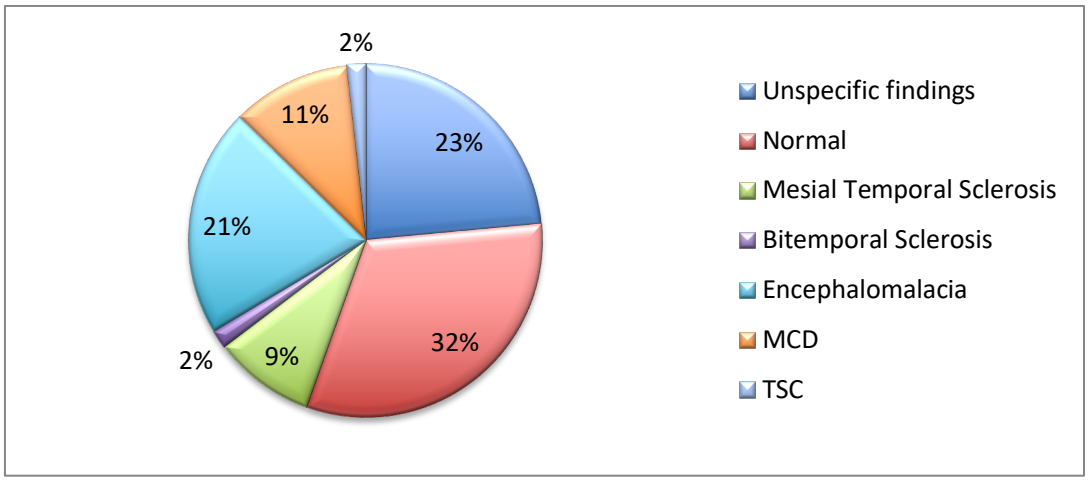


Figure 21. Different MRI findings of patients who underwent VNS implantation. MCD: Malformation of the cortical development; TSC: Tuberous Sclerosis Complex.

The EEG pattern of each patient was collected. The most frequent abnormalities were generalized discharges in 27% (n=31), multifocal pattern in 26.1% (n=30) and the association of generalized epileptiform discharges and multifocal spikes in 20% (n=23). The rest of the EEG abnormalities are summarized in the **figure 22**.

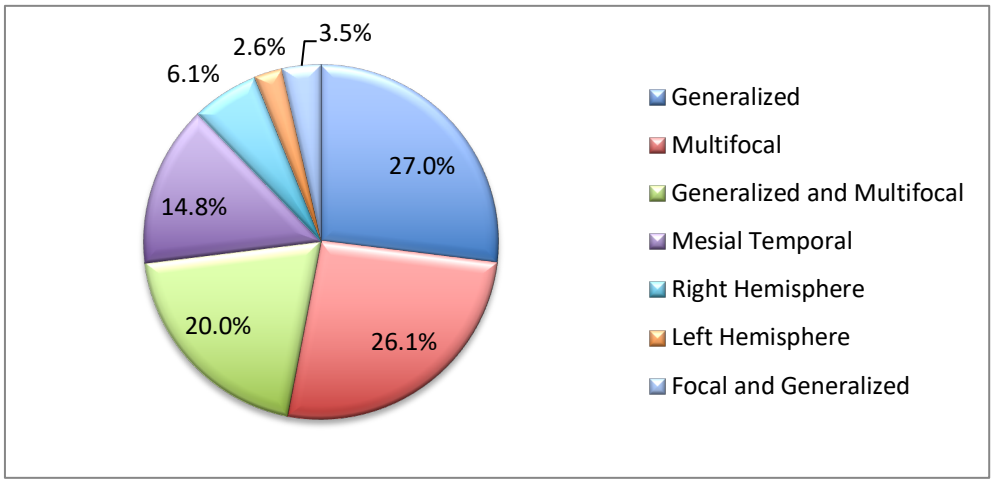


Figure 22. Different EEG abnormalities in the patients of the study.

In relation to the etiology of the patients implanted with VNS, the most frequent were unknown cause in 25% (n=38), related to structural abnormality in 20% (n=31), Lennox-Gastaut Syndrome (LGS) 19% (n=29). See **figure 23**.

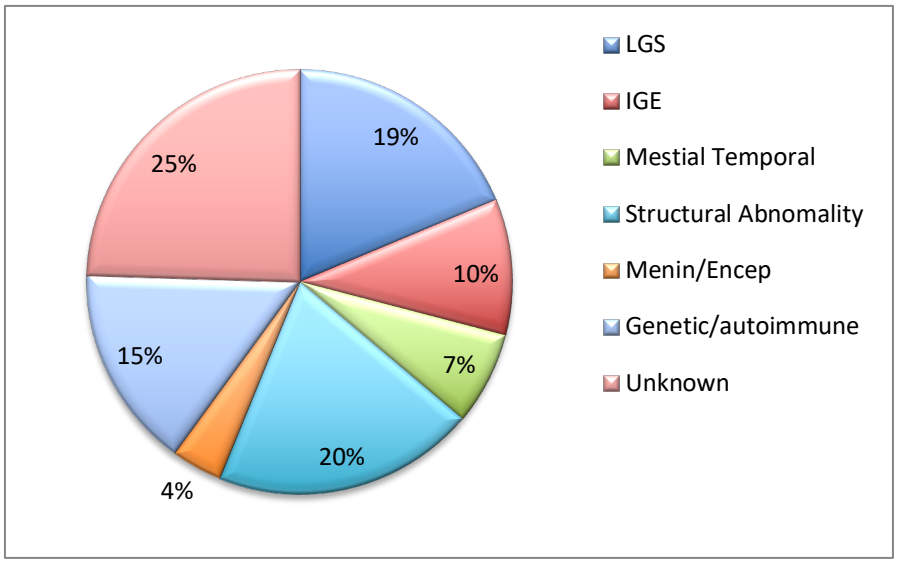


Figure 23. Different epilepsy etiologies. LGS: Lennox-Gastaut Syndrome; IGE: Idiopathic Generalized Epilepsy; Menin/Encep: Meningitis/Encephalitis.

The median number of different types of seizure was 3 (IQR= 2.75-4). The most frequent types were focal with impairment of awareness in 60 patients, focal in 55 and generalized tonic clonic in 54. The rest of the seizure types are shown in **figure 24** and **table 10**. The median number of seizures per month was 25 (IQR= 8.7-60).

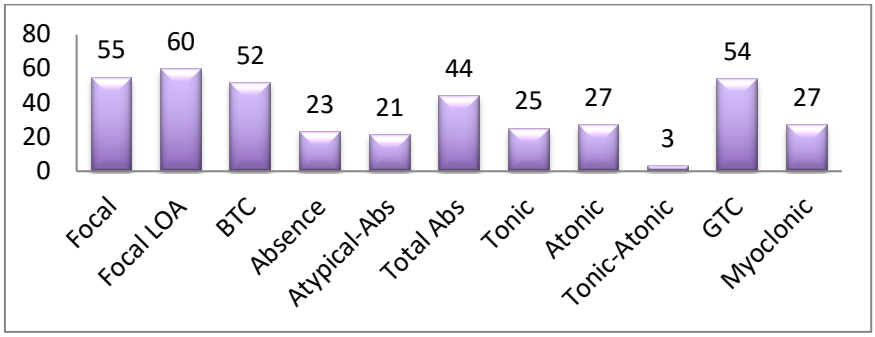
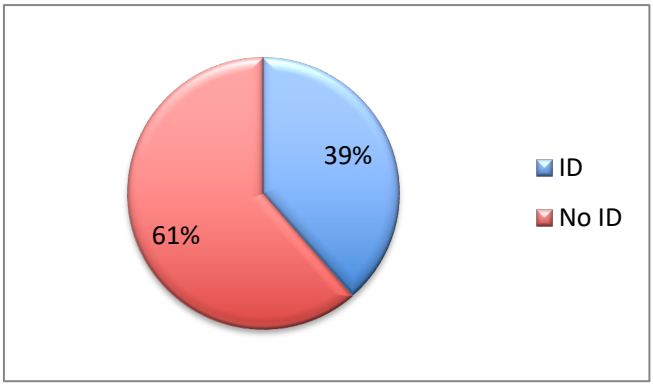


Figure 24: Distribution of the different types of seizures. LOA: Impairment of awareness; BTC: focal to bilateral tonic-clonic; Atypical-Abs: atypical absence; GTC: Generalized Tonic-Clonic.

Type Seizure	Media	IQR	Minimum	Maximum
GTC	6.5	2-22	0.5	330
Absence	30	12.13-110	4	600
Tonic	33.4	12.8-120	6	300
Atonic	37.5	30-56.3	30	60
Tonic-Atonic	6	1.8-30	1	60
Myoclonic	20	8-30	3.5	60
Focal	21	3.25-37.5	0.5	90
FocalLOA	10	5.5-30	1	900
BTC	2.5	1-7.5	0.1	375
Total	**25**	**8.7-60**	**2**	**901**

Table 10. Frequency of the different type of seizures. LOA: Impairment of awareness; BTC: focal to bilateral tonic-clonic; Atypical-Abs: atypical absence; GTC: Generalized Tonic-Clonic.

Another important characteristic about the sample was the proportion of patients with a history of intellectual disabilities, affection 38.6% (n=44) (see **figure 25**). Other interesting features were headache in 9.7% (n=11), 21.1% (n=24) psychiatric comorbidities, tumors (any type) in 2.6% (n=3) and PNES 7% (n=8).



.

Figure 25. Proportion of the sample with history of Intellectual disabilities. ID: Intellectual disabilities.

4.1.2. POSTIMPLANTATION VARIABLES

4.1.2.1. SEIZURE RESPONSE AFTER VNS IMPLANTATION

The average follow up of those patients was 46 m (IQR= 21.5-79.3 m), with a maximum of 268 months, over 22.3 years. The last follow up was the last time the VNS response was used for the evaluation of the outcome. The seizure freedom of all types of seizure was achieved in 21.1% (n=24), with a median period of seizure freedom of 3 months (IQR= 1-7.8m) (see **figure 26.a**). When it was considered only the generalized tonic-clonic, 14.1% (n=16) patients were seizure free for 9 m of median (IQR= 6.5-11.5). It represents 29% of the total patients with generalized seizure achieved seizure freedom for several months (see **figure 26.b**).

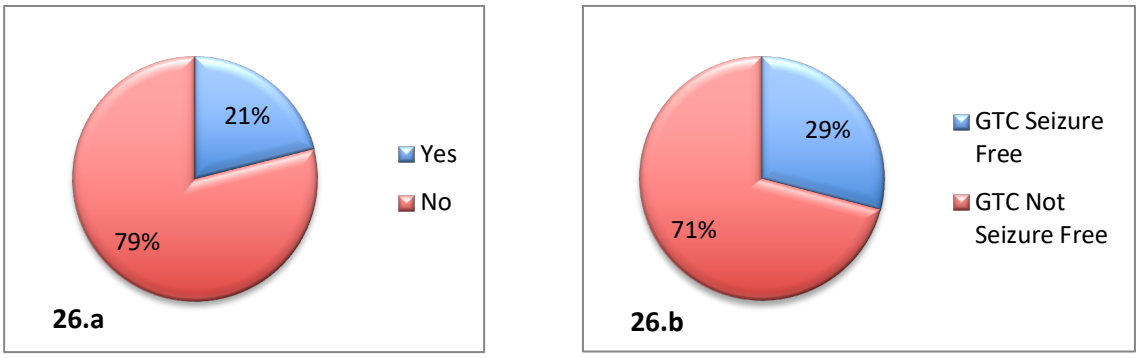


Figure 26: 26 a. Seizure freedom considering all types of seizures. **26 b.** Percentage of patients with generalized tonic-clonic seizures who achieved seizure freedom from generalized tonic-clonic. GTC: Generalized tonic-clonic seizures.

The median seizure rate reduction was -67.75% (IQR= (-92.55%)-(-37.17%)). The seizure reduction rate was divided into groups: 50% or more response, less than 50% response and no response. We found that 55.6% (n=41) had 50% or more seizure reduction, 21.2% (n=24) less than 50% and 23% (n=26) there was no effect (see **figure 27.a**). In the group with 50% or more seizure reduction, 17.5 % (n=11) of patients had a seizure response

between 50-60%, 17.5% (n=11) between 60% and less than 75%, and 34.9% (n=22) 75% or more (see **figure 27.b**).

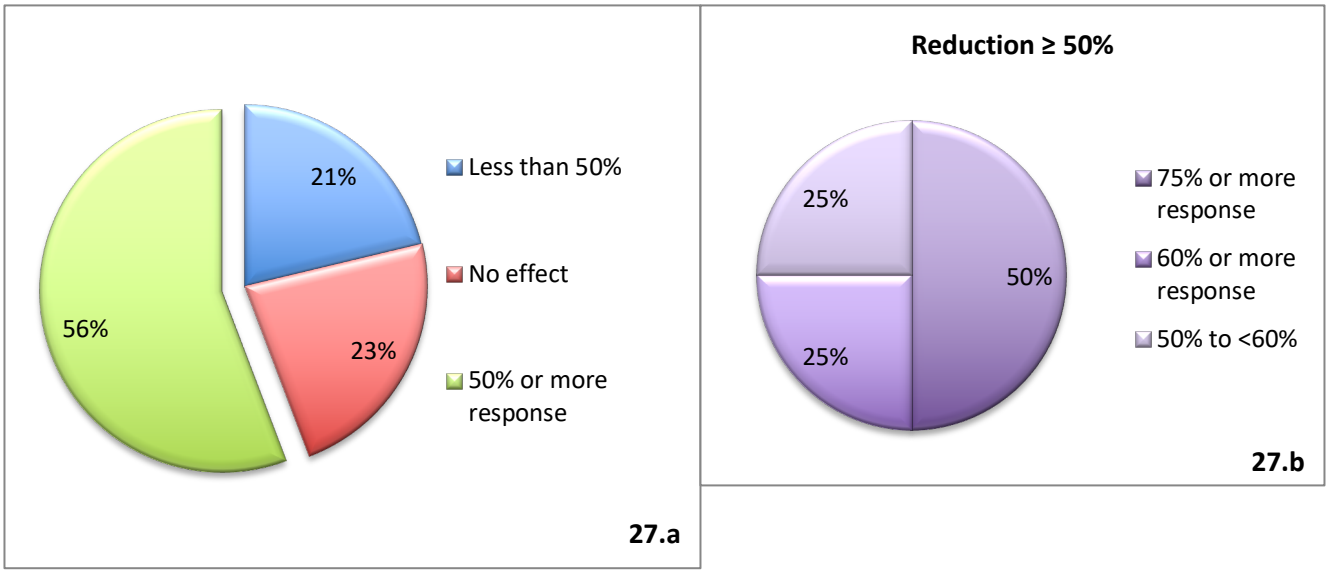


Figure 27 The **figure 27.a** shows the percentage of seizure reduction rate and in **figure 27.b** shows the percentages of responses that achieved a seizure reduction rate equal or greater than 50%.

The age was used as a parameter and it was divided into three groups. In the youngest group, with five year old or younger (n=5), there were four responders. In the middle group, there were four responders between six and fourteen (n=12) and older than fourteen (n=97). The seizure reduction was significant in the oldest group. See **table 11**.

Age Group	Total	Responders	No Responders	p-value
≤ 5 y-o	5	4 (80%)	1 (20%)	p=0.063
6 to 14 y-o	12	4 (33.3%)	8 (66.7%)	p=0.055
≥ 14 y-o	97	55 (56.7%)	42 (43.3%)	p>0.0001

Table 11. Number of responders and non-responders classified by age of VSN implantation.

The response of the VNS to control seizures was calculated over time. A linear regression model was used to analysis if the VNS effect improves over time, and there wasn't any clear improvement over time, taking into consideration the response at the last follow up. The p-value was 0.26. See **figure 28.**

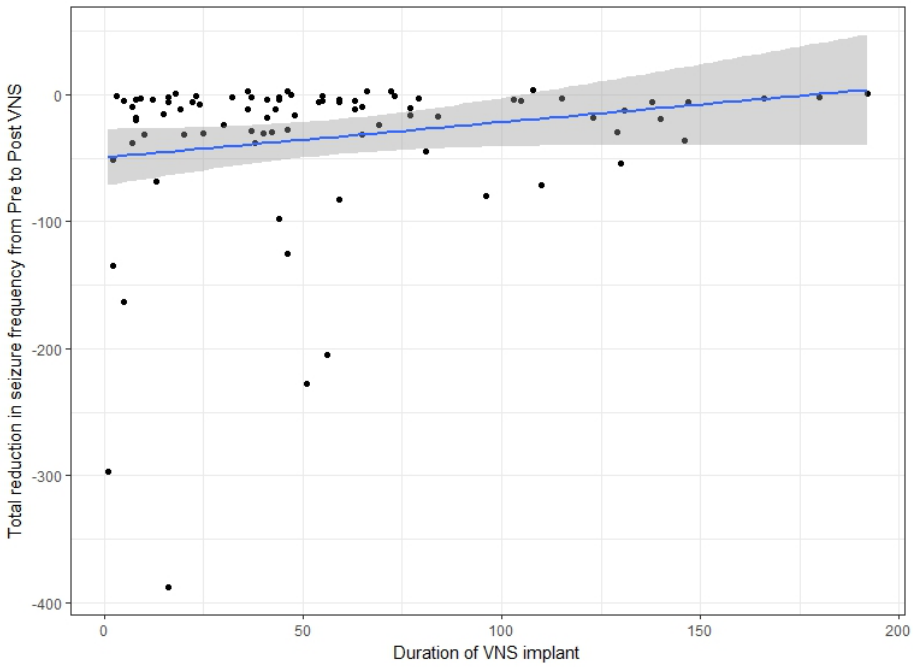


Figure 28. The regression model shows no clear improvement of the seizure reduction over the time of follow-up, with outliners removed.

In the analysis of the response of the VNS by type of seizure, there was a reduction in the number of each type of seizure, with variable responses. Findings show the VNS was effective in significantly reducing the seizures in focal with impairment of awareness (p=0.00013, focal to bilateral tonic-clonic (p=0.0007), generalized tonic clonic (p=0.0037) (see **figure 29**). The seizure types that didn't show a significant reduction were: focal (p=0.063), absence (p=0.092) and myoclonic (p=0.81). **Figure 30** shows the number of seizures before and after VNS implantation.

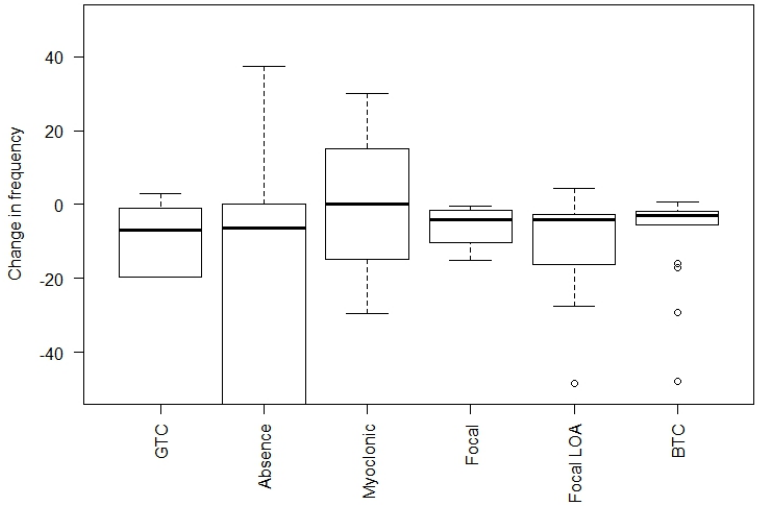


Figure 29. Seizure reduction after VNS implantation classified by type of seizures, outliners removed. GTC: Generalized tonic-clonic seizures; Focal LOA: Focal seizures with impairment of awareness; BTC: focal to bilateral tonic-clonic.

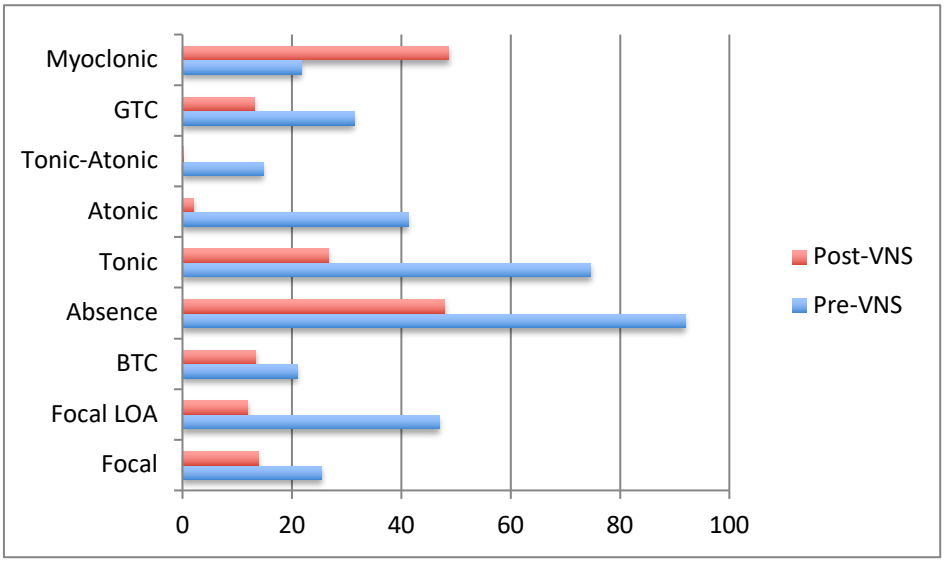


Figure 30. The number of each type of seizure before and after VNS implantation (in the last follow-up). GTC: Generalized tonic-clonic seizures; Focal LOA: Focal seizures with impairment of awareness; BTC: focal to bilateral tonic-clonic; Pre-VNS: pre-VNS implantation; Post-VNS: Post-VNS implantation.

Another analysis that we conducted was the response of the VNS was dependent upon the number of seizures before the implantation. It was analysed using a regression model. The result was not significant, representing that the total amount of seizures does not have better reduction than the ones with just a few seizures. The p-value was 0.155 and it is represented in **figure 31**.

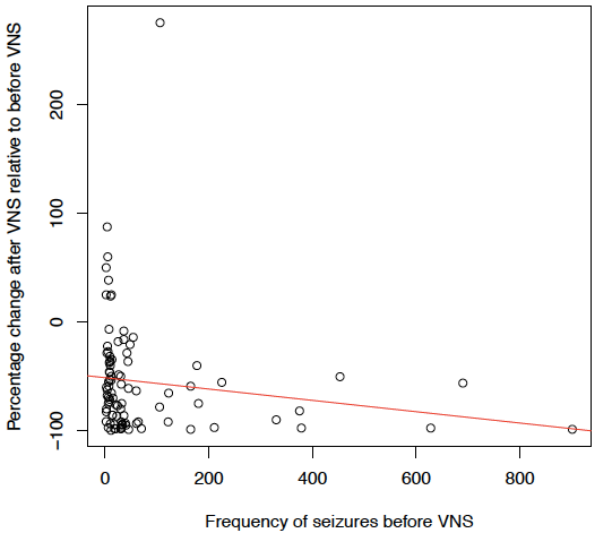


Figure 31. Percent of change after VNS implantation in reference to the frequency of seizures (total number of seizures) before VNS implantation.

4.1.2.2. SEIZURE RESPONSE OVER THE TIME

In 26 patients we were able to analyse the response over time in three different timelines: 6 months, 1 year and 2 years. There was not any improvement over time in those timelines. See **figure 28, 32, 33** and **table 12.**

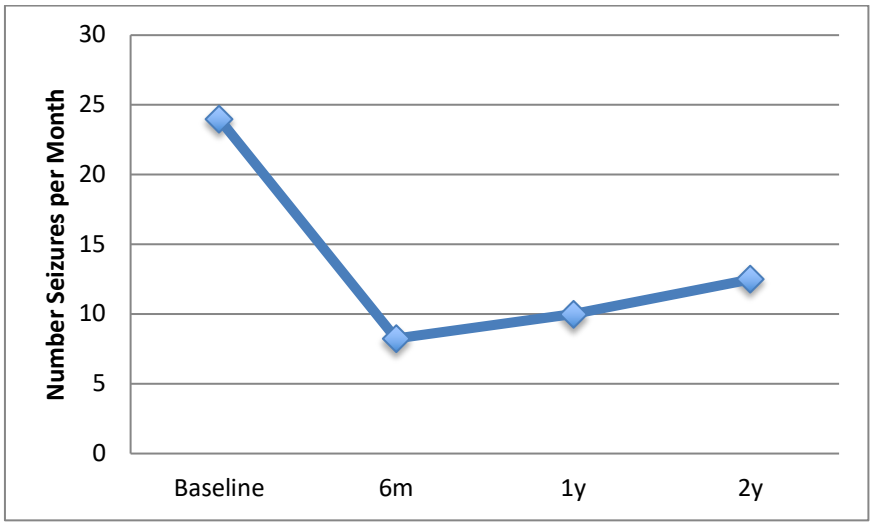


Figure 32. Median number of seizures per month in the different times of follow-up (baseline, six months, one year, two years).

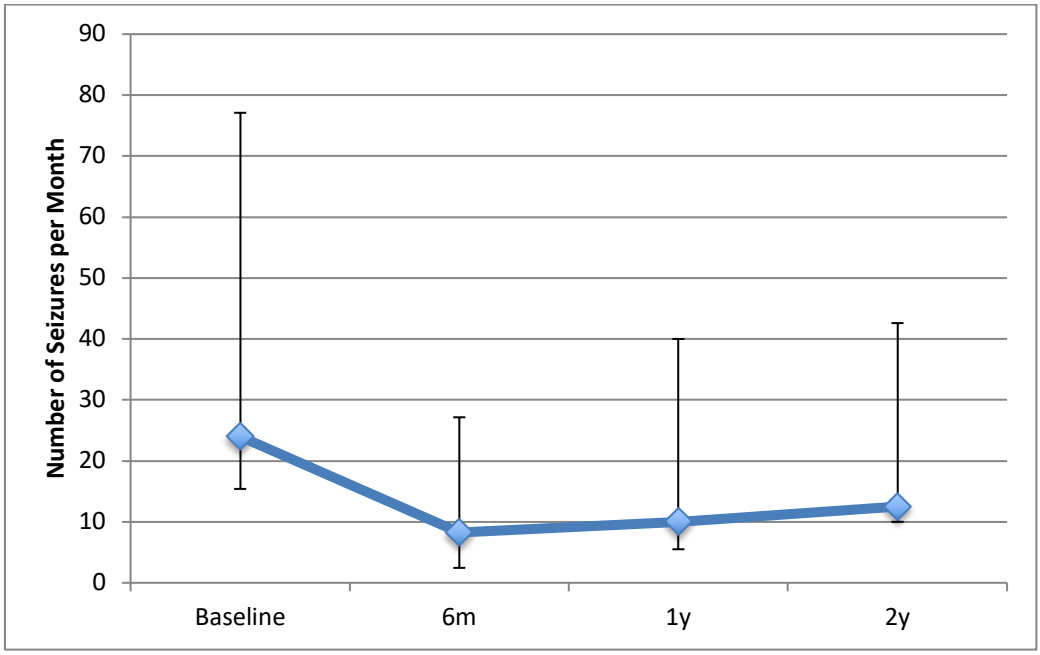


Figure 33. Median and the interquartile range of seizure frequency per month, before and after VNS implantation in different times of follow-up different times (baseline, six months, one year, two years).

	Median	IQR	Range
Baseline (before VNS implantation)	24	8.6-53.1	2-901
6 month after VNS implantation	8.25	5.8-18.9	1-165
1 year after VNS implantation	10	4.5-30	1-210
2 years after VNS implantation	12.5	2.5-30.1	0.33-125

Table 12. The number of seizure per month (all type of seizures) before VNS implantation, at six months, one year and two years since time of implantation.

We studied the subgroup of patients in which that information was available, demonstrating the frequency of seizures per month at the different times of the follow up and how this number changed in response to the VNS. It shows that with focal and focal with impairment of awareness there was a reduction over time. In the generalized

tonic clonic and focal to bilateral tonic-clonic, 1 year was the maximum seizure reduction, increasing after that. There was not an effect in the absence seizures. See **figure 34**.

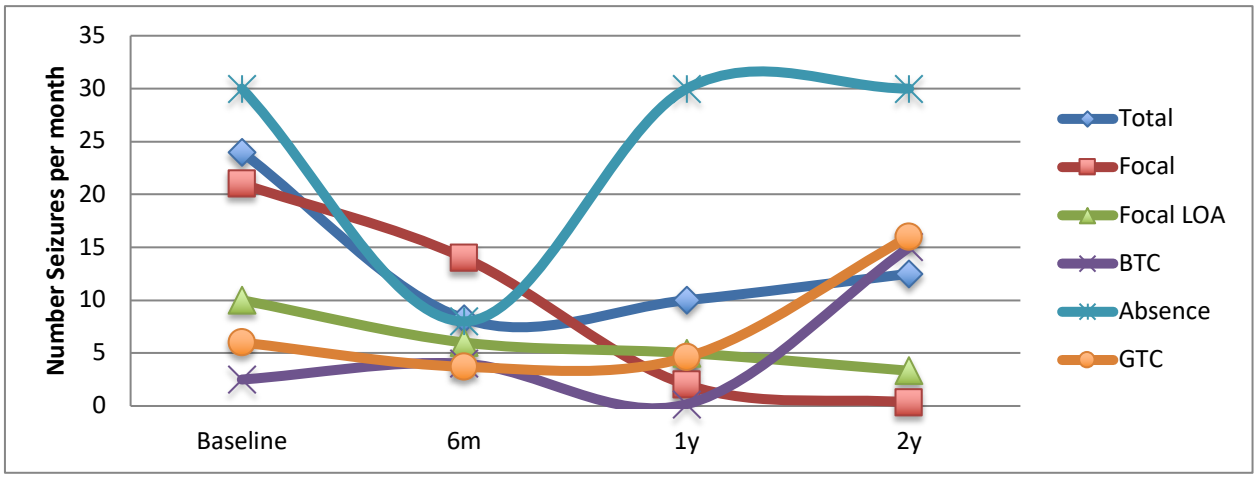
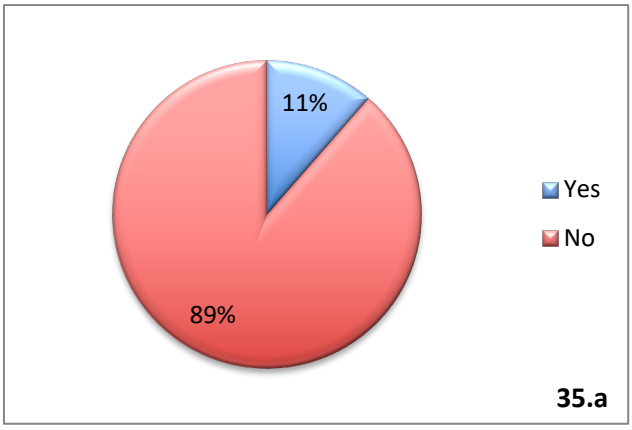


Figure 34. Subanalysis of seizure types per month and its' evolution over time, at different time intervals (baseline, six months, one year, two years). GTC: Generalized tonic-clonic seizures; Focal LOA: Focal seizures with impairment of awareness; BTC: focal to bilateral tonic-clonic.

4.1.2.3. ABSENSE OF VNS EFFICACY

If the patients, the relatives of the patients' or/and the epileptologist felt that VNS was not working, the device was turned off in 11.4% (n=13). In those cases, there were 53.9% (n=6) cases that underwent to the VNS explantation, representing 6.1% of the total sample.



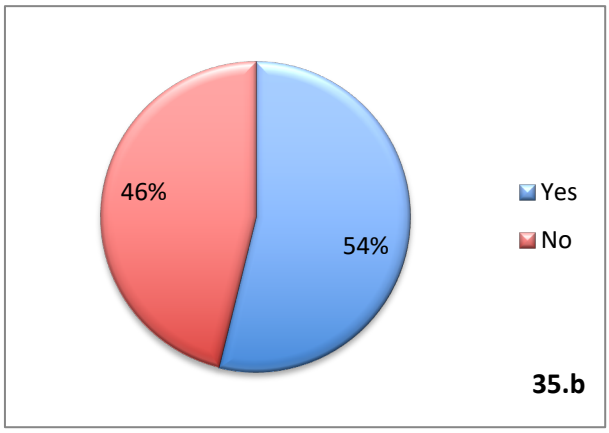


Figure 35. 35.a. Percentage of patients who were implanted with VNS devices which were required to be turned off due to a lack of efficacy. **Figure 35.b.** Percentage of patients who underwent VNS explantaion, from the group who stopped using the device.

Six cases of the no responders, were implanted with Deep-Brain-Stimulation. It represent 23.08% of the total or no responders, or 5.26% of the total patients implanted with VNS. See **figure 36**.

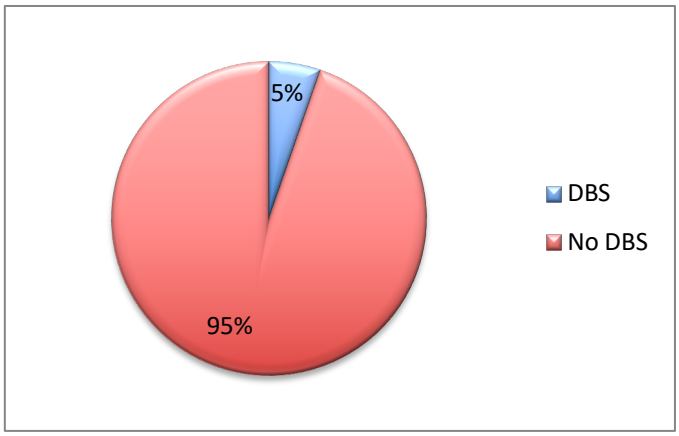


Figure 36. Percentage of patients implanted with DBS. DBS: Deep brain stimulation.

4.1.2.4. ANALYSIS OF THE EFFICACY BY CATEGORIES

Analysis was completed to measure if there was a positive correlation between the age of implantation and a better response, with 50% or more seizure reduction. In the linear model, used for seizure reduction and the time of VNS implantation, there wasn't statistical significance, with p-value of 0.094. In the same way, there was not a significant difference between the age of seizure onset and the seizure reduction (p= 0.181), using also a linear model.

This was done using the multivariant analysis of the efficacy of the VNS, to determine predictive factors of a good response. The analysis used EEG patterns, MRI findings, epilepsy type and epilepsy etiology. There was no specific predictive factor as a group. The results are summarized in **table 13**.

Variable	p-value
EEG-patern	0.21
Generalized	0.0001
Multifocal	0.0002
Generalized & Multifocal	0.0002
Bitemporal	0.0001
Right/left Hemisphere	0.008
Epilepsy Type	0.66
Generalized	0.00013
Multifocal	0.0002
Focal-Regional	<0.0001
Mixed pattern	0.0008
MRI findings	0.82
Normal MRI	<0.0001
Unspecific finding	<0.0001
Mesial Temporal Sclerosis	<0.0001
MCD	0.002
Epilepsy Etiology	0.88
Lennox-Gastaut Syndrome	0.0006
Genetic Generalized Epilepsy	0.0001
Genetic/Autoimmune	0.0002
Structural Abnromality	<0.0001
Meningitis/encephalitis	0.13
Unknown	<0.001
Mesial Temporal Sclerosis	0.004

Table 13. P-values of the association between VNS reponders and different epilepsy characteristics, such as EEG-pattern, epilepsy type, MRI findings and epilepsy etiology. MRI: Magnetic Resonance Imagine; MCD: Malformation Cortical Development.

Other linear models were used to detect if there was a statistical significance of a good response to the VNS in the group with intellectual disabilities. However the result was higher than 0.05 (p=0.22). In the case of the patients who underwent palliative surgeries, there was no better response than the ones who did not undergo surgery (p=0.442).

4.1.2.5. OTHER EFFICACY OUTCOMES

Antiseizure drugs were analyzed the after VNS implantation. The total number of ASD after the implantation was three, with a minimum of one ASD and maximum six. There was no statistical significance between the number of ASD before and after the implantation (p>0.05).

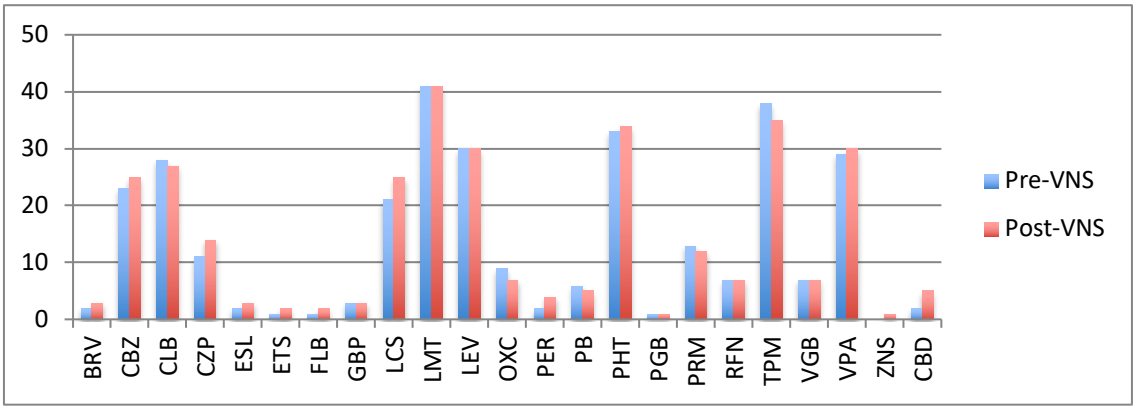


Figure 37. Most common antiseizure drug at the VNS implantation moment, compared to postimplantation. BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol.

The analysis of the dose of each ASD before and after the implantation, without significant difference (p>0.05). See **table 14** and **figure 38**.

ASD	Pre-VNS			Post-VNS		
	Median (mg/24h)	IQR	Range	Median (mg/24h)	IQR	Range
BVR	125	50-125	50-200	200	50	50-200
CBZ	1200	1000-1600	800-2800	1200	800-1400	400-2800
CLB	20	10-30	10-70	20	50	10-70
CLONAZ	1.5	1-2	1-4	1.5		0.5-3.5
ESL	800		800-800	800		800 - 1200
ETX	1500		1500-1500	1250		1000 -1500
FLB	1650		1650-1650	1425		1200 - 1650
GBP	2400		1900-2400	3000		300 - 4225
LCS	400	400-450	300-600	400	375-450	50 -600
LMT	300	200-400	50-775	300	200-400	50-775
LEV	2000	1000-3000	500-4000	2000	1000-3000	500 - 4000
OXC	1500	600-1650	300-2300	1500	900-1800	300 - 2300
PER	11		10-12	11	8- 12	8-12
PB	90	21.88-135	20-180	90	21.25-150	20
PHT	300	200-475	50-600	300	200-425	50 -600
PGB	225		225	225		225
PRM	500	312.5-500	250-875	500	375-687.5	250-1125
RFN	1200	800-2100	800-2400	1200	800-2400	800-3200
TPM	225	200-381.25	50-600	200	200-350	50-500
VGB	1400	1000-3000	1000-4000	1400	1000-3000	1000-4000
VPA	1000	750-1625	250-3000	1250	750-1500	250-3000
CBD	6.5		4-9	2	1-7.75	1-9

Table 14. Different ASM drugs, using the median dose of medications, interquartile range (IQR), and the minimum and the maximum dose of each one. ASM: Antiseizure drugs; BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol; Pre-VNS: pre VNS implantation; Post-VNS: Post VNS implantation.

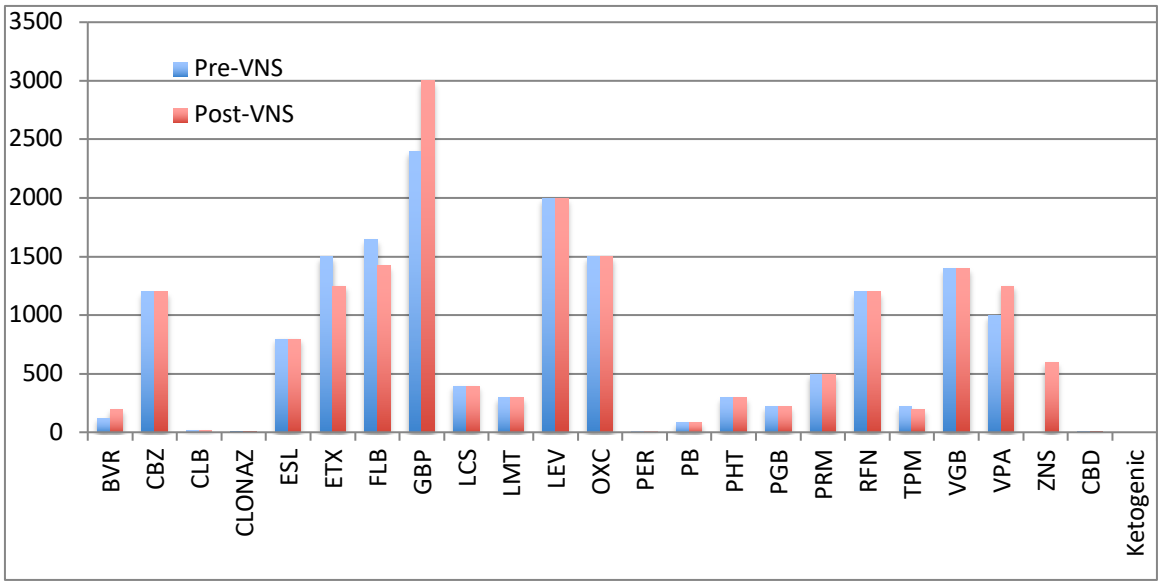


Figure 38. Doses of each ASM before and after the VNS implantation. ASM: Antiseizure drugs; BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol; Pre-VNS: pre VNS implantation; Post-VNS: Post VNS implantation.

Another outcome analysed is the number of hospitalizations before and after VNS implantation. It was found that 89.5% (n=102) required hospitalization before the VNS implantation compared to 45.6% (n=52). There was 43.8% (n=50) less hospitalization related to uncontrolled seizures. There was a statistical reduction of hospitalization related to uncontrolled seizures with a p=0.049. See **figure 39.**

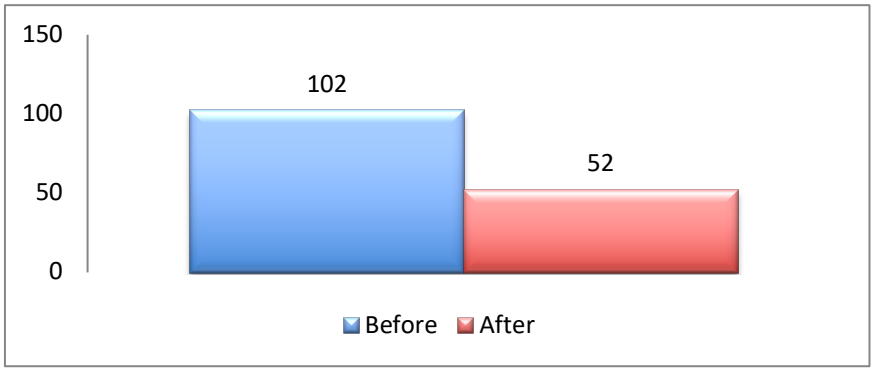


Figure 39. Number of hospitalizations due to an uncontrolled seizure(s) before and after the VNS implantation.

Considering the subjective efficacy perceived by the patients, patient caregiver and/or the attending epileptologist, the VNS efficacy was classified as a good response, mild response, no effect and worse control than without VNS. 41.3% (n=45) reported a good response and 18.3% (n=20) no response. The rest of the end points are represented in **figure 40**.

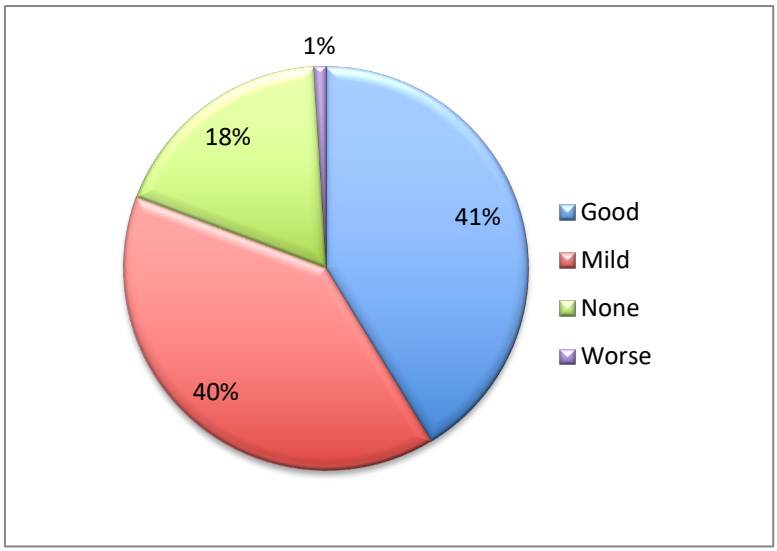


Figure 40. The patients'/ caregivers'/ epileptologists' perception of VNS response.

In association, in 11.4% (n=13) it was reported by the patient and/or patient caregivers a reduction of seizure intensity and in 13.2% (n=15) a reduction of duration. However, those reductions were not statistically significant ($p>0.05$).

Another improvement was related to mood and energy. Those who found improvement in this area were 13.2% (n=15). It was included in this variable, mood in 7% (n=8=, energy in 5.3% (n=6), alertness in 5.3% (n=6). Some of those patients had improvement in more of the previously described points.

4.1.2.6. VARIABLES RELATED TO THE DEVICE

The median VNS battery duration was 43.5 months (IQR= 20-73.24). 19.3% (n=22) of cases required re-implantation. The most common pulse generator in the first implantations was 102/102R in 40.9% (n=45), followed by the 103 model in 21.8% (n=24) and the 106 model in 17.3% (n=19) (see **figure 41**). Two cases of the first pulse generator model and one of the second were missing. In the case of the second VNS pulse generator, the median duration was 22 months (IQR= 12.75-41.25). In the second PG VNS model, the most frequent PG model was the 106 in 42.86% (n=9), 102/102R in 28.57% (n=6) and 101 in 14.29% (n=3) (see **figure 42**).

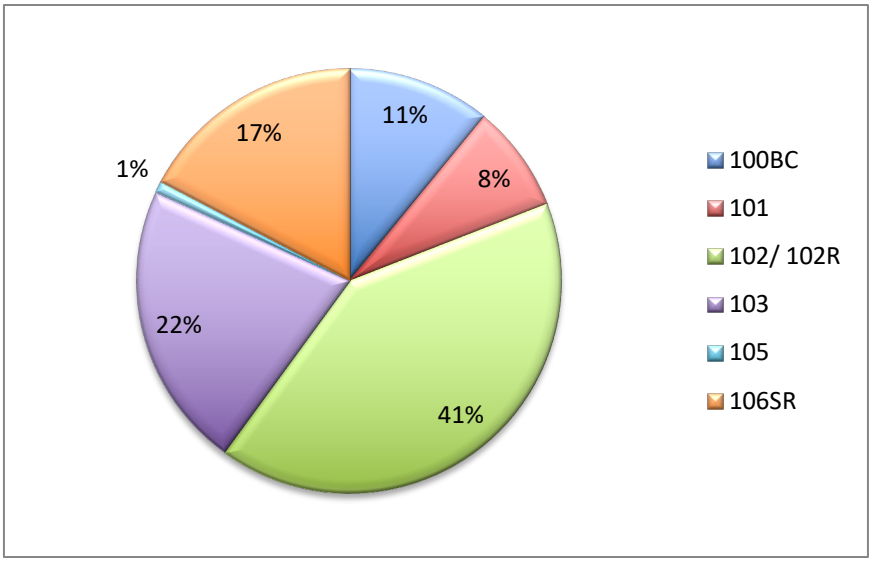
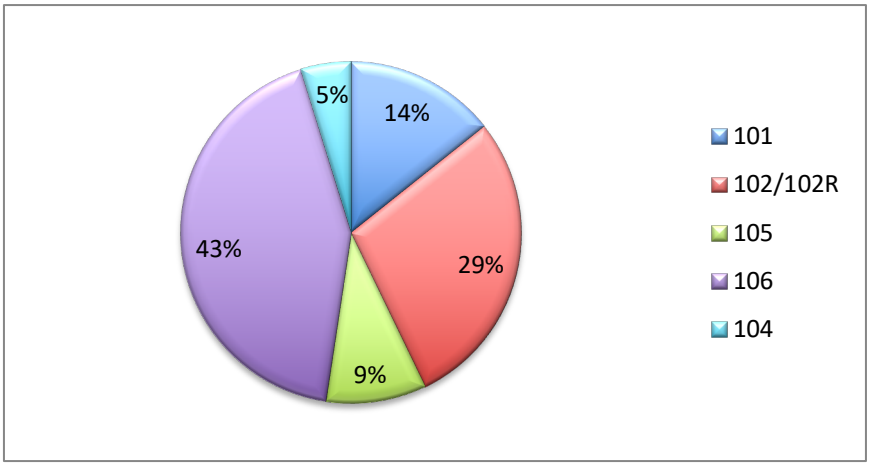


Figure 41. Different types of pulse generator VNS models implanted in the first instance. Models: 100BC, 101, 102 or 102R, 103, 105 and 106SR.

Figure 42. Percentage of the patients who underwent a second pulse generator implantation. Models: 101, 102 or 102R, 104, 105 and 106SR.



Considering the responder group and the association with the VNS model implanted in the first instance, considered as a group, there was a statistical significance with a p-value of 0.011. When each type of VNS mode was analysed, results found that all models are related with a significant reduction of seizures. However, the models with most significant p values were 102/102R (p=0.000004), 106 (p=0.000031) and 103 (p=0.00012). See **table 15**.

Model Type	p-value
100	0.043
101	0.031
103	0.00012
102/102R	<0.00001
106	0.00003

Table 15. Different grade of significance in each pulse generator model. Models: 100BC, 101, 102 or 102R, 103, 105 and 106SR.

VNS parameters can be divided into three groups, the models related to the standard stimulation, the magnet stimulation, and AutoStim stimulation (model 106). The parameters are represented in the next table (**table 16**).

PARAMETERS	MEDIAN	IQR
Standard Stimulation		
Output current minimum	0.25	0.25-0.25
Output current	2.25 mA	1.5-2.75
Signal frequency	30 Hz	30-30
Pulse width	500 microsec	250-500
Signal on	30 sec	30-60
Signal off	5 min	5-5
Magnet Stimulation		
Output current	2 mA	1.5-3
Pulse Width	500 microsec	500-500
Signal On	60 sec	30-60
AutoStim Stimulation		
Output current	1.25 mA	0.725-2.31
Pulse Width	500 microsec	250-500
Signal On	60 sec	60-60
Threshold AutoStim	40%	40-40

Table 16. Principal parameters used by the VNS in the different modalities of stimulation and the interquartile range.

In the logistic regression of the responder group and the parameter of output current, there was no significance, with a p-value of 0.224. However, in the analysis of the relation between responders and signal on time, there was significant association, with a p-value of 0.015.

4.1.2.7. SAFENESS OF THE DEVICE

Side effects could be divided into the side effects related to the implantation (complications of the implantation) and the side effects related to the stimulation.

The side effects related to the implantation occurred in 5.3% (n=6) of patients. Two cases had an infection in the area the pulse generator was implanted, one only required antibiotics and the other case required antibiotics and the device to be removed. Two other cases experienced hoarseness, which was probably related to the lead implantation. One case of acute stridor with hard breathing, which was probably related to the lead implantation, and spontaneously improved. One case experienced discomfort related to the lead a few of months after implantation.

Side effects related to the stimulation were reported in 63.16% (n=72) patients. The most common side effects were hoarseness in 26.4% (19), cough in 26.4% (19), voice change in 19.4% (14), sore throat in 16.7% (n=12) and pain in the neck in 16.7% (n=12). See **table 17**.

Side Effects	N	%
Pain Neck	12	16.67
Pain arms	2	2.78
Jaw pain	2	2.78
Chest pain	6	8.33
Hoarseness	19	26.39
Voice Change	14	19.44
Sore throat	12	16.67
Cough	19	26.39
Paresthesia	5	6.94
Burn Sensation	1	1.39
Choking/swelling difficulties	7	9.72
Vomit-reflux	1	1.39
Hiccups	2	2.78
Nocturnal Stridor	1	1.39
Lost weight	3	4.17
Breath Problem	1	1.39
Drooling	1	1.39

Table 17. Summary of the side effects related to the stimulation.

4.2. VNS IN PAEDIATRICS

4.2.1 PRE-IMPLANTATION VARIABLES

In the subanalysis of the paediatric population implanted with VNS, there were 22 patients implanted with VNS when they were 17 years old or younger (see **figure 43**). The median age of the group was 15.8 years old (IQR= 6.0-24.3) and 13 years old (IQR= 9.5-15) at the time of VNS implantation. 72.7% (n=16) were males and 40.9% (n=9) were right handed (see **figure 44**).

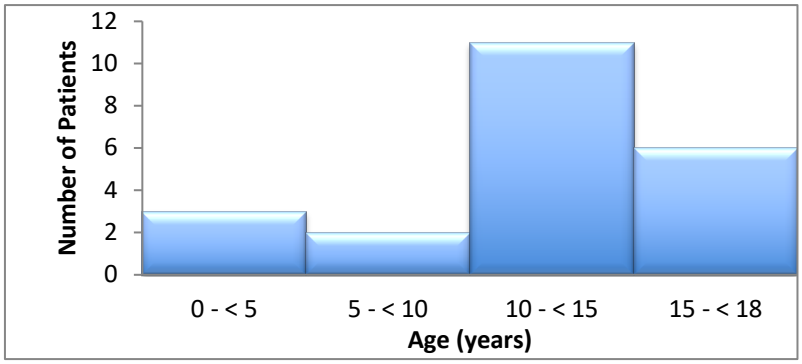
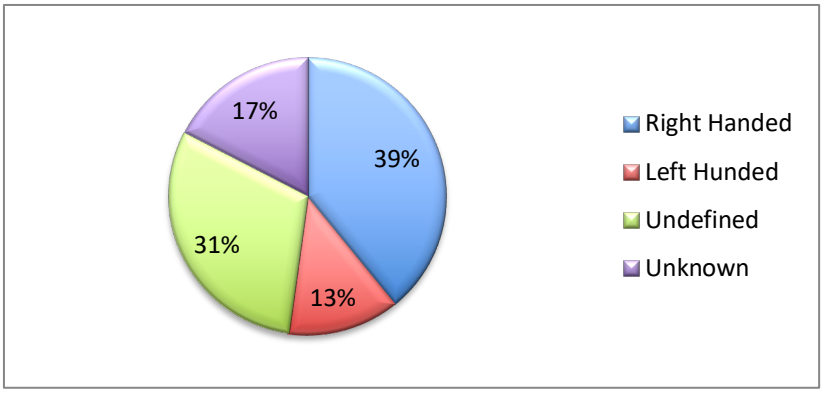


Figure 43. Distribution of the age of the paediatric group at VNS implantation.

Figure 44. Dominant hand in the paediatric group.



The median seizure onset was at 3 years-old (IQR= 1.6-5). The median epilepsy duration of the paediatric group was 13.1 years (IQR= 5.2-23.3) and the median duration at the time of the VNS implantation was 9 years (IQR= 6.2-13.2).

There was a family history of epilepsy in 31.8% (n=7) patients. In 86.4% (n=19) had some grade of intellectual disabilities, and 9.1% (n=2) had autism. All of the patients were admitted to the hospital for seizure management and 72.7% (n=16) had a history of status epilepticus. 95.5% (n=21) were investigated in the EMU with a median of three days admission (IQR= 2-5.25).

The most common epilepsy type in the paediatric group was a mix of patterns, which included focal and generalized, and generalized and multifocal, in 31.8%(n=7), followed by multifocal in 27.3% (n=6) and generalized in 22.7% (n=5). See **figure 45**.

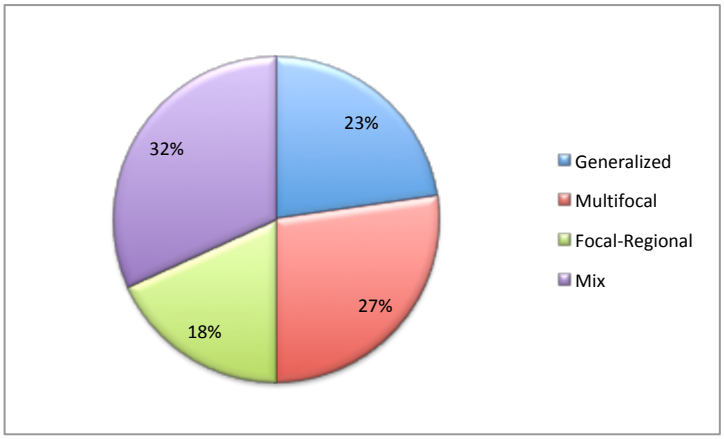


Figure 45. Epilepsy type in the paediatric group.

All patients underwent neuroimaging technics. Brain-MRI was completed in 95.5% (n=21) of cases and one case had only a head-CT. The most common finding in the neuroimagine examination was normality in 36.4% (n=8), followed by encephalomalacia in 27.3% (n=6) and nonspecific in 18.2% (n=4). See **figure 46**.

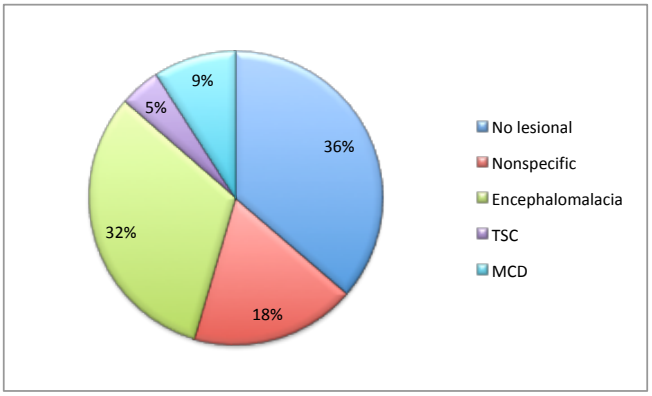


Figure 46. Neuroimaging findings in the paediatric group. MCD: Malformation of the cortical development; TSC: Tuberous Sclerosis Complex.

EEG was conducted for diagnostic purposes and epilepsy management in all the patients. The most common epileptic pattern was multifocal in 27.3% (n=6), followed by generalized alone in 22.7% (n=5) and, the combination of generalized and multifocal in 22.7% (n=5). See **figure 47**.

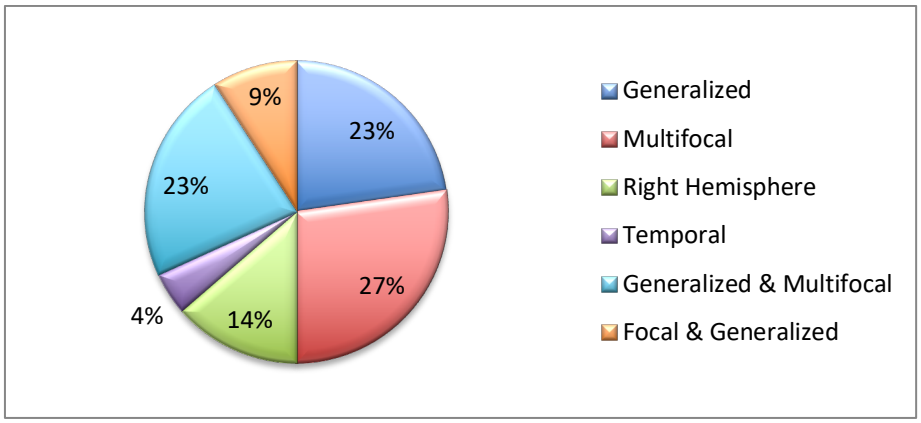


Figure 47. Electrographic epileptic abnormalities patterns of the paediatric group.

Concerning the epilepsy etiologies, the most frequent was Lennox Gastaut Syndrome in 45.5% (n=10), followed by genetic-syndromes in 31.8% (=7) and encephalomalacia in 27.3% (n=6). The rest of the etiologies are shown in **table 18.**

Etiology	N	%
Lennox Gastaut Syndrome	10	45.5%
Genetic-Other Syndromes	7	31.8%
Encephalomalacia	6	27.3%
MCD	2	9.1%
TSC	1	4.5%
Trauma	1	4.5%
Unknown	3	13.6%

Table 18. Different etiologies in the paediatric group.

There were ten cases (45.5%) with clinical and electrographic history compatible with Lennox-Gastaut Syndrome. In 18.2% (n=4) there were nonspecific findings in the MRI and 13.6% (n=3) were normal. The rest of etiologies are shown in the **figure 48.**

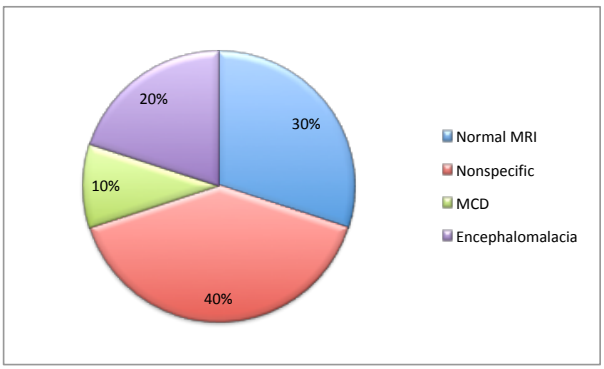


Figure 48. MRI Abnormalities associated with the Lennox-Gastaut Syndrome group (n=10). MCD: Malformation of the cortical development.

The paediatric group had a median of three different types of seizures (IQR= 3-6), and the most common types were generalized tonic-clonic in 68.2% (n=15) and myoclonic in 45.5% (n=10). The frequency of seizures, including all types of seizures, was 108 seizures per month (IQR=16-216.5). See **figure 49**.

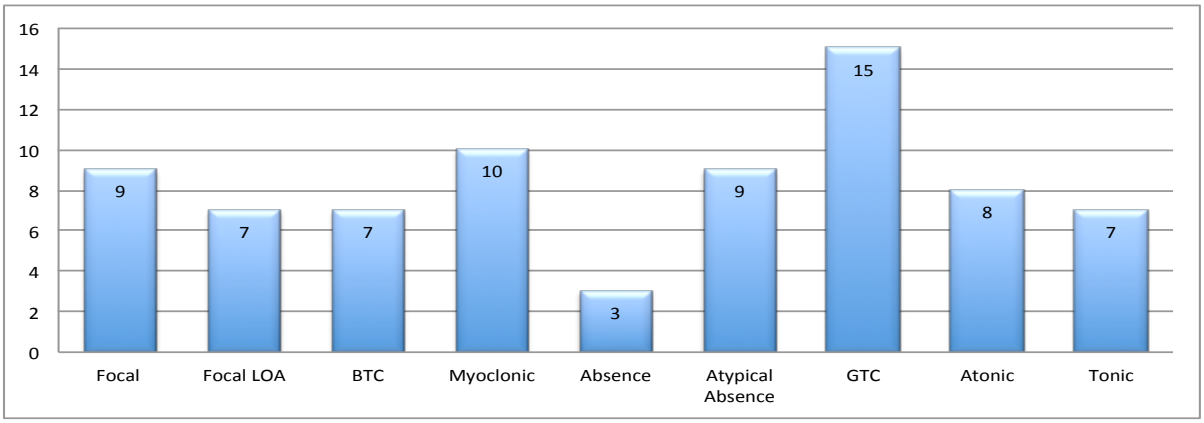


Figure 49. Number of patients with each type of seizure. GTC: Generalized tonic-clonic seizures; Focal LOA: Focal seizures with impairment of awareness; BTC: focal to bilateral tonic-clonic.

Concerning their pharmacological treatment, the median antiseizure drug failure was 3.5 (IQR= 2-6). The most common antiseizure drug failures were valproic acid in 59.1% (n=13), phenytoin in 40.9% (n=9) and phenobarbital in 40.9% (n=9). At the moment of the VNS implantation the patients were taking, as a median, 2 ASD (IQR= 2-3). The most frequently used ASDs at the time of implantation were levetiracetam in 45.5% (n=10), lamotrigine in 31.8% (n=7) and topiramate 27.3% (n=6). See **figure 50**.

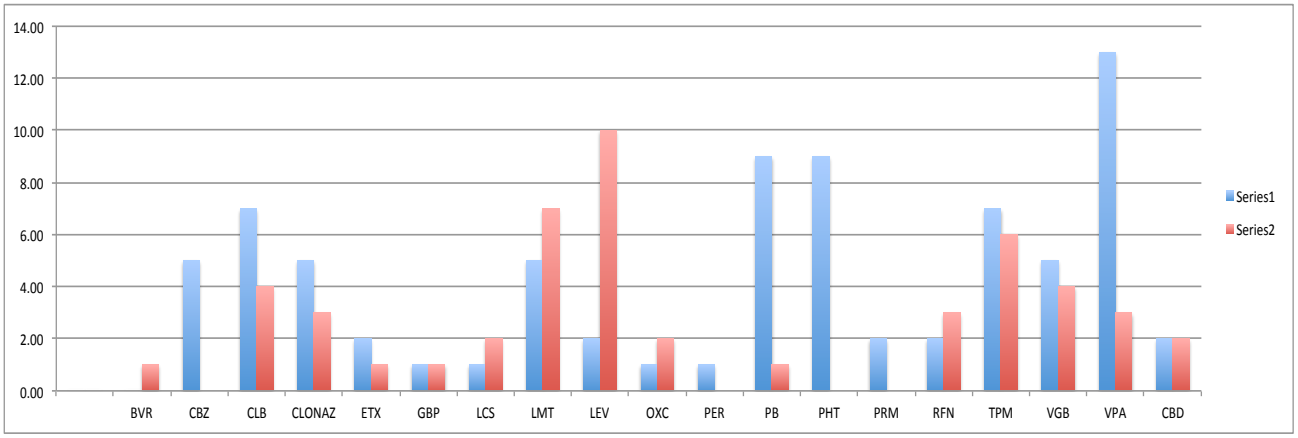


Figure 50. Antiseizure medication in the paediatric group. Series1: the failure ASD. Series2: the ASD that patients were taking at the moment of VNS implantation. ASD: antiseizure drugs; BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol.

4.2.2. POSTIMPLANTATION VARIABLES

4.2.2.1. VNS EFFICACY

The paediatric group was followed up for 35.5 months (IQR=6.75-151). The median of patients with 50% or more seizure reduction was 50% (n=11). This group was considered responders. The subanalysis of this group found that 9.1% (n=2) had 50-60% seizure reduction and 40.9% (n=9) had 75% or more seizure reduction. A seizure reduction of less than 50% was found in 31.8% (n=7) of cases and no response was found in 18.2% (n=4) of cases (see **figure 51**). There was a reduction of seizure intensity in 31.8% (n=7) of cases. No patients became seizure free after implantation when considering all types of seizures. However, a period of seizure freedom from generalized tonic-clonic seizures was found in 18.2% (n=4) of cases. The median seizure reduction rate expressed in percentage was

-75% (IQR= (-95.3)- (44.3%)). There was a significant difference between responders and non-responders when considering the total number of seizures (p=0.014).

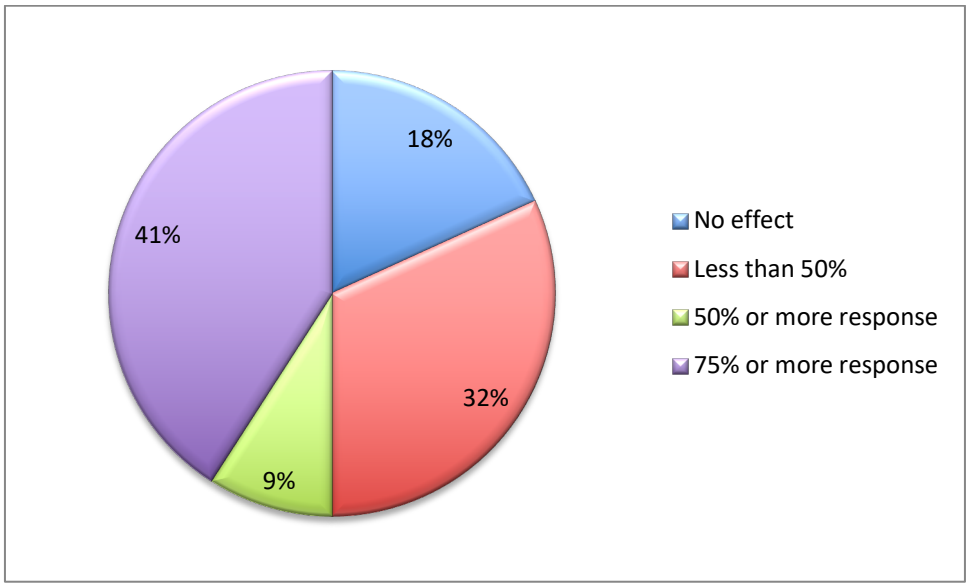


Figure 51. Seizure reduction rate in the paediatric group.

The evolution of the number of seizures over time was analysed. The median number of seizures after six months of implantation was 10 (IQR=6.5-42.8), after one year it was 10 (IQR=3.25-50.8) and after two years it was 11.3 seizures per month (IQR=4.4-15.1). In two cases the data was available after three years, and the median was 9.5 (range 7-12). See **figure 52**.

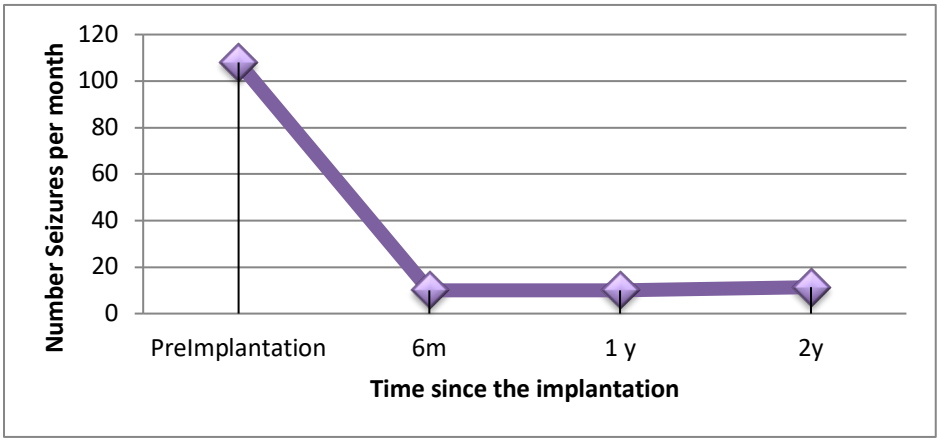


Figure 52. Number of seizures over time considering all type seizures.

In the analysis of efficacy of VNS by seizure type, it was discovered that not all types of seizures have the same response in seizure reduction. The seizure types with significant seizure reduction, comparing before and after VNS implantation, were focal with impairment of awareness (p=0.022), focal with progression to bilateral tonic-clonic (p=0.022) and generalized tonic-clonic (p=0.022). Other types didn't show a significant reduction. The results are shown in **table 19**.

Epilepsy type did not show a significant difference when taking into consideration all epilepsy types (p=0.36).

When distinguishing the efficacy of each EEG pattern, no significant differences between EEG patterns were found. There was no difference after taking into consideration the EEG pattern as a group (p=0.51). The p-values are summarized **in table 19**.

Taking into consideration epilepsy etiology as a group, there was no significant difference between different entities (p=0.86). However, the only etiology with a significant reduction of seizures was Lennox-Gastaut Syndrome with a p-value of 0.03. No other etiologies had a significant difference in the number of seizures before versus after the implantation.

	p-value
Type of Seizures	
Focal	0.08
Focal LOA	0.022
BTC	0.022
GTC	0.022
Absence	0.53
Atypical Absence	0.19
Atonic	0.38
Tonic	0.065
Myoclonic	0.39
EEG patterns	0.38
Generalized	0.61
Multifocal	1
Generalized and multifocal	0.34
Temporal	0.31
Regional	0.53
Focal and Generalized	0.14
Epilepsy Etiology	0.86
Lennox Gastaut Syndrome	0.03
Genetic-Other Syndromes	0.14
Encephalomalacia	0.54
MCD	0.14
TSC	0.31
Trauma	0.31
Unknown	0.28
Epilepsy type	0.95
Generalized	0.61
Multifocal	1
Focal-regional	0.31
Mix	0.34
MRI Findings	0.16
No lesional	0.28
Unspecific findings	0.31
Encephalomalacia	
Other	

Table 19. VNS response depending upon the type of seizures, EEG pattern and epilepsy etiology.

4.2.2.1. OTHER OUTCOMES

Another outcome related to VNS efficacy was the hospital admissions. After implantation only 36.4% (n=8) of patients were admitted to the hospital for seizure related issues. However, there was no significant difference compared to pre-implantation hospital admissions (p=0.65).

The improvement in the seizure control perceived by the patients and/or the patients' caregivers was also collected, retrospectively. In 40.9% (n=9) a good response in seizure control was reported, in 31.8% (n=7) there was a mild improvement and in 9.1% (n=2) it were no noticed improvement(s). There was a significant difference between the number of good (p=0.002) and mild (p=0.02) seizure improvement. Another interesting insight noted in the chart was that 9.1% (n=2) referred, spontaneously, a reduction in seizure intensity, 9.1% (n=2) reported a reduction in the seizure duration and 13.6% (n=3) reported an improvement in the alertness and energy.

The median number of antiseizure medications was 3 (IQR= 2-3) and in 13.6% (n=3) the number of ASDs was higher than before the implantation, however the change was not statistically significant (p=0.15). The most commonly used antiseizure medication was levetiracetam, used in 45.5% (n=10), followed by lamotrigine in 31.8% (n=7), phenytoin in 22.7% (n=5) and topiramate in 22.7% (n=5). There were only two medications associated with the responders group. They were lamotrigine (p=0.022) and vigabatrin (p=0.027). When the Bonferroni correction was applied, the p-value needed to be smaller than 0.0029 to be significant. After that alteration none of the medication showed a significant difference. In the analysis of the dose for the responders and non-responders, there were no significant differences in any of the medications. See **table 20.**

	N	Dose	IQR	Range	p-values
BVR	1	200	200-200	200	0.31
CBZ	2	950	800-(Q2(950)	800-1100	0.14
CLB	4	16.25	11.25-56.88	10-70	1
CZP	4	1.75	1.13-3.13	43468.00	0.27
ETX	1	1500	1500	1500	0.31
GBP	1	4225	4225	4225	0.31
LCS	2	350	300-350	300-400	1
LMT	7	350	150-450	100-775	0.022
LEV	10	1250	712-2500	500-3000	0.39
OXC	2	1500	1500	1500	0.14
PB	1	22.5	22.5	22.5	0.31
PHT	5	200	87.5-245	50-290	0.61
RFN	3	800	800	800-1200	0.53
TPM	5	180	65-300	50-400	0.61
VGB	4	2250	1425-3750	1400-4000	0.027
VPA	3	1500	500-1500	500-3000	0.06
CBD	2	4	4	4	0.48

Table 20. Summary of the antiseizure medication after the implantation. BVR: Bivaracetam; CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; ESL: eslicarbazepine; ETX: Ethoxusamide; FLB: Felbamate; GBT: gabapentin; LCS: lacosamide; LTG: lamotrigine; LEV: levetiracetam; OXC: oxcarbazepine; PB: phenobarbital; PHT: phenytoin; PGB: pregabalin; PRM: primidone; RFN: rufinamide; TPM: topiramate; VPA: valproic acid; VIGB: Vigabatrin; ZNS: zonisamide; CBD: Cannabidiol.

4.2.2.3. SAFTENESS

Only one patient (4.5%) had a complication after implantation related to stiffness in the neck that improved over time. It was not necessary to turn off the device. Concerning the side effects related to the stimulation, 54.5% (=12) reported side effects. The most common side effect was cough, representing 25% (n=3) of the total side effects. There

were no statistical differences between responders and non-responders in side effect or by type of side effect. See **figure 53**.

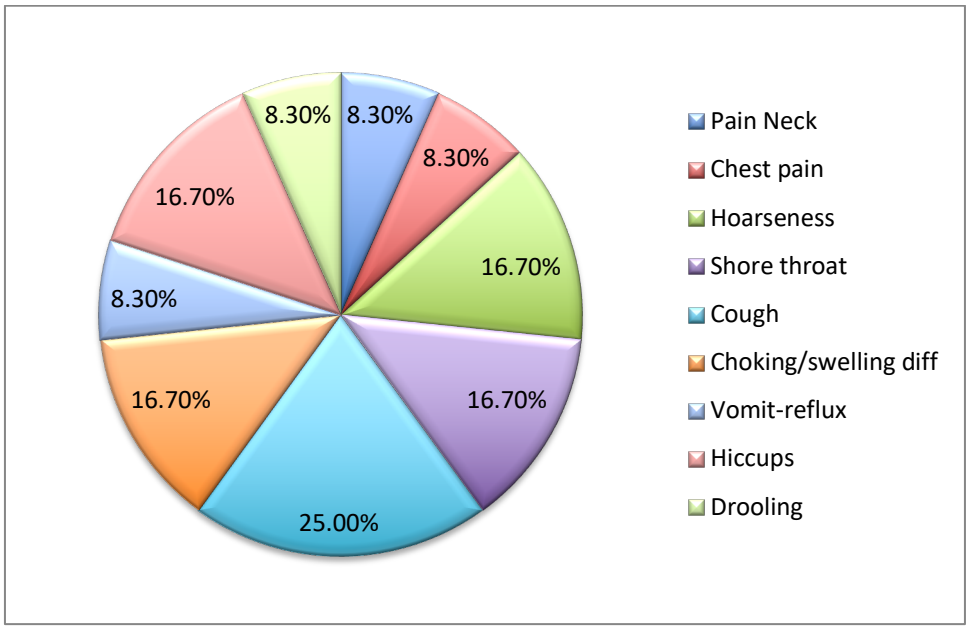


Figure 53. Percentages of side effects related to the stimulation in the paediatric group.

4.2.2.4. DEVICE RELATED PARAMETERS

The most common pulse generator of the VNS was the model type 106SR, implanted in 45.5% (n=10) of the patients, followed by the 100BC with 13.6% (n=3) and 103 in 13.6% (n=3) (see **figure 54**). There was no significant difference between the different pulse generator models (p=0.73). Also, none of the models resulted in a higher rate of responders than another.

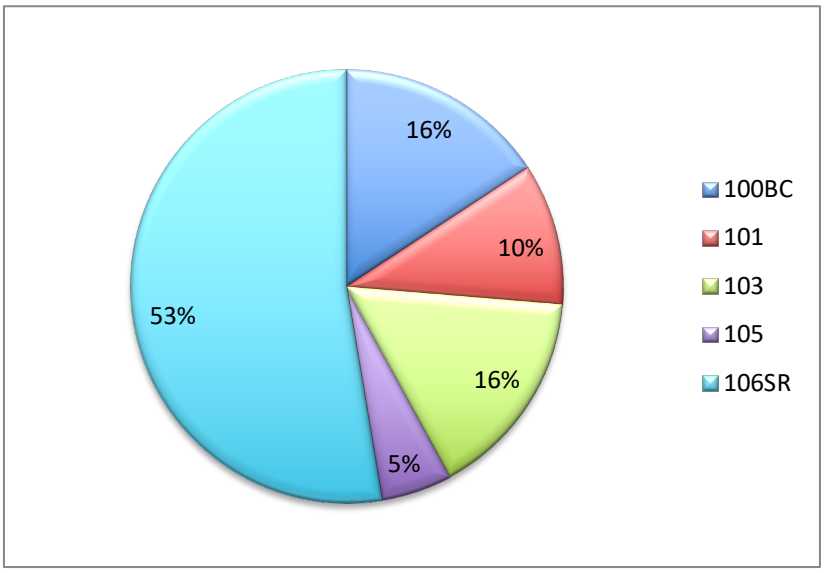


Figure 54. Distribution of the different VNS pulse generators in the paediatric group. Models of VNS pulse generator: 100BC, 101, 103, 105 and 106SR.

In two cases (9.1%) underwent reimplantation for a new pulse generator due drained battery. The median duration of the VNS battery was 35.5 months (IQR= 7-63).

The median output current in the paediatric population was 3.25 mA (IQR= 1.25-2.75) and the time on was 30 seconds (IQR= 30-30). The median magnet output current was 2.5 mA (IQR= 1.25-3.125) and time on 60 seconds. In the cases that were implanted with model type 106SR, the median autostimulation output current was 1.5mA (IQR= 0.75-2.75) and the heart detection threshold 40% of increment (IQR= 32.5-40%). In the analysis comparing responders and non-responders, there were no significant differences in the values of the VNS parameters. See **table 21**.

	Media	IQR	Range	p-values
Minimal Output current (mA)	0.25	0.25	0.125-0.25	0.329
Maximal Output current (mA)	3.25	1.25-2.875	0.375-3.25	0.237
Signal Frequency (Hz)	30	30-30	30-30	0.5
Signal On Time (Sec)	30	30-30	7-60	0.278
Signal Off Time (min)	5	5-5	3-5	0.724
Pulse Width (microseconds)	500	250-500	250-500	0.237
Magnet: Output Current (mA)	2.5	1.25-3.12	0.625-3.5	0.191
Magnet: Pulse Width (microSec)	500	500-500	250-500	0.945
Magnet: Signal On time (sec)	60	60-60	30-60	0.339
If Autostimulation: Output current (mA)	1.5	0.75-2.75	0.5-3	0.13
If Autostimulation: % threshold	40	32.5-40	30-40	0.188
If Autostimulation: Pulse Width	375	250-500	250-500	1
If Autostimulation: Signal On	60			

Table 21. Summary of VNS parameters used in the paediatric subgroup.

4.3. VNS IN GENERALIZED EPILEPSY

4.3.1. PRE-IMPLANTATION VARIABLES

A total of 46 patients fulfilled the inclusion criteria of this subanalysis.

The median age of the patients included in the study was 35.8 years (IQR= 24.8-43.4) and 50% were female (n=23). The median age at epilepsy onset was 6 years (IQR= 1.2-10.5) and the median age at implantation was 24 years (IQR= 17.8-31). There was a history of previous status epilepticus in 39.2% (n=11) and developmental delay in 45.2% (n=14). The median number of ASMs tried in the past was 5 (IQR= 2.8-7). Twenty-six (56.5%) tried phenytoin and twenty-one (45.7%) valproic acid (VPA).

At the time of the implantation the median number of ASMs was 3 (IQR= 2-3) without statistical differences between the groups. The most common antiseizure drug at the time of the implantation was VPA (41.3%, n=19), followed by phenytoin (PHT) (37%, n=17), and levetiracetam (LEV) (30%, n=14).

Twenty-nine cases had LGS (representing 63% of the sample) and 17 had GGE (37%). In those with LGS, the most common finding in EEG recordings was generalized abnormalities in 48.3% (n=14), followed by generalized abnormalities in addition to multifocal independent spikes foci in 34.5% (n=10). In those with LGS, 63% (n=17) had an unremarkable MRI, 22.2% (n=6) had malformations of cortical development. Generalized tonic-clonic seizures (GTC) were the most frequent type of seizures, occurring in 75.9% (n=22), followed by atypical absences and tonic seizures, both detected in 44.8% (n=13).

In the group with GGE we found that 76.5% (n=13) had generalized spikes in EEG recordings and 17.7% (n=3) had a combination of generalized spikes and multifocal independent spikes. MRI was unremarkable in 88.2% (n=15), with the exception of two cases with small areas of encephalomalacia, of unclear etiology. The most common type of seizure was GTC in 82.4% (n=14), followed by absences in 58.8% (n=10) and myoclonic seizures in 35.3% (n=6). Other characteristics of both groups are summarized in **Table 22.**

Characteristic	LGS % (29)	GGE % (17)	p
Age	35.8 (IQR= 26.6-40.5)	32.1 (IQR= 24.7-47)	0.51
Age of implantation	23 (IQR= 14.5-29.5)	30 (IQR= 21.5-37)	0.01
Age of implantation (<18y-o)	37.9 (11)	0 (0)	0.00
Intellectual disabilities	100 (29)	0 (0)	0.000
History SE	65.5% (19)	5.9 (1)	P<0.0001
Seizures type number	3(IQR= 3-4)	3 (IQR= 2-3)	0.007
Total Seizure number (m)	43.5(IQR= 14.5-98.3)	36 (IQR= 25-68)	0.96
Number GTC (m)	14.3(IQR= 2-41.3)	3.4 (IQR= 1.5-6)	0.04
Number Absence (m)	25 (IQR= 9-30)	30 (IQR= 12.5-142.5)	0.11
Previous palliative surgery	34.5 (10)	11.8 (2)	0.16
Antiseizure Medications at the time of VNS implantation	3 (IQR= 2.5-3)	2 (IQR= 2-3)	0.19

Table 22. Summary of clinical features in both groups. LGS: Lennox-Gastaut Syndrome; GGE: Genetic Generalized Epilepsy. SE: Status Epilepticus; GTC: Generalized Tonic-Clonic seizures; VNS: Vagus Nerve Stimulation; m: month.

4.3.2. POSTIMPLANTATION VARIABLES

4.3.2.1. VNS EFFICACY

The median period of follow-up was 63 months (IQR= 31-112.8). 41.4% (n=12) of the LGS group were responders and 64.7% (n=11) of the GGE group were responders, at the last follow up (p=0.048). The seizure reduction rate was 59% (IQR= 92.5-38.8) in the LGS group and 86% (IQR= 97.9-44.9) in the GGE group, at the last follow up, without statistical differences between them. In those with GGE, 35.3% (n=6) became seizure free, with a median duration of ten months (IQR= 6-21.5).

Characteristic	LGS % (29)	GGE % (17)	p
Seizure Free	0	35.3(6)*	
Total Sz postVNS	11.7 (IQR= 4.4-48.7)	3.3 (IQR= 0.5-20.6)	0.46
Seizure Reduction Rate	59.1 (IQR= 92.5-38.8)	86 (IQR= 97.9-44.9)	0.35
Responders (≥ 50%)	41.4 (12)	64.7 (11)	0.048
≥ 75%	27.6 (8)	47.1 (8)	0.2
≥ 50-74%	13 (4)	17.7 (3)	0.2
< 50%	27.6 (8)	17.7 (3)	0.72
No effect-Worsening	31 (9)	17.7 (3)	0.49
Number ASD postVNS (n)	3 (IQR= 3-3)	3 (IQR= 2-3.5)	0.19
Duration F-u (m)	66 (IQR= 42.5-126.5)	51 (IQR= 14-75)	0.08

Table 23. Seizure outcome in both groups after the last follow-up since VNS was implanted.
ASD: Antiseizure drugs; Fq: Frequency.
*Median of 10 months seizure free (IQR= 6-21.5)

When assessing response rate based on seizure type in the LGS group, we found a reduction of GTC from 14.3 per month (IQR=14.5-98.3) to 10 per month (7.5-15) (p=0.46). There was no effect on other types of seizures including atypical absence and typical absence, and myoclonic seizures. In the GGE group, the number of GTC decreased from 3.4 (IQR= 1.5-6) per month to 0.3 (IQR=0.2-2.3) (p=0.043). In the case of absence seizures, there was a reduction from 30 (IQR= 12.5-142.5) per month to 17.5 (IQR=2.5-126.5) (p=0.07). See **table 23.**

The response rate did not increase over time, when using a simple linear regression (p=0.27).

4.3.2.2. OTHER OUTCOMES

There was a reduction of seizure-related hospital admissions from 91.3% (n=42) pre-implantation to 43.5% (n=20) post-implantation. In the LGS group, 96.6% (n=28) required seizure-related admissions to the hospital before VNS implantation, and 51.7% (n=15) after implantation. In the GGE group, before implantation 82.4% (n=14) were admitted to the hospital due to seizures and after implantation only 29.4% (n=5) were admitted. Both groups had a meaningful difference in the reduction of hospital admissions related to seizures' control ($p<0.001$ in LGS and $p=0.003$ in GGE). In addition, seizure improvement indicated that each patient would require one hospitalization related to seizures every 11.9 patient-years in GGE, and one hospitalization every 10.3 patient-years in LGS.

The median number of antiseizure drugs after implantation was 3 in both groups, without significant difference when compared to before implantation.

4.3.2.3. SAFENESS

One patient had an infection in the area of implantation and two developed pain in relation to the VNS lead. Stimulation related side effects were reported in 63% (n=29). The most frequent side effect was coughing in 37.9 % (n=11), voice change in 20.7% (n=6) and sore throat in 13.8 % (n=4). There were no differences between the two groups. In 17.4% (n=8) the device was turned off because of a lack of efficacy, with only one of them in the GGE group. **See table 24.**

Characteristic	LGS % (29)	GGE % (17)	p
Side Effect Implantation	0	17.7 (3)	0.37
Side Effect Stimulation	62.1 (18)	64.7 (11)	1
Type of Side Effect			
Neck pain	6.9 (2)	0	0.52
Jaw pain	0	5.9 (1)	0.37
Chest Pain	6.9 (2)	5.9 (1)	1
Hoarseness	10.3 (3)	5.9 (1)	1
Voice Change	6.9 (2)	11.8 (2)	0.62
Sore Throat	13.8 (4)	11.8 (2)	1
Cough	24.1 (7)	23.5 (4)	1
Burn Sensation	0	5.9 (1)	0.37
Chocking Difficulties	10.3 (3)	5.9 (1)	1
Vomit-Reflux	3.4 (1)	0	1
Hiccups	3.4 (1)	0	1
Breathing Difficulties	0	5.9 (1)	0.37
Turn Off	24.1 (7)	5.9 (1)	0.12
Duration VNS battery (m)	60 (IQR= 37.5-113)	43 (IQR= 14-59.9)	0.04
VNS Parameters			
Output (mA)	2 (1.75-2.75)	2.125 (IQR= 1.375-3.125)	0.89
Pulse Width (µsec)	500	500 (IQR=250-500)	0.15
Signal Fq (Hz)	30	30	-
Time On (sec)	30 (IQR= 30-60)	30 (IQR= 30-60)	0.88
Time Off (min)	5	5	0.66

Table 24. Summary of the side effects related to VNS. Fq: frequency; m: months; mA: milliamps; min: minutes; sec: seconds, µsec: microseconds.

4.3.2.4. VARIABLES RELATED TO DEVICE

The median output current for the normal VNS stimulation was 2.0 mA (IQR= 1.75-2.750), the time ON was 30 seconds (IQR= 30-30), time OFF 5 min (IQR= 5-5), pulse width 500µs (IQR= 500-500). For the magnet, the median output current was 2 mA (IQR: 1.7-2.8), time ON 60 seconds (IQR= 30-60) and pulse width 500 µs (IQR= 500-500). No differences in the VNS parameters were seen between the two groups.

The most implanted model was the 102, seen in 28.3% (n=13) of patients, followed by 103 in 26.1% (n=12) and 101 in 15.2% (n=7). There was no difference in response between pulse generators. The pulse generator was replaced in 21.7 % (n=10) of the cases. The median duration of the battery was 60 months (IQR= 37.5-113) in the LGS group and 43 months in the GGE group (IQR= 14-59.9) (p=0.04). **See table 24.**

4.4 VNS DURING PREGNANCY

Four patients were identified who got pregnant while they were using the VNS and, collectively, had a total of seven babies. One of the women had three babies and another women had two babies. The history of each case is explained below and summarized in **table 25.**

The first case was a 24 year-old, right-handed woman, with medically resistant genetic generalized epilepsy (GGE) manifested by daily abscences and infrequent generalized tonic-clonic seizures. The patient had tried three different antiseizure drugs (ASD). Her brain MRI was normal and she had a positive family history of epilepsy. She underwent insertion of a VNS. The first pregnancy occurred at the age of 24, more than a year after the implantation of the VNS. There were no changes to the VNS output during pregnancy. Delivery occurred at 38 weeks via cesarean section due to a failure to progress. The baby was healthy. The same patient had a second pregnancy at the age of 27, without changes in her medication regimen and no changes to the settings of the VNS were made during pregnancy. She had an elective cesarean section at 38 weeks. There were no complications during delivery and the baby was healthy.

The second case was a right-handed woman with bilateral temporal periventricular nodular heterotopias and bitemporal epilepsy. She had previously tried four ASDs and was on 2 of them at the time of her pregnancy at the age of 31. During pregnancy, no

changes were made to the settings of the VNS. Vaginal delivery occurred at 40 weeks without complications.

The third case was a 18 year-old female who had 3 pregnancies after VNS implantation. She had GGE, she tried six different ASDs and two during the pregnancy. She had daily absence seizures and two generalized tonic-clonic seizures per month. She required an urgent cesarean section due to pre-eclampsia at week 37 of gestation, just ten months after the VNS implantation. The baby was born without complications. The second pregnancy occurred three years after the VNS implantation and resulted in a healthy baby, born via vaginal delivery at 39 weeks without any complications. The third pregnancy occurred at the age of 22, over four years after VNS implantation. She had a vaginal delivery at 38 weeks without complications resulting in a healthy baby.

The fourth case was a 22 year-old female who had 1 pregnancy, more than three years after VNS implantation. She had GGE, mild intellectual disabilities (ID) and tried eight different ASDs. She had one generalized tonic-clonic seizure every two to three months. The VNS was turned off at 26 weeks of pregnancy citing pregnancy concerns. But due to an increase in seizure frequency the stimulation was turned on a month later. She had a C-section, due to spontaneous rupture of the amniotic sac and breech presentation. At the last follow up there were some concerns of mild dismorphic features of the baby and a possible heart murmur. The heart murmur was found to be related to a possible interventricular aneurysm. Unfortunately, the patient was lost to follow up. No further information could be obtained about the well being of the baby.

	Patient 1		Patient 2	Patient 3			Patient 4
	Pregnancy 1	Pregnancy 2		Pregnancy 1	Pregnancy 2	Pregnancy 3	
Age	24 y-o	27 y-o	31 y-o	18 y-o	21 y-o	22 y-o	22 y-o
Type Epilepsy	GGE		Focal due to PVNH	GGE			GGE
Sz-Types	Absence, GTC		Focal w/o IOA Focal IOA	Absence, GTC			Absence, GTC, myoclonic
Time since VNS implantation	1 y, 4 m	2y, 9 m	5 y, 5 m	10 m	3y, 2 m	4 y, 4 m	3y, 2m
VNS current	3.5 mA	3.5 mA	1.5 mA	0.75 mA	2.75 mA	2.75 mA	1.75
Sz-Reduction Rate	91.1%		85.7%	50.3%			35.8%
ASD (mg/24 hours)	VPA 250mg RFN 800mg PHT 300mg	VPA 1000mg PHT 400mg	TPM 400mg LMT 400mg	CLB 30mg CLZ 1mg	CLB 20mg CLZ 2mg	CLB 25mg CLZ 1mg	LEV 3000mg PRM 750mg CLB 30mg
Gestational Age	38 w + 4 d	38 w + 1 d	40 w	37 w	39 w	38 w + 2 d	35 w + 2 d
Type Delivery	c-section	c-section	Vaginal	c-section	Vaginal	Vaginal	c-section
Reason	Failure progression	Elective, previous c-section		PE			PROM Breech presentation
Apgar (10')	9	9	dm	9	9	9	dm
Baby Weight	4420 g	3710 g	3402 g	3371 g	3373	3147 g	dm
Malformations	None	None	None	None	None	None	See comments *
Current Newborn Age	4 y-o	1 y-o	2 m-o	5 y-o	2 y-o	1 y-o	12 y-o

Table 25. ASD: antiseizure drugs; CLB: clobazam; CLZ: clonazepam; d; days; dm: data missing; GGE: Genetic Generalized Epilepsy; GTC: Generalized Tonic Clonic; IOA: impairment of awarness; LMT: lamotrigine; m: months; m-o: month-old; PE: pre-eclampsia PHT: phenytoin; PVNH: periventricular nodular heterotopia; PRM: primidone; PROM: premature rupture of membranes; RFN: rufinamide; Sz: seizure; TPM: topiramate ; VPA: valproic Acid; w: weeks; y: years; w/o: without; y-o; year-old.

* The baby had mild dismorphic features, delay in reaching developmental milestones and a possible heart murmur, related to an interventricular aneurysm. Unfortunately, the patient was lost to follow up.

5. DISCUSSION

5.1. VNS IN EPILEPSY

5.1.1 OUTCOME IN SEIZURE REDUCTION

5.1.1.1 SEIZURE FREEDOM

In our study after a median follow-up of 46 months, almost four years, we found that 21.1% of total patients implanted with VNS had a period of seizure freedom. However, this period was relatively short, with a median of 3 months, and all periods were shorter than a year. This represents a good response, without being sustained for a long the time. Slightly better results, concerning seizure freedom, were found in patients with generalized tonic-clonic seizures. (GTC) When solely analysing GTC seizures in patients (GTC), 29% of the total patients with GTC had a period of seizure freedom. With the median of 9 months, the median was longer than the general group, and again, nobody was GTC seizure free for over a year. The literature shows a broad range of percentages of seizure freedom, between 0 to 24% (136, 191, 196, 225, 277, 318, 319, 320), although many studies don't specify the duration of seizure freedom. In the metanalysis of Englot, there was 2.6% seizure freedom at 0-4 months and 8.1% at 48 months, without clarifying the duration of the period without seizures (207). Janszky's et al study found 12.8% (6/47) were seizure free for a period of 6-20 months (321). Ghaemi et al conducted a similar study, but defined seizure freedom as when the patients didn't have seizures for over a year the percentage of seizure freedom gets smaller. Ghaemi et al found 6.9% of the patients were seizure free for more than one year and 3.5% for more than two years (322). The seizure freedom from all types of seizures or GTC can be explained with different hypothesis. One hypothesis that needs to be considered is related to the "honey-moon" effect, previously described as associated to the new onset of antiseizure medications (323). Some studies define this period as until the patients fail to respond to the new ASM, between 1 month to 6 months (323, 324). Another possibility is that it is due to multiple therapeutic changes, with dose increments of ASM or addition of new

ASM. Unfortunately, with the retrospective character of the study, it was not possible to control for these factors.

5.1.1.2. SEIZURE REDUCTION AND RESPONDERS

5.1.1.2.1 RESPONDERS

Follow up is an important factor to take into consideration, because the adjustment of the parameters requires a period of time. In our study, the median follow up was 46 months, up to 22.3 years since VNS implantation. In most of the studies published the follow up is up to 24 months (206). Exceptions to this could be the Ben-Menachen et al (5 years) (322), Elliot et al study (10 years) (221) and Galbarriatua et al (15 years) (325).

One of the most important landmarks of the efficacy of VNS is seizure reduction, comparing the average and median frequency of seizures per month compared to the last follow-up, including at different time intervals (baseline, six months, one year, two years). With that data we can quantify the response, however there are other considerations that can have a direct impact on the efficacy, and which we will discuss later.

The seizure reduction rate was -67.8% (IQR= (-92.6)-(-37.2%)). There is a wide range of seizure reduction rates, varying from -6.1% as the worst result to -84% as the best result. Our result is included in the upper part of that range. In the metanalysis published by Englot et al, the median seizure reduction was 47% at 0-4 months after the implantation and 63% after 24-48 months (207). Our result is slightly higher and it may be related with the longer follow up periods.

Another aspect related to the seizure reduction has been that patients are considered responders when the seizure reduction is at least 50% (308). Patients with higher percentages of seizure reductions have better outcomes. In the previously mentioned

study by Englot, the percentage of responders was 49% at 0-4 months and 63% at 24-48m (207). In our study the responders was slightly smaller, 55.6% compared to the metanalysis. Other long-term studies showed a frequency of responders of 40% (221) and 34.5% (325).

The number of responders, the seizure reduction, as well as seizure freedom has been shown, in some studies, to improve over time (207, 241, 319). This could be related to the modulatory effect and changes in the releasing neurotransmissor in the CNS to decrease the hyperexitability and potentiate the inhibitory systems (166). But, the improvement over time was not found in our results, and we found a higher reduction at six months compared to two months. We recognize that the sample analysed in three periods of time was small, representing less than a quarter of the total sample. Related to the retrospective nature of the study, it was impossible to analyze the rest of the patients in the 3 periods of time. But, there are other study(s) that point to the same conclusion of no improvement over time. The Elliot et al. study found an improvement of seizure control and after two years of therapy a plateau begins (221).

5.1.1.2.2. RESPONDERS BY GROUP

Several factors can have an impact into the improvement over time, including heterogeneity of the sample, variable follow-ups and other associated therapies. In our sample, there were no significant differences in the number of ASM, comparing before and after the implantation or a significant difference the dose of each ASM. Our results are supported by previous studies that found no changes in ASD (227, 326, 327), and Qiabi et al. with only 9% of the responders with lower antiepileptic medication compared to the baseline (241). Elliot et al. found an increment of the final dose of all the medications in the last follow-up (221). However, related to the retrospective nature of our study, we could not control for all the ASM changes. Only one of the few prospective studies of VNS efficacy controlled for changes in ASM and doses at different points in time, comparing

patients who received VNS and the patients without VNS (246). They study found that the maximal improvement with VNS therapy was concurrent with when more medication changes were done (246). Similar results were obtained by Ryvlin et al. (329) and McLachlan et al. found a reduction of the ASM in 43% of the responders group (238).

In our sample, the age of the patient at time of VNS implantation varies from just over a year to 56 years. The age group with the best response was 14 years old or older. However, the younger groups were small. In our analysis that used linear regression model, there was not a significant improvement in relation to the age or duration of the epilepsy at the time of the VNS implantation. Several publications have shown the VNS's efficacy in all group ages, especially in children. Publications show that the decrease in the seizure frequency can improve the patients' quality of life and cognitive development. Englot et al. found a seizure reduction of 49.5% ± 4.2% and 55.3% ± 4.1% in children with a greater benefit in the paediatric population ($p>0.001$) (330). More details will be discussed in the paediatric discussion.

Vagus nerve stimulation was approved for the treatment of focal onset medically resistant epilepsy, however in many countries it has also been used for generalized MRE. In our sample, the VNS was used in focal and non-focal onset epilepsy, being used for generalized (27%) and for multifocal (30%) the most frequent epilepsy. In the analysis, all types of epilepsy had a significant reduction, however there was no statistical significance between groups. There is no clear response indicating which epilepsy type has a better VNS response. For example Rychlicki et al suggested that focal epilepsy has a better response, and Montanvout et al. suggested the opposite, that generalized epilepsy has a better response (193,331). The metanalysis done by Englot et al. suggested that generalized seizures had a better response (57.5%±1.9%) than focal seizures (42.5%±0.9%) (330). In relation to that, analysing the type of seizures and the percentage of responders, we found a significant reduction in the seizure types focal with impairment of awareness, focal to bilateral tonic clonic and generalized tonic clonic. The other types were not significant (focal without impairment of awareness, absence seizures or

myoclonic) or it was not possible to analyze due to the limited number of patients with those types of seizures. Some of those seizure types are difficult to quantify because they are subtle and many of them can be missed. There are contradictory results concerning absence, myoclonic, tonic and atonic seizure response (196, 205, 208, 332, 333, 334, 445, 336).

We analysed the possible relation between becoming a responder and different EEG patterns. The EEG pattern has to have a direct impact on the type of epilepsy and also on the type of seizures. However, in our multivariant analysis there was no difference in the type of EEG pattern per se, and all the EEG patterns included in the analysis were significant in the reduction of seizures. There is no clear data in the literature concerning the best EEG profile, due to existing contradictory information. Janszky et at. analysed the outcome of 47 patients implanted with VNS and classified their EEG pattern in the presence of bitemporal interictal epileptiform discharges (IED), and with the absence of generalized discharges (321). That study found the absence of IED was associated with seizure freedom (321). Another study found just the opposite (337), that the presence of bitemporal could be associated with a good outcome.

Similarly, there was no specific MRI finding that was related to better a outcome than the other MRI findings. The presence of lesion(s) in the MRI has been related with better surgical outcomes, compared to non-lesional (338). However, Englot's metanalysis stated that the absence of a lesion has been associated with better outcomes. In general, the patients with a lesion should be considered for other studies assessing the MRI findings with a descriptive analysis (331).

We considered epilepsy etiology as a potentially good feature for possible help in selecting better responders to the VNS implantation. We found all etiologies have good response to the VNS except meningitis/encephalitis, possibly related to the small number of patients included. The good response in the GGE shows a therapeutic option for the patients with generalized medically resistant epilepsy. The structural cases also showed a

good outcome. The largest metanalysis found that patients with unknown or idiopathic epilepsy (51.1% ± 3.8%) had a smaller seizure reduction than patients with posttraumatic epilepsy (78.6% ± 8.7%) and tuberous sclerosis (68.1% ± 4.6%), but better than Lennox-Gastaut syndrome or other epileptic encephalopathies (47.8% ± 1.9%) (330). Englot et al. stated that nonlesional etiology was a predictive factor for good response to treatment (207).

5.1.2.2.3. OTHER SUBGROUPS

People with Intellectual disabilities (ID) are at a higher risk of developing epilepsy. The prevalence of epilepsy in people with ID is estimated to be 26% to 70% (339, 340, 341, 342). It was found that as the severity of Intellectual disabilities increases, the seizure frequency and the resistance to treatment increases (328). Many patients with severe ID have medically-resistant epilepsy (MRE) (343). Uncontrolled seizures increase the risk of injuries, and decrease quality of life, resulting in higher morbidity and mortality (242, 344). In our simple 38.6% of the patients implanted with VNS had some grade of DD. When we analysed the response to the device, there was no significant difference. Similarly, what has been described with patients with LGS, in the cases of ID is also controversial. Some authors state the VNS is able to control the seizures in patients with ID (274, 345). Others obtained similar results as this study, showing no clear response to the VNS in this group of patients (54).

In this population with MRE is not uncommon to undergo epilepsy surgery, such as a palliative procedure or initially curative procedure. These types of resections were represented in one third of our patients. There is limited information concerning the response in patients with previous epilepsy surgery. In a study that investigated the influence of previous epilepsy surgery and seizure control, it showed no significant seizure reduction compared to the ones without, and there was no correlation between the seizure reduction and the type of epilepsy surgery (335). We obtained similar results, with

no difference in seizure reduction. However, in the case of CC, there are several authors that show good results in seizure control in patients with CC and VNS (9, 15, 14, 346, 347, 348, 348, 350).

5.1.2. OTHER OUTCOMES

Even though seizure reduction is the parameter most commonly used to evaluate the efficacy of therapies, including VNS, their is information to consider others such as seizure intensity reduction and seizure duration. In our retrospective analysis, the information related to those parameters was not always mentioned in the notes. We found a good response in intensity reduction and duration in 11-13% of the patients. In animal's models, McLachlan et al., showed a reduction in the duration of tonic-clonic seizures (from 30.2 ±15.7 to 5±1.8) (144).

Another interesting parameter that we collected was the reduction of hospitalizations in patients with uncontrolled seizures and we found a significant reduction. Similar results were found in the studies of Camp et al. (351) and Bernstein et al. (316).

The interest of VNS's effect on mood and cognition is growing, especially considering VNS was approved for the management of treatment-resistant depression. In our retrospective analysis we also found that 13% of the patients actively described an improvement in mood, energy and/or attention. The positive effect of VNS in mood-cognition is not completely understood. There is mixed evidence, but there is general supports for the positive effect the VNS has on mood-cognition (352, 353, 354, 355, 356, 357).

We considered it important to assess the patients overall satisfaction with the efficacy of the device, relative of the patients/caregivers and the attending physician. We found that more than 40% of patients gave a good response. Hilderink et al. analyzed the patient's

opinion in a similar way and found a number reported a greater patient satisfaction of 62% (358). However, the best way to analyze satisfaction of the device and quality of live is through questionnaires.

5.1.3. DEVICE RELATED

There are different parameters analyzed concerning the device. The model type implanted can have an impact into the outcome. We found a higher chance of responders with the PG 102, 103 and 106SR. The evolution of the mechanism of stimulation has not changed too much between the models, except the 106SR, which has the heart increment detection that acts as a closed loop. This propriety can have a direct effect, leading to improved seizure control. However, more data is required to confirm this. The duration of the battery of the PG is similar to the rate of almost four years, as previously published (361).

The duty cycle's effect into the efficacy of the VNS to control seizures has been previously described (220). Our results support that information, showing an association between the increase of time on responders.

5.1.4. SAFENESS

There are two factors to consider before deciding on using medication or a device, efficacy and safeness. Safeness needs to be evaluated carefully and explained to the patients and relatives to avoid future misunderstandings.

The VNS is a relatively safe technique, however it is associated with some risk, including complications of the implantation of the device and also risks related to the stimulation. In most of the cases, the most severe risks are related to the implantation, especially

infection of the area of implantation. Infection has been previously described as occurring in 3-6% of cases (58, 65, 88, 280). In our series occurred only in 1.8% of the patients.

In relation to the stimulation, we found 63.2% of the patients implanted with the VSN had some side effects. The most common was hoarseness in 26.4% and voice change in 19.4%, which also were described as the most frequent side effects (58, 88, 198).

5.2 VNS IN PAEDIATRICS

5.2.1 PAEDIATRIC GROUP AND CLINICAL CHARACTERISTICS

The inclusion criteria in this subanalysis was the age of implantation, which has a median13 y-o and is 13 years younger than the general group. In relation to that, the epilepsy duration at the time of VNS implantation was significantly shorter in the paediatric group than the general group The most numerous group was 10-15 y-o, but important metion needns to be tomade for the youngest onepatients (0-5 y-o). One patient was implanted at 1.3 y-o, representing the youngest children implanted with VNS in Canada. The peadiatric population represents almost a third of the total VNS implantation patients and VNS should offered to this epileptic group (361, 362). On many occasions, VNS is the only therapeutic strategy left to try to control seizures and improve longterm outcome in realtion to seizure control and cognitive improvement (12, 65, 363, 364). In addition, there is limited information on the population younger than 12 years-old, and even less information on patients younger than five years-old, partly due to small patient cohorts or reported cases (337, 361, 365).

Another important feature of this group is its' association with cognitive impairment present in almost 90% and past history of status epilepticus in a quarter. 75% of epileptic

patients experienced cognitive impairment and a past history of status epilepticus is more prevalent in the paediatric group compared to the general population.

The MRI, EEG and epilepsy type were similar in both groups. However, the etiologies were different, with a higher percentage of LGS and less related to unknown cause. In relation to ASM, the paediatric group, probably in realtion with the shorter epilepsy duration, had less trails with antiseizure medications, but at the time of VNS implatation, in both groups were taking the same number of ASM.

5.2.2 PAEDIATRIC GROUP AND OUTCOMES

5.2.2.1 PAEDIATRIC GROUP AND SEIZURE REDUCTION

The seizure reduction rate in this group was higher than in the general group, but the number of responders were slightly smaller. Both results suggest comparable response in our sample. Elliot et al. published their series that included 141 children with medically-resistant epilepsy implanted with VNS, and also reviewed previous publications (348). They had a follow-up slightly longer than previous studies, with 5.3 years of follow-up and obtained seizure reduction ≥ 75% in 41.4%(348). This is really similar to our 40.9% at almost three years of follow-up. However, there is a variability of the seizure reduction and responders, for example in the case of seizure reduction ≥ 75%, it goes from 25% of the children implanted to 78% (348). This could be related to many different factors, some of them could be the type of patients implanted and the time of follow up. In relation to that, the seizure reduction rate can also change. In our case it was considerably higher than the results published by Helmers et al. at 3 and 6 moths with 36% and 45% of seizure reduction (348), and higher than Levy's et al. at 12 months of 55% (366).

When we analyzed the outcome in relation to the age, there was no statistical significance. We obtained the same nul effect considering the age in the general analysis of the sample. This results were obtained by several other studies, clearly represented in the Elliot et al study (348), including the group of patients ≥ 12 y-o compared to < 12 y-o.

5.2.2.2 PAEDIATRIC GROUP AND OTHER OUTCOMES

There are several other outcomes that need to be evaluated to consider the efficacy of a therapy, in this case VNS. In this paediatric population with severe epilepsy, all of them required hospitalization at some point for seizure control before the VNS implantation. However, the reduction was not statistically significant. Half of the patients (n=8) were not admitted to the hospital for seizure management after the VNS. In a similar study done by Bodin et al found a significant reduction of number of days of epilepsy-related hospitalization (367).

In many other studies (227, 356, 367) as well as in our results show that the number of antiseizure medications before and after the VNS implantation didn't change. Some papers hypothesized that there will be a reduction if we follow the patients for enough time. In our study, we went a step further and we mentioned the most common ASD used. Even if at the beginning we found that lamotrigine and viagabatrine were most frequently seen in the responder group, the results were not statistically significant.

Finally, a subjective improvement was extracted from annotation in the chart perceived by the caregivers or the physician in more than two fifths of the patients implanted. Even if there was not a direct impact in the seizure control, there was an impact on the life of the patient implanted with VNS. Bordin et al analysed their data in a similar way, through the impact on the quality of life, and obtained similar results(367). Other

studies used standarized questionnaries (227). This will be the next step to obtain more objective information.

5.2.2.3 PAEDIATRIC GROUP AND DEVICE RELATED EFICACY

As described previously, there are minor differences concerning the different types of PG. Our series showed an increment in the number of VNS implantations in the last years, for that reason the most common type was 106SR. However, there was not significant differences between the different types. In the literature we couldn't find any reports concerning different PG models.

The duration of the battery was almost three years. In the adult group the battery duration was slightly longer. Another other study pointed to approximatete battery duration of five years (196, 367). The duration of the battery could be related to the parameters used for the VNS stimulation. The output current was higher than the previous paediatric study (3.25 mA), for example Orosz et at used 1.8 mA on average in the stimulation (227). We didn't find any significant difference concerning the different parameters applied in those patients comparing responders and non responders.

5.2.3 PAEDIATRIC GROUP AND SAFTENESS

The rate of complications related to VNS implantation is significantly lower than other epilepsy surgeries (365). The rate of permanent complications originated from the implantation is approximatetely 0-8%, and the risk of infection is around 3%. In our case, we didn't have any infection and only one case of severe pain in the neck, that slowly improved.

In addition, many studies described the frequent side effects, most of them minor, that improved over the time. In our series, 54.5% noticed side effects related to the stimulation, cough being the most frequently described (192, 204, 224, 276).

5.3 VNS IN GENERALIZED EPILEPSY

Patients with refractory generalized epilepsy are not generally considered to be candidates for resective surgery. Treatment with VNS can improve the seizure management in this population as well as their quality of life (368). The results of our study add information to the existing literature on the use of VNS for generalized MRE, with 59% of seizure reduction in the LGS group and 86% in GGE group. In relation to seizure types, results showed that VNS appeared to be more effective in decreasing the number of generalized tonic-clonic seizures, when compared to other types of seizures. We also identified a decrease in seizure-related hospital admissions post-implantation. This is likely due to the reduction in the total number of seizures resulting from VNS implantation.

We decideded to divide the generalized epilepsy population in two main categories: Lennox Gastaut Syndrome (LGS) and Genetic Generalized Epilepsy (GGE). Seizure reduction after the VNS implantation was greater in the GGE group compared to the LGS group. Similarly, the number of patients who achieved a seizure reduction of 75% or greater in the GGE was significantly higher than the LGS group. Interestingly, six patients with GGE were seizure free for several months, which was not seen in the LGS group. In previous studies with a small series of patients, the percentage of responders varied from 7.7% to 66.7% (203, 207, 330, 332, 333, 334, 335, 369). Studies published on the use of VNS in GGE are scarce. But, the findings obtained in our study are similar to the two largest series of patients conducted by Nei et al. and Labar et al, which included 25 and 24 patients respectively (203, 207). However, our results are more promising with a

higher rates of responders compared to previous studies. This may partly be explained by the adoption of stricter selection criteria for patients with GGE. This finding suggests that the VNS is beneficial for patients with GGE that do not respond to any antiseizure medications, and these patients should be implanted with VNS. In the LGS group, 48.3% had a reduction of seizures greater than 50% after the VNS implantation. This was similar to what has been previously described (242, 276, 379, 371). In addition, we found that almost a quarter of the patients with LGS turned off the device due its lack of efficacy. These patients experienced less promising results in relation to their seizure control after VNS implantation.

The overall seizure frequency reduction for all types of seizures was higher in the GGE. Furthermore, we found that generalized tonic-clonic seizures responded better than other types of seizures. Some effect was seen for absence seizures, however no clear effect was seen for myoclonic seizures. In addition, in the LGS group, the GTC seizures number reduced after the VNS implantation. But there was no improvement in atypical absence seizures as well as other type of seizures in the LGS. In a previous study of LGS, which analysed at patients with LGS who were implanted with VNS, the authors found a higher tonic and atonic seizure reduction compared to GTC (372). Other studies, with small sample sizes, found contradictory results in relation to a direct impact on seizure reduction in other types of seizures (203, 207, 330, 332, 333, 334, 335, 369). **Table 4** summarizes the findings in the literature.

VNS has been approved in patients who are 12 years or older, however several publications have reported using the device in much younger populations (219, 221, 222, 224, 225, 226, 227, 228, 229, 239, 231, 232). In our study there were no patients younger than 18 years old with GGE implanted, a difference with LGS group where the youngest implanted patient was 11 years old. In addition, the age of implantation was remarkably younger in cases of LGS compared to GGE. This finding reflects the severity of LGS, with

an earlier age of onset and earlier age to become therapy resistant, and the need to initiate more aggressive treatments earlier than in other groups of patients with epilepsy.

Several publications have found an incremental response to the VNS treatment over time among all types of MRE (58, 129, 206, 331). In contrast, Elliot et al, found an initial improvement, but after two years of therapy, improvement in GTC plateaued, with only marginal gains between the fourth and the tenth year after the implantation (220). Our results reproduced a similar plateau period, without significant improvement over time.

Our study is unique because it provides information over five years after implantation of VNS in patients with generalized epilepsy (LGS and GGE). No differences were seen in the mean number or doses of ASMs before and after implantation. This was a novel finding, as this was not previously reported in the literature (10, 203, 207, 220). See **table 26**.

The reduction in hospitalization was another useful measure to evaluate the efficacy of the device. Our results showed a significant reduction in the number of seizure-related hospitalizations. A finding not previously reported. Several authors have found a significant cost reduction after VNS by analyzing the number of visits to the emergency department (ED) , hospitalizations and length of hospital stay after VNS implantation (234, 312, 314, 316). Further, the reduction in the ED visits and hospitalizations has an indirect effect on the quality of life of the people with epilepsy that are implanted with VNS.

Our safety data suggested a similar percentage of infection (2.2%) compared with other studies (3-4%) (206). The side effects related to the stimulation were similar to other studies (301). The most frequent side effect in our study was coughing (203). Those side effects were considered mild to moderate and reversible in most of the cases (97.8%) and only rare cases required explantation of the VNS due to side effects (301). In some cases it is necessary to readjust the output current, with slower increments, or decrease the pulse width, to help decrease the side effects and maximize the effectiveness of the VNS

(196, 373). In more than half of the cases the side effects improved progressively over time, most of them resolving within two to three years after the implantation (10, 196, 274).

In our series, the majority of patients who had their VNS turned off due to lack of efficacy were in the LGS group. Finally, the duration of the battery was significantly longer in patients with LGS compared to GGE. The average duration of VNS battery was 40 months, with a range from 28 to 80 m (317).

The present study had several limitations including those inherent to any retrospective study. Even though some variables could not be analyzed adequately due to insufficient data, this did not alter the final analysis. Additionally, even though our study is one of the largest, the sample size remains small (203, 207, 330, 332, 333, 334, 335, 369, 374). Larger prospective multicenter studies are needed to address the limitations of this study.

Study	Cases	Type of GE	≥50% Reduction	≥75% Reduction	Sz Reduction
Holmes et al. (2004) [16]	16	8 GGE 8 SGE	43.8%	31.3%	18.8% with 90% reduction
Kostov et al. (2007) [15]	12	GGE	66.7%	33.3%	
Ng et al. (2004) [13]	27/16 5	13 SGE 14 GGE	SGE 7.7% IGE 35.7%		
Shen et al. (2004) [17]	13/10 2	GE			46% to 78% of GTC reduction
Farrag et al. (2002) [18]	3	GE (Absence)		2 patients	1 patient
Parain et al. (2003) [19]	3	GE (CAE)			N=1, Sz Free at 18m N=2, 70% and 85% seizure reduction 12m
Labar et al. (1999) [12]	24	GE	45.8%		46% SGE 40% GGE 60%
Nei et al. (2006) [14]	25	GE	40%	20%	
Frost et al. (2001) [21]	24	LGS	58%	38%	6 m follow up
Kostov et al. (2009) [22]	30	LGS			60.6% at 52 m
Suller et al. (2020)	17 29	GGE LGS	64.7% 48.3%	47.1% 27.6%	86% at 51 months 59% at 66 months

Table 26. Summary of the up-to-date evidence on the use VNS in generalized (203, 207, 330, 332, 333, 334, 335, 369, 374). CAE: Childhood Absence Epilepsy; GE: Generalized Epilepsy; GGE: Genetic Generalized epilepsy; IGE: Idiopathic generalized epilepsy; m: months; SGE: Symptomatic Generalized Epilepsy; Sz: Seizures.

5.4 VNS DURING PREGNANCY

VNS is a therapy used in cases of medically resistant epilepsy to improve seizure management. This device is used in all ages, including the potential childbearing population. There are concerns that VNS can increase the risk of obstetric complications during the pregnancy and at the time of the delivery, as well as possible teratogenic effects to the fetus / newborn. The information in that regard is limited even though it is a device commonly used to treat epilepsy. There are only 34 cases published worldwide investigating the outcome of those with epilepsy on treatment with VNS during pregnancy (in **table 27**, we summarized the cases reported in the literature) (181, 182, 183, 184, 322, 325, 375, 376, 377).

Study	N Woman	Epilepsy Type	N Pregnan-cies	Age at time pregnan-cy	Average current	Type Delivery	Maternal Complica-tions	Malfor-mation	Maternal, fetus or baby death
Ben-Menachen et al (1999)	2	Dm	2	Dm	Dm	Dm	None	None	None
Kalayjian & Heck (2005)	2	Focal	3	38	0.5 mA	Dm	None	None	None
Houser et al (2010)	1	Generalized	1	19	Dm	Vaginal	1 PE	None	None
Galbaniatu et al (2015)	1	Focal	1	Dm	Dm	Dm	None	None	None
Salerno et al (2016)	1	Focal	1	27 y-o	2 mA	c-section	None	None	None
Rodriguez-Osorio et al (2017)	4	4 Focal	5	31.8 y-o	1.25	2 c-section 2 vaginal	1 PROM 1 Rh Incompatibility	None	1 miscarriage (1st T)
Sabers et al (2017)	25	17 Focal 3 GGE 5 Unclassified	26	31 y-o	1.6-1.8 mA	10 vaginal 10 c-section 2 vacuum extraction 2 induced labors	None	1 major malformation	1 miscarriage (8 w-p)
Housain et al (2005)	1	Depression	1	28	0.25 mA	Vaginal	None	None	None
Suller et al (2019)	4	3 GGE 1 Focal	7	22 y-o	1.75 mA	4 c-section 3 vaginal	1 PE 1 PROM & BP 1 FTP	1 major malformation	None

Table 27. Summary of the publications reporting the use of VNS in pregnancy (181, 182, 183, 184, 322, 325, 375, 376, 377).

Avg: Average; BP: breech presentation; Dm: data missing; GGE: Genetic Generalized Epilepsy; FTP: failure to progress; PE: pre-eclampsia; PROM: premature rupture of membranes; T: trimester; w-p: weeks of pregnancy.

We presented four patients with MRE who underwent VNS implantation prior to pregnancy. There were seven pregnancies resulting in six healthy babies. One of the seven babies had intellectual disability and cardiac malformation. Even though this could have been related to VNS, there were other risk factors including high doses of ASM and

potential genetic influence. In all cases, birth weight, Apgar scores and duration of pregnancy were normal.

Another important outcome is the type of the delivery and obstetric complications. Several studies of pregnant woman who have epilepsy have shown that this population has increased risk of obstetric complications (291, 378, 379). In our series there were three obstetric complications over seven deliveries, requiring four c-sections, and only one was elective. Therefore, c-section was necessary in 57% of the pregnancies observed in this series. This number is higher in comparation to the Canadian rate of 26.9% (380). The pathophysiology of the obstetric complications may be related to the uterine input received from the vagus nerve, which behaves as a biderectional bridge between the central nervous system and the uterus (381).

The refractoriness of the patients included in this series is something to consider as the refractory nature of their epilepsy was the reason for VNS implantation. All patients were taking several ASM during their pregnancy. Polytherapy has shown to increase the risk of fetal malformation (291). VNS can reduce seizure frequency, and might mitigate teratogenic risk if the number or doses of ASM can be reduced.

The VNS has also been approved in some countries for refractary depressive cases. There is less research focusing on VNS and refractory depressive patients, particularly comparisons to those with epilepsy. One case was publised which investigated a depressive pregnant women who became pregnant while she was using the device and had an uneventful delivery with a full term healthy baby (376).

Experimental epilepsy models using rats and rabbits receiving VNS stimulation during pregnancy, found no adverse effect on either the pregnancy or on neonatal viability (382). In a similar study with rabbits, the fetuses did not show any skeletal and soft tissue abnormalities (383). Both studies used 1mA as output current, and a pulse width of 500

microseconds. However they used different durations of the stimulation (time on), in the first case 30 seconds and 30 min in the second. It is not clear if the total time during which the fetus was exposed to the stimulation can impact the outcome. Another important finding in a different study found that VNS does not affect the level of pittuitary hormons (LH, FSH, prolactin).

Other implatable devices which have been used more frequently, such as cardiac pacemakers, do not cause any limitations during pregnancy (384). In the case of Deep Brain Stimulation (DBS), a small case series including eleven pregnant women implanted with DBS found no side effects or complications for the mother or the baby (385).

6. CONCLUSIONS

VNS IN EPILEPSY

1. The results of our study support that VNS is effective in patients with medically resistant epilepsy, with a frequency of seizure reduction of 50% or more in 56% of the patients with a VNS implant.
2. There is a low chance of becoming seizure free, but GTC seizure freedom can occur in almost one third of patients with these types of seizures, for less than a year.
3. We found predictive factors for good a VNS response: for patients with a history of GTC, BTC, Focal LOA; there is a better response if the EEG shows multifocal, generalized and multifocal; GGE as etiology; with higher signal On time; and VNS models 102,103,105 and 106.
4. The VNS showed a significant reduction in hospitalization rates due to uncontrolled seizures in patients implanted with VNS.
5. There is less than a 2% risk of a severe complication, with 63% of side effects related to the stimulation, with cough and hoarseness being the most frequent. This side effect improved over time in many cases.

VNS IN PAEDIATRICS

1. In patients ≤ 15 y-o, VNS had a significant seizure reduction in 50% of the patients implanted.
2. There were no differences regarding the age of implantation ≤6 vs >6 y-o.
3. There were no severe complications and mild side effects improved over time.

VNS IN GENERALIZED EPILEPSY

1. Patients with generalized epilepsy who do not respond to antiseizure drugs should be considered for VNS therapy. The present study illustrated a significant reduction in the number of seizures in generalized MRE patients.
2. The responders rate was particularly high in the GGE group with 64.7% being responders and the LGS group with 41.7% being responders.
3. VNS seemed to be more effective at reducing GTC seizures in both groups of generalized epilepsy.
4. Improvement in seizure control has a notable impact on patients' quality of life as well as a decrease in costs to the health care system, through the reduction of admissions to the hospital.
5. These results add more information to the therapeutic value of neuromodulation, through VNS, as an important co-adjuvant treatment in patients with generalized MRE.

VNS DURING PREGNANCY

1. Even though our sample is small, it suggests that VNS is a well tolerated therapy during pregnancy that may reduce polypharmacy and is likely safe for the fetus.
2. The obstetrical complications may be higher, with a low risk of congenital malformations.
3. A prospective multicentre study or a larger sample of patients is needed to accurately determine safety and potential teratogenicity of VNS.

7. REFERENCES

1. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004; 62; 1252-1260.
2. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JC, Elger CE, et al. A practical clinical definition of epilepsy. Epilepsia 2014; 55(4): 475–482.
3. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005; 46(4): 470-472. doi:10.1111/j.0013-9580.2005.66104.x
4. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the “common” neurologic disorders? Neurology 2007; 68(5): 326-37.
5. Helmers SL, Thurman DJ, Durgin TL, Pai AK, Faught E. Descriptive epidemiology of epilepsy in the U.S. population: A different approach. Epilepsia 2015; 56(6): 942-8.
6. Sillanpää M, Kälviäinen R, Klaukka T, Helenius H, Shinnar S. Temporal changes in the incidence of epilepsy in Finland: nationwide study. Epilepsy Res 2006 Oct; 71(2-3): 206-15.
7. Besocke AG, Rosso B, Cristiano E, Valiensi SM, García Mdel C, Gonorazky SE et al. Outcome of newly-diagnosed epilepsy in older patients. Epilepsy Behav. 2013 Apr;27(1):29-35.
8. Scharfman HE. The neurobiology of epilepsy. Curr Neurol Neurosci Rep. 2007;7(4):348-354. doi:10.1007/s11910-007-0053-z
9. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia. 1993;34(4):592-596. doi:10.1111/j.1528-1157.1993.tb00433.x

10. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58(4):512–521.
11. Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58(4):531-542. doi:10.1111/epi.13671
12. Berg AT, Millichap JJ. The 2010 revised classification of seizures and epilepsy. Continuum (Minneap Minn). 2013;19(3 Epilepsy):571-597. doi:10.1212/01.CON.0000431377.44312.9e
13. Dash D, Dash C, Primrose S, et al. Update on Minimal Standards for Electroencephalography in Canada: A Review by the Canadian Society of Clinical Neurophysiologists. Can J Neurol Sci. 2017;44(6):631-642. doi:10.1017/cjn.2017.217
14. Zivin L, Marsan CA. Incidence and prognostic significance of "epileptiform" activity in the eeg of non-epileptic subjects. Brain. 1968;91(4):751-778. doi:10.1093/brain/91.4.751
15. Eeg-Olofsson O, Petersén I, Selldén U. The development of the electroencephalogram in normal children from the age of 1 through 15 years. Paroxysmal activity. Neuropadiatrie. 1971;2(4):375-404. doi:10.1055/s-0028-1091791
16. Bihege CJ, Langer T, Jenke AC, Bast T, Borusiak P. Prevalence of Epileptiform Discharges in Healthy Infants. J Child Neurol. 2015;30(11):1409-1413. doi:10.1177/0883073814565457
17. Borusiak P, Zilbauer M, Jenke AC. Prevalence of epileptiform discharges in healthy children--new data from a prospective study using digital EEG. Epilepsia. 2010;51(7):1185-1188. doi:10.1111/j.1528-1167.2009.02411.x
18. So EL. Interictal epileptiform discharges in persons without a history of seizures: what do they mean?. J Clin Neurophysiol. 2010;27(4):229-238. doi:10.1097/WNP.0b013e3181ea42a4

19. Salinsky M, Kanter R, Dasheiff RM. Effectiveness of multiple EEGs in supporting the diagnosis of epilepsy: an operational curve. Epilepsia. 1987;28(4):331-334. doi:10.1111/j.1528-1157.1987.tb03652.x
20. Spencer D. MRI (minimum recommended imaging) in epilepsy. Epilepsy Curr. 2014;14(5):261-263. doi:10.5698/1535-7597-14.5.261
21. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. CME Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004;62; 1261-1273.
22. Kanner AM, Ashman E, Gloss D, et a. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy. Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Currents 2018; 18 (4): 260–268.
23. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment resistant epilepsy. Report of the American Epilepsy Society and the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Epilepsy Currents 2018; 18 (4): 269–278.
24. Mauri Llerda JA, Suller Marti A, de la Peña Mayor P, et al. The Spanish Society of Neurology's official clinical practice guidelines for epilepsy. Special considerations in epilepsy: comorbidities, women of childbearing age, and elderly patients. Neurologia. 2015 Oct; 30(8):510-7.
25. Brodie MJ, Barry SJE, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. Neurology 2012; 78:1548-1554.
26. Faught E. Treatment of refractory primary generalized epilepsy. Rev Neurol Dis. 2004;1 Suppl 1:S34-S43.

27. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies [published correction appears in Epilepsia. 2010 Sep;51(9):1922]. Epilepsia. 2010;51(6):1069-1077. doi:10.1111/j.1528-1167.2009.02397.x
28. Strine TW, Chapman DP. Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. Sleep Med. 2005;6(1):23-27. doi:10.1016/j.sleep.2004.06.003
29. Téllez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. Epilepsia. 2005;46(12):1955-1962. doi:10.1111/j.1528-1167.2005.00344.x
30. Wiebe S, Bellhouse DR, Fallahay C, Eliasziw M. Burden of epilepsy: the Ontario Health Survey. Can J Neurol Sci. 1999 Nov; 26(4):263-70.
31. Strine TW, Kobau R, Chapman DP, Thurman DJ, Price P, Balluz LS. Psychological distress, comorbidities, and health behaviors among U.S. adults with seizures: results from the 2002 National Health Interview Survey. Epilepsia. 2005 Jul;46(7):1133-9.
32. Kanner AM. Can neurobiological pathogenic mechanisms of depression facilitate the development of seizure disorders? Lancet Neurol. 2012;11(12):1093-1102. doi:10.1016/S1474-4422(12)70201-6
33. Forsgren L, Nystrom L. An incident case-referent study of epileptic seizures in adults. Epilepsy Res 1990; 6: 66–81.
34. Hesdorff er DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. Ann Neurol 2000; 47: 246–49.
35. Hesdorff er DC, Hauser WA, Ludvigsson P, Olafsson E, Kjartansson O. Depression and attempted suicide as risk factors for incident unprovoked seizures and epilepsy. Ann Neurol 2006; 59: 35–41.

36. Adelow C, Anderson T, Ahlbom A, Tomson T. Hospitalization for psychiatric disorders before and after onset of unprovoked seizures/epilepsy. Neurology 2012; 78: 396–401.
37. McAfee AT, Chilcott KE, Johannes CB, Hornbuckle K, Hauser WA, Walker AM. The incidence of fi rst unprovoked seizure in pediatric patients with and without psychiatric diagnsoses. Epilepsia 2007; 48: 1075–82.
38. Alper KR, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007; 62: 345–54.
39. Robertson, MM . Suicide, parasuicide, and epilepsy. In: Epilepsy: A Comprehensive Textbook. (Engel, J , Pedley, TA , eds.). Philadelphia: Lippincott–Raven, 1997:2141–2151.
40. Harris EC, Barraclough B. Suicide as an outcome for mental disorders: a meta-analysis. Br J Psychiatry 1997;170: 205–28.
41. Kobau R, DiIorio CA, Price PH, et al. Prevalence of epilepsy and health status of adults with epilepsy in Georgia and Tennessee: Behavioral Risk Factor Surveillance System, 2002. Epilepsy Behav. 2004;5(3):358-366. doi:10.1016/j.yebeh.2004.02.007
42. Tellez-Zenteno JF, Pondal-Sordo M, Matijevic S, Wiebe S. National and regional prevalence of self-reported epilepsy in Canada. Epilepsia. 2004;45(12):1623-1629. doi:10.1111/j.0013-9580.2004.24904.x
43. Kobau R, Gilliam F, Thurman DJ. Prevalence of self-reported epilepsy or seizure disorder and its associations with self-reported depression and anxiety: results from the 2004 HealthStyles Survey. Epilepsia. 2006;47(11):1915-1921. doi:10.1111/j.1528-1167.2006.00612.x
44. Baker GA, Brooks J, Buck D, Jacoby A. The stigma of epilepsy: a European perspective. Epilepsia. 2000;41(1):98-104. doi:10.1111/j.1528-1157.2000.tb01512.x

45. DiIorio C, Osborne Shafer P, Letz R, et al. The association of stigma with self-management and perceptions of health care among adults with epilepsy. Epilepsy Behav. 2003;4(3):259-267. doi:10.1016/s1525-5050(03)00103-3
46. Dalkilic EB. Neurostimulation Devices Used in Treatment of Epilepsy. Curr Treat Options Neurol. 2017;19(2):7. doi:10.1007/s11940-017-0442-9
47. Terra VC, Amorim R, Silvado C, et al. Vagus nerve stimulator in patients with epilepsy: indications and recommendations for use. Arq Neuropsiquiatr. 2013;71(11):902-906. doi:10.1590/0004-282X20130116
48. McNamara JO, Wada JA. Kindling model. In: Engel J, Pedley TA, editors. Epilepsy: A Comprehensive Textbook. Philadelphia: Lippincott-Raven Publishers; 1997. pp. 419–425.
49. Goddard GV, McIntyre DC, Leech CK. A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol. 1969;25(3):295-330. doi:10.1016/0014-4886(69)90128-9
50. Hiyoshi T, Wada JA. Lasting nature of both transfer and interference in amygdaloid kindling in cats: observation upon stimulation with 11-month rest following primary site kindling. Epilepsia. 1992;33(2):222-227. doi:10.1111/j.1528-1157.1992.tb02310.x
51. Engel J Jr, Wiebe S, Radhakrishnan K, Palmini A. Surgical treatment for epilepsy. Neurologisch (Wien). 2013;2013:12-14.
52. Burakgazi E, French JA. Treatment of epilepsy in adults. Epileptic Disord. 2016;18(3):228-239. doi:10.1684/epd.2016.0836
53. Rathore C, Radhakrishnan K. Concept of epilepsy surgery and presurgical evaluation. Epileptic Disord 2015; 17 (1): 19-31.
54. Jayakar P, Gotman J, Harvey AS, et al. Diagnostic utility of invasive EEG for epilepsy surgery: Indications, modalities, and techniques. Epilepsia. 2016;57(11):1735-1747. doi:10.1111/epi.13515

55. Zangaladze A, Sharan A, Evans J, et al. The effectiveness of low-frequency stimulation for mapping cortical function. Epilepsia. 2008;49(3):481-487. doi:10.1111/j.1528-1167.2007.01307.x
56. Kalitzin S, Velis D, Suffczynski P, Parra J, da Silva FL. Electrical brain-stimulation paradigm for estimating the seizure onset site and the time to ictal transition in temporal lobe epilepsy. Clinical Neurophysiology 2005; 116: 718–728.
57. Wiebe S, Blume WT, Girvin JP, Eliasziw M; Effectiveness and Efficiency of Surgery for Temporal Lobe Epilepsy Study Group. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345(5):311-318. doi:10.1056/NEJM200108023450501
58. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial onset seizures: a randomized active control trial. Neurology 1998; 51:48-55.
59. Fauser S, Zentner J. Critical review of palliative surgical techniques for intractable epilepsy. Adv Tech Stand Neurosurg. 2012;39:165-194. doi:10.1007/978-3-7091-1360-8_7
60. Engel J Jr. Update on surgical treatment of the epilepsies. Summary of the Second International Palm Desert Conference on the Surgical Treatment of the Epilepsies (1992). Neurology. 1993;43(8):1612-1617. doi:10.1212/wnl.43.8.1612
61. Thakur KT, Probasco JC, Hocker SE, et al. Ketogenic diet for adults in super-refractory status epilepticus. Neurology. 2014;82(8):665-670. doi:10.1212/WNL.0000000000000151
62. Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3(2):175-192. Published 2018 May 21. doi:10.1002/epi4.12225
63. Ye F, Li XJ, Jiang WL, Sun HB, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015;11(1):26-31. doi:10.3988/jcn.2015.11.1.26

64. Keller T, Krames ES. "On the shoulders of giants": a history of the understandings of pain, leading to the understandings of neuromodulation. Neuromodulation. 2009;12(2):77-84. doi:10.1111/j.1525-1403.2009.00196.x
65. Ardesch JJ, Buschman HP, Wagener-Schimmel LJ, van der Aa HE, Hageman G. Vagus nerve stimulation for medically refractory epilepsy: a long-term follow-up study. Seizure. 2007;16(7):579-585. doi:10.1016/j.seizure.2007.04.005
66. Löscher W, Schmidt D. Modern antiepileptic drug development has failed to deliver: ways out of the current dilemma. Epilepsia. 2011;52(4):657-678. doi:10.1111/j.1528-1167.2011.03024.x
67. Simon Hornblower; Antony Spawforth; Esther Eidinow (11 September 2014). The Oxford Companion to Classical Civilization. OUP Oxford. pp. 352–. ISBN 978-0-19-101676-9 .
68. Piccolino M. Animal electricity and the birth of electrophysiology: the legacy of Luigi Galvani. Brain Res Bull. 1998;46(5):381-407. doi:10.1016/s0361-9230(98)00026-4
69. Caputi F, Spaziante R, de Divitiis E, Nashold BS Jr. Luigi Rolando and his pioneering efforts to relate structure to function in the nervous system. J Neurosurg. 1995;83(5):933-937. doi:10.3171/jns.1995.83.5.0933
70. Yildirim FB, Sarikcioglu L. Marie Jean Pierre Flourens (1794 1867): an extraordinary scientist of his time. J Neurol Neurosurg Psychiatry. 2007;78(8):852. doi:10.1136/jnnp.2007.118380
71. Carlson C, Devinsky O. The excitable cerebral cortex Fritsch G, Hitzig E. Uber die elektrische Erregbarkeit des Grosshirns. Arch Anat Physiol Wissen 1870;37:300-32. Epilepsy Behav. 2009;15(2):131-132. doi:10.1016/j.yebeh.2009.03.002
72. Borchers S, Himmelbach M, Logothetis N, Karnath HO. Direct electrical stimulation of human cortex - the gold standard for mapping brain functions?. Nat Rev Neurosci. 2011;13(1):63-70. Published 2011 Nov 30. doi:10.1038/nrn3140

73. Gowers, W. R. Epilepsy And Other Chronic Convulsive Diseases: Their Causes, Symptoms, & Treatment. London: Churchill, 1881.
74. Horsley V. Case of occipital encephalocele in which a correct diagnosis was obtained by means of the induced current. Brain 1884;7:228–243.
75. Bidwell LA. Focal Epilepsy: Trephining and Removal of Small Haemorrhagic Focus: No Improvement; Removal of Part of Leg Centre after Electrical Stimulation: Improvement. Br Med J. 1893 Nov 4;2(1714):988-9. doi: 10.1136/bmj.2.1714.988.
76. Cushing, H. A Note upon the Faradic Stimulation of the Postcentral Gyrus in Conscious Patients. Brain: A Journal of Neurology 1909, 32, 44–53. https://doi.org/10.1093/brain/32.1.44
77. Penfield, W. The Excitable Cortex in Conscious Man (The Sherringon, Lectures V. Charles C Thomas, Springfield, Illinois) 1958.
78. Dalkilic EB. Neurostimulation Devices Used in Treatment of Epilepsy. Curr Treat Options Neurol. 2017;19(2):7. doi:10.1007/s11940-017-0442-9
79. DeGiorgio CM, Soss J, Cook IA, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. Neurology. 2013;80(9):786-791. doi:10.1212/WNL.0b013e318285c11a
80. Cooper IS, Upton AR, Amin I. Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Appl Neurophysiol. 1980;43(3-5):244-258. doi:10.1159/000102263
81. Boon P, Vonck K, van Rijckevorsel K, et al. A prospective, multicenter study of cardiac-based seizure detection to activate vagus nerve stimulation. Seizure. 2015;32:52-61. doi:10.1016/j.seizure.2015.08.011
82. Mirski MA, Fisher RS. Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia. 1994;35(6):1309-1316. doi:10.1111/j.1528-1157.1994.tb01803.x

83. Mirski MA, Rossell LA, Terry JB, Fisher RS. Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat. Epilepsy Res. 1997;28(2):89-100. doi:10.1016/s0920-1211(97)00034-x
84. Moeller F, Siebner HR, Wolff S, et al. Changes in activity of striato-thalamo-cortical network precede generalized spike wave discharges. Neuroimage. 2008;39(4):1839-1849. doi:10.1016/j.neuroimage.2007.10.058
85. Tyvaert L, Chassagnon S, Sadikot A, LeVan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: an EEG-fMRI study. Neurology. 2009;73(23):2018-2022. doi:10.1212/WNL.0b013e3181c55d02
86. Salanova V, Witt T, Worth R, et al. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology. 2015;84(10):1017-1025. doi:10.1212/WNL.0000000000001334
87. Penfield W, Jasper H. Electrocorticography. In: Epilepsy and the functional anatomy of the human brain. Boston: Little, Brown; 1954. p. 692–738.
88. Kossoff EH, Ritzl EK, Politsky JM, et al. Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring. Epilepsia. 2004;45(12):1560-1567. doi:10.1111/j.0013-9580.2004.26104.x
89. Morrell MJ; RNS System in Epilepsy Study Group. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77(13):1295-1304. doi:10.1212/WNL.0b013e3182302056
90. Benifla M, Rutka JT, Logan W, et al. Vagal nerve stimulation for refractory epilepsy in children: indications and experience at the hospital for sick children. Childs Nerv Syst 2006;22:1018-26.
91. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. Biol Psychiatry. 2000;47(4):276–86.

92. Saper CB, Kibbe MR, Hurley KM, et al. Brain natriuretic peptide-like immunoreactive innervation of the cardiovascular and cerebrovascular systems in the rat. Circ Res. 1990;67(6):1345-1354. doi:10.1161/01.res.67.6.1345
93. Rutecki P: Anatomical, physiological and theoretical basis for the antiepileptic effect of vagus nerve stimulation. Epilepsia 1990, 31:S1–S6.
94. Foley JO, DuBois F. Quantitative studies of the vagus nerve in the cat. 1. The ratio of sensory to motor fibers. J Comp Neurol 1937;49-97.
95. Ronkainen E, Korpelainen JT, Heikkinen E, Myllylä VV, Huikuri HV, Isojärvi JI. Cardiac autonomic control in patients with refractory epilepsy before and during vagus nerve stimulation treatment: a one-year follow-up study. Epilepsia. 2006;47(3):556-562. doi:10.1111/j.1528-1167.2006.00467.x
96. Henry TH. Vagus nerve stimulation for epilepsy: anatomical, experimental and mechanistic investigations. Schachter SC, Schmidt D. Vagus nerve stimulation. Second Edition. Ed. Martin Dunita. United Kingdom, 2003, pp. 1-31.
97. Henry TR. Therapeutic mechanisms of vagus nerve stimulation. Neurology 2002;59:3-14.
98. Beckstead R.M, Norgren R. An autoradiographic examination of the central distribution of the trigeminal, facial, glossopharyngeal, and vagus nerve in the monkey. J Comp Neurol 1979; 184:455-72.
99. Kalia M, Sullivan M. Brainstem projections of sensory and motor components of the vagus nerve in rat. J Comp Neurol 1966; 211:530-40.
100. Rhoton AL, O'Leary JL, Ferguson JP. The Trigeminal, Facial, Vagal, and Glossopharyngeal Nerves in the Monkey. Arch Neurol 1966; 14:530-40.
101. Ricardo JA, Koh ET (1978) Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures. Brain Res 153:1–26.
102. Nieuwenhuys R, Voogd J, Van Hijzen C. The Human Central Nervous System. Third edition. Ed. Springer-Verlag, Berlin, 1983.

103. Parent A. Carpenter's Human Neuroanatomy. Ninth edition. Ed. Williams & Wilkins, Baltimore, 1995.

104. Schmidt D. Vagus nerve stimulation in the current treatment of epilepsy. Vagus nerve stimulation. Second Edition. Ed. Martin Dunita, United Kingdom, 2003, pp.123-39.

105. Parry CH. On the effects of compression of the arteries in various diseases, and particulary in those of the head; with hints towards a new mode of treating nervous disorders. Mem Med Soc Lond 1792; 3:77-113.

106. Bailey P, Bremer F. A sensory cortical representation of the vagus nerve with a note on the effects of low blood pressure on the cortical electrogram. J Neurophysiol 1938; 1:405-12.

107. Corning JL. Carotid compression and brain rest. Anson DF Randolph & Co, New York, 1882.

108. Parry CH. Elements of pathology and therapeutics, being the outlines of a work intended to ascertain the nature, causes, and most efficacious modes of prevention and cure, of the greater number of diseases incidental to the human frame; illustrated by numerous cases and dissections. Vol. 1. General pathology. 2nd ed. Bath, England: Richard Cruttwell, 1825: 246–255.

109. Corning JL. On the treatment of congestive headache. Medical Record 1882;22:708–709.

110. Corning JL. The endermic use of cocaine in the treatment of certain phases of neuralgia. Intl J Surg Antiseptics 1888; 1:13-14.

111. Corning JL. Epilepsy: Its clinical manifestations, pathology, and treatment. [Part 2]. New York Med J 1887; 46:154-8.

112. Lanska DJ. J.L. Corning and vagal nerve stimulation for seizures in the 1880s. Neurology 2002; 58:452-9.

113. Boggs JG, Nowack WJ, Drinkard CR. Analysis of the “honeymoon effect” in adult epilepsy patients. Epilepsia 2000; 41(Suppl. 7): 222.

114. Corning JL. Prolonged instrumental compression of the primitive carotid artery as therapeutic agent. Medical Record 1882; 21:173-4.

115. Corning JL. Electrization of the sympathetic and pneumogastric nerves, with simultaneous bilateral compression of the carotids. New York Med J 1884;39:212–215.

116. Corning JL. The bromide of sodium in the treatment of epilepsy. Medical Record 1883;24:345.

117. Corning JL. Brain-rest: being a disquisition on the curative properties of prolonged sleep. 2nd ed. New York: GP Putnam's Sons, 1885. (page 101-102).

118. Corning JL. Considerations on the pathology and therapeutics of epilepsy. J Nerv Ment Dis 1883;10:243–248.

119. Dell P, Olson R. Projections "secondaries" mésencéphaliques, diencéphaliques et amygdaliennes des afférences viscérales vagales [Secondary mesencephalic, diencephalic and amygdalian projections of vagal visceral afferences]. C R Seances Soc Biol Fil. 1951;145(13-14):1088-1091.

120. Dell P, Olson R. Projections thalamiques, corticales et cérébelleuses des afférences viscérales vagales [Thalamic, cortical and cerebellar projections of vagal visceral afferences]. C R Seances Soc Biol Fil. 1951;145(13-14):1084-1088.

121. Zanchetti A, Wang Sc, Moruzzi G. The effect of vagal afferent stimulation on the EEG pattern of the cat. Electroencephalogr Clin Neurophysiol. 1952;4(3):357-361. doi:10.1016/0013-4694(52)90064-3

122. Chase MH, Sterman MB, Clemente CD. Cortical and subcortical patterns of response to afferent vagal stimulation. Exp Neurol. 1966;16(1):36-49. doi:10.1016/0014-4886(66)90084-7

123. Chase MH, Nakamura Y, Clemente CD, Sterman MB. Afferent vagal stimulation: neurographic correlates of induced EEG synchronization and desynchronization. Brain Res. 1967;5(2):236-249. doi:10.1016/0006-8993(67)90089-3

124. Zabara J. Peripheral control of hypersynchronous discharge in epilepsy, Electroencephalogr Clin Neurophysiol 1985;61:162.

125. Zabara J. Time course of seizure control to brief repetitive stimuli, Epilepsia 1985;26:518.

126. Zabara J. Controlling seizures by changing GABA receptor sensitivity. Epilepsia 1987;28:604.

127. Zabara J. Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 1992;33:1005-1012.

128. Penry JK, Dean JC. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia. 1990;31 Suppl 2:S40-S43. doi:10.1111/j.1528-1157.1990.tb05848.x

129. Ben-Menachem E, Mañon-Espaillat R, Ristanovic R, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia. 1994;35(3):616-626. doi:10.1111/j.1528-1157.1994.tb02482.x

130. DeGiorgio CM, Schachter SC, Handforth A, et al. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia. 2000;41(9):1195-1200. doi:10.1111/j.1528-1157.2000.tb00325.x

131. Schachter SC. Vagus nerve stimulation therapy summary: five years after FDA approval. Neurology. 2002;59(6 Suppl 4):S15-S20. doi:10.1212/wnl.59.6_suppl_4.s15

132. Smyth MD, Tubbs RS, Bebin EM, Grabb PA, Blount JP. Complications of chronic vagus nerve stimulation for epilepsy in children. J Neurosurg. 2003;99(3):500-503. doi:10.3171/jns.2003.99.3.0500

133. Tatum WO 4th, Moore DB, Stecker MM, et al. Ventricular asystole during vagus nerve stimulation for epilepsy in humans. Neurology. 1999;52(6):1267-1269. doi:10.1212/wnl.52.6.1267

134. Uthman BM, Wilder BJ, Hammond EJ, Reid SA. Efficacy and safety of vagus nerve stimulation in patients with complex partial seizures. Epilepsia. 1990;31 Suppl 2:S44-S50. doi:10.1111/j.1528-1157.1990.tb05849.x

135. Uthman BM, Wilder BJ, Penry JK, et al. Treatment of epilepsy by stimulation of the vagus nerve. Neurology. 1993;43(7):1338-1345. doi:10.1212/wnl.43.7.1338

136. Duncan AG, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev 2005; 29:493-500.

137. Grastyan E, Hasznost T, Lissak K, et al. Activation of the brain stem activating system by vegetative afferents; a preliminary report. Acta Physiol Hung. 1952;3:103-22.

138. Padel Y, Dell P. Bulbar and reticular effects of soporific stimulation of the vagoaortic trunk. J Physiol 1965;57:269-70.

139. Saper CB, Loewy AD. Efferent connections of the parabrachial nucleus in the rat. Brain Res 1980;197:291-317.

140. Marrosu F, Serra A, Maleci A, Puligheddu M, Biggio G, Piga M. Correlation between GABA(A) receptor density and vagus nerve stimulation in individuals with drug-resistant partial epilepsy. Epilepsy Res. 2003;55(1-2):59-70. doi:10.1016/s0920-1211(03)00107-4

141. Ben-Menachem E. Modern management of epilepsy: Vagus nerve stimulation. Baillieres Clin Neurol. 1996;5(4):841-848.

142. Krahl SE, Clark KB, Smith DC, Browning RA. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. Epilepsia. 1998;39(7):709-714. doi:10.1111/j.1528-1157.1998.tb01155.x

143. McLachlan RS. Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia. 1993;34(5):918-923. doi:10.1111/j.1528-1157.1993.tb02112.x

144. Henry TR, Votaw JR, Pennell PB, et al. Acute vagus nerve stimulation selectively alters blood flow in somatosensory and limbic cortex and the cerebellum of patients with complex partial seizures. Epilepsia 1997;8:144.

145. Henry TR, Bakay RA, Votaw JR, et al. Brain blood flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: I. Acute effects at high and

low levels of stimulation. Epilepsia. 1998;39(9):983-990. doi:10.1111/j.1528-1157.1998.tb01448.x

146. Henry TR, Votaw JR, Pennell PB, et al. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. Neurology. 1999;52(6):1166-1173. doi:10.1212/wnl.52.6.1166

147. Van Laere K, Vonck K, Boon P, Versijpt J, Dierckx R. Perfusion SPECT changes after acute and chronic vagus nerve stimulation in relation to prestimulus condition and long-term clinical efficacy. J Nucl Med. 2002;43(6):733-744.

148. Vonck K, De Herdt V, Bosman T, Dedeurwaerdere S, Van Laere K, Boon P. Thalamic and limbic involvement in the mechanism of action of vagus nerve stimulation, a SPECT study. Seizure. 2008;17(8):699-706. doi:10.1016/j.seizure.2008.05.001

149. Marrosu F, Santoni F, Puligheddu M, et al. Increase in 20-50 Hz (gamma frequencies) power spectrum and synchronization after chronic vagal nerve stimulation. Clin Neurophysiol. 2005;116(9):2026-2036. doi:10.1016/j.clinph.2005.06.015

150. Ben-Menachem E, Hamberger A, Hedner T, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res. 1995;20(3):221-227. doi:10.1016/0920-1211(94)00083-9

151. Hammond EJ, Uthman BM, Wilder BJ, et al. Neurochemical effects of vagus nerve stimulation in humans. Brain Res. 1992;583(1-2):300-303. doi:10.1016/s0006-8993(10)80038-1

152. Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation for epilepsy and depression. Neurotherapeutics. 2008;5(1):75-85. doi:10.1016/j.nurt.2007.10.071

153. Carpenter LL, Moreno FA, Kling MA, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. Biol Psychiatry. 2004;56(6):418-426. doi:10.1016/j.biopsych.2004.06.025

154. Andersson U, Tracey KJ. Neural reflexes in inflammation and immunity. J Exp Med. 2012;209(6):1057-1068. doi:10.1084/jem.20120571

155. Rao Y, Wong K, Ward M, Jurgensen C, Wu JY. Neuronal migration and molecular conservation with leukocyte chemotaxis. Genes Dev. 2002;16(23):2973-2984. doi:10.1101/gad.1005802

156. Mirakaj V, Brown S, Laucher S, et al. Repulsive guidance molecule-A (RGM-A) inhibits leukocyte migration and mitigates inflammation. Proc Natl Acad Sci U S A. 2011;108(16):6555-6560. doi:10.1073/pnas.1015605108

157. Serhan CN, Petasis NA. Resolvins and protectins in inflammation resolution. Chem Rev. 2011;111(10):5922-5943. doi:10.1021/cr100396c

158. Mirakaj V, Dalli J, Granja T, Rosenberger P, Serhan CN. Vagus nerve controls resolution and pro-resolving mediators of inflammation. J Exp Med. 2014;211(6):1037-1048. doi:10.1084/jem.20132103

159. Rosas-Ballina M, Olofsson PS, Ochani M, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. Science. 2011;334(6052):98-101. doi:10.1126/science.1209985

160. Wu JY, Feng L, Park HT, et al. The neuronal repellent Slit inhibits leukocyte chemotaxis induced by chemotactic factors. Nature. 2001;410(6831):948-952. doi:10.1038/35073616

161. Waldburger JM, Boyle DL, Pavlov VA, Tracey KJ, Firestein GS. Acetylcholine regulation of synoviocyte cytokine expression by the alpha7 nicotinic receptor. Arthritis Rheum. 2008;58(11):3439-3449. doi:10.1002/art.23987

162. van Maanen MA, Stoof SP, van der Zanden EP, et al. The alpha7 nicotinic acetylcholine receptor on fibroblast-like synoviocytes and in synovial tissue from rheumatoid arthritis patients: a possible role for a key neurotransmitter in synovial inflammation. Arthritis Rheum. 2009;60(5):1272-1281. doi:10.1002/art.24470

163. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature. 2000;405(6785):458-462. doi:10.1038/35013070

164. Huston JM, Ochani M, Rosas-Ballina M, et al. Splenectomy inactivates the cholinergic antiinflammatory pathway during lethal endotoxemia and polymicrobial sepsis. J Exp Med. 2006;203(7):1623-1628. doi:10.1084/jem.20052362

165. Meregnani J, Clarençon D, Vivier M, et al. Anti-inflammatory effect of vagus nerve stimulation in a rat model of inflammatory bowel disease. Auton Neurosci. 2011;160(1-2):82-89. doi:10.1016/j.autneu.2010.10.007

166. Koopman FA, Chavan SS, Miljko S, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2016;113(29):8284-8289. doi:10.1073/pnas.1605635113

167. Hammond EJ, Uthman BM, Reid SA, Wilder BJ. Electrophysiological studies of cervical vagus nerve stimulation in humans: I. EEG effects. Epilepsia. 1992;33(6):1013-1020. doi:10.1111/j.1528-1157.1992.tb01752.x

168. Salinsky MC, Burchiel KJ. Vagus nerve stimulation has no effect on awake EEG rhythms in humans. Epilepsia. 1993;34(2):299-304. doi:10.1111/j.1528-1157.1993.tb02415.x

169. Koo B. EEG changes with vagus nerve stimulation. J Clin Neurophysiol. 2001 Sep;18(5):434-41. doi: 10.1097/00004691-200109000-00008. PMID: 11709649.

170. Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. Epilepsia. 1990;31 Suppl 2:S7-S19. doi:10.1111/j.1528-1157.1990.tb05852.x

171. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. Seizure. 2014;23(7):496-505. doi:10.1016/j.seizure.2014.02.012

172. Fisher RS, Afra P, Macken M, et al. Automatic Vagus Nerve Stimulation Triggered by Ictal Tachycardia: Clinical Outcomes and Device Performance--The U.S. E-37 Trial. Neuromodulation. 2016;19(2):188-195. doi:10.1111/ner.12376

173. Boon P, Vonck K, Van Walleghem P, et al. Programmed and magnet-induced vagus nerve stimulation for refractory epilepsy. J Clin Neurophysiol. 2001;18(5):402-407. doi:10.1097/00004691-200109000-00003

174. Fromes GA, Edwards JC, Holland KD, Sagher Oren, Garton HJL, Ross DA. Clinical utility of on-demand magnet use with vagus nerve stimulation (2.109). Epilpesia 2000; 41 (S7): 117.

175. Schachter SC, Saper CB. Vagus nerve stimulation. Epilepsia. 1998;39(7):677-686. doi:10.1111/j.1528-1157.1998.tb01151.x

176. Amar AP, Heck CN, Levy ML, et al. An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. Neurosurgery. 1998;43(6):1265-1280. doi:10.1097/00006123-199812000-00001

177. Forcadas-Berdusán MI. Indicaciones y resultados de los tratamientos no farmacológicos de las epilepsias: estimulación vagal, dieta cetógena y rayos gamma [Indications and results of nonpharmacological treatments of epilepsies: vagal stimulation, ketogenic diet and gamma rays]. Rev Neurol. 2002;35 Suppl 1:S144-S150.

178. Malow BA, Edwards J, Marzec M, Sagher O, Fromes G. Effects of vagus nerve stimulation on respiration during sleep: a pilot study. Neurology. 2000;55(10):1450-1454. doi:10.1212/wnl.55.10.1450

179. Marzec M, Edwards J, Sagher O, Fromes G, Malow BA. Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia. 2003;44(7):930-935. doi:10.1046/j.1528-1157.2003.56202.x

180. Turak B, Roux FX. Chronic therapeutic stimulation of the vagal nerve for epilepsy: surgical considerations. Epilepsies 2008;20:18-31.

181. Houser MV, Hennessy MD, Howard BC. Vagal nerve stimulator use during pregnancy for treatment of refractory seizure disorder. Obstet Gynecol. 2010;115(2 Pt 2):417-419. doi:10.1097/AOG.0b013e3181bd1a8b

182. Salerno G, Passamonti C, Cecchi A, Zamponi N. Vagus nerve stimulation during pregnancy: an instructive case. Childs Nerv Syst. 2016;32(1):209-211. doi:10.1007/s00381-015-2897-x

183. Sabers A, Battino D, Bonizzoni E, et al. Maternal and fetal outcomes associated with vagus nerve stimulation during pregnancy. Epilepsy Res. 2017;137:159-162. doi:10.1016/j.eplepsyres.2017.05.013

184. Rodríguez-Osorio X, López-González FJ, Garamendi Í, et al. VNS and pregnancy: A multicentric experience of four cases. Acta Neurol Scand. 2017;136(4):372-374. doi:10.1111/ane.12780

185. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology. 1995;45(2):224-230. doi:10.1212/wnl.45.2.224

186. Hatton KW, McLarney JT, Pittman T, Fahy BG. Vagal nerve stimulation: overview and implications for anesthesiologists. Anesth Analg. 2006;103(5):1241-1249. doi:10.1213/01.ane.0000244532.71743.c6

187. Kemeny AA. Surgical technique in vagus nerve stimulation. Schachter SC, Schmidt D. Vagus nerve stimulation. Second Edition. Ed. Martin Dunita. United Kingdom, 2003, pp. 33-48.

188. Arcos-Algaba A, Rodriguez-Osorio X, Prieto-Gonzalez P, et al. Marcapasos vagal: una alternativa al tratamiento de la epilepsia. Neurocirugía Contemporánea 2008;2:1-6.

189. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. Lancet Neurol. 2002;1(8):477-482. doi:10.1016/s1474-4422(02)00220-x

190. Lundgren J, Amark P, Blennow G, Strömblad LG, Wallstedt L. Vagus nerve stimulation in 16 children with refractory epilepsy. Epilepsia. 1998;39(8):809-813. doi:10.1111/j.1528-1157.1998.tb01173.x

191. Alvarez LA, Dean P, Jayakar P, et al. Tratamiento de la epilepsia por medio de la estimulación vagal [Epilepsy treatment by vagal stimulation]. Rev Neurol. 1999;29(4):385-387.

192. Rychlicki F, Zamponi N, Trignani R, Ricciuti RA, Iacoangeli M, Scerrati M. Vagus nerve stimulation: clinical experience in drug-resistant pediatric epileptic patients. Seizure. 2006;15(7):483-490. doi:10.1016/j.seizure.2006.06.001

193. Mapstone TB. Vagus nerve stimulation: current concepts. Neurosurg Focus. 2008;25(3):E9. doi:10.3171/FOC/2008/25/9/E9

194. Heck C, Helmers SL, DeGiorgio CM. Vagus nerve stimulation therapy, epilepsy, and device parameters: scientific basis and recommendations for use. Neurology. 2002;59(6 Suppl 4):S31-S37. doi:10.1212/wnl.59.6_suppl_4.s31

195. Labar D, Ponticello L, Nikolov B, Bellapu S, Schwartz TH. Stimulation parameters after Vagus Nerve Stimulator Replacement. Neuromodulation 2008; 11 (2): 132-134.

196. Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05 [published correction appears in Neurology 2000; 54(8):1712]. Neurology. 1999;53(8):1731-1735. doi:10.1212/wnl.53.8.1731

197. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol. 2001;18(5):415-418. doi:10.1097/00004691-200109000-00005

198. Labiner DM, Ahern GL. Vagus nerve stimulation therapy in depression and epilepsy: therapeutic parameter settings. Acta Neurol Scand 2007;115:23–33.

199. Lockard JS, Congdon WC. Effects of vagal stimulation on seizure rate in monkey model. Epilepsia 1986;27: 626-628.

200. Terry R, Tarver WB, Zabara J. An implantable neurocybernetic prosthesis system. Epilepsia. 1990;31 Suppl 2:S33-S37. doi:10.1111/j.1528-1157.1990.tb05846.x

201. Stoica I, Tudor I. Vagal trunk stimulation influences on epileptic spiking focus activity. Rev. Roum.Neurolog 1968; 5(1): 203-210.

202. Hammond EJ, Uthman BM, Reid SA, et al. Vagus nerve stimulation in human: neurophysiological studies and electrophysiological monitoring. Epilepsia 1990;31(S2):S51-S59.

203. Labar D, Murphy J, Tecoma E. E04 VNS Study Group. Vagus nerve stimulation for medication-resistant generalized epilepsy. Neurology 1999;52:1510-2.

204. Amar AP, DeGiorgio CM, Tarver WB, Apuzzo ML. Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial. Stereotact Funct Neurosurg. 1999;73(1-4):104-108. doi:10.1159/000029764

205. Müller K, Fabó D, Entz L, et al. Outcome of vagus nerve stimulation for epilepsy in Budapest. Epilepsia. 2010;51 Suppl 3:98-101. doi:10.1111/j.1528-1167.2010.02620.x

206. Englot DJ, Rolston JD, Wright CW, Hassnain KH, Chang EF. Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. Neurosurgery. 2016;79(3):345-353. doi:10.1227/NEU.0000000000001165

207. Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. Seizure. 2004;13(3):176-178. doi:10.1016/S1059-1311(03)00147-X

208. Purves SJ, Wada JA, Woodhurst WB, et al. Results of anterior corpus callosum section in 24 patients with medically intractable seizures. Neurology. 1988;38(8):1194-1201. doi:10.1212/wnl.38.8.1194

209. Spencer SS, Spencer DD, Williamson PD, et al. Corpus callosotomy for epilepsy, I: Seizure effects. Neurology 1988;38:19–24.

210. Fuiks KS, Wyler AR, Hermann BP, et al. Seizure outcome from anterior and complete corpus callosotomy. J Neurosurg 1991;74:573– 578.

211. Oguni H, Olivier A, Andermann F, et al. Anterior callosotomy in the treatment of medically intractable epilepsies: a study of 43 patients with a mean follow-up of 39 months. Ann Neurol 1991;30:357–364.

212. Mamelak AN, Barbaro NM, Walker JA, et al. Corpus callosotomy: a quantitative study of the extent of resection, seizure control, and neuropsychological outcome. J Neurosurg 1993;79:688–695.

213. Reutens DC, Bye AM, Hopkins IJ, et al. Corpus callosotomy for intractable epilepsy: seizure outcome and prognostic factors. Epilepsia 1993;34:904–909.

214. Sorenson JM, Wheless JW, Baumgartner JE, et al. Corpus callosotomy for medically intractable seizures. Pediatr Neurosurg 1997;27:260–267.

215. Shimizu H. Our experience with pediatric epilepsy surgery focusing on corpus callosotomy and hemispherotomy. Epilepsia 2005;46(suppl 1):30–31.

216. McInerney J, Siegel AM, Nordgren RE, et al. Long-term seizure outcome following corpus callosotomy in children. Stereotact Funct Neurosurg 1999;73:79–83.

217. Bogen JE. Linguistic performance in the short term following cerebral commissurotomy. In: Whitaker HA, Whitaker H, eds. Perspectives in Neurolinguistics and Psycholinguistics, Vol. 2, New York: Academic Press, 1976:193–224.

218. Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. Milbank Mem Fund Q Health Soc. 1982;60(3):429-462.

219. Patwardhan RV, Stong B, Bebin EM, Mathisen J, Grabb PA. Efficacy of vagal nerve stimulation in children with medically refractory epilepsy. Neurosurgery. 2000;47(6):1353-1358.

220. Elliott RE, Morsi A, Kalhorn SP, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav. 2011;20(1):57-63. doi:10.1016/j.yebeh.2010.10.017

221. Coykendall DS, Gauderer MW, Blouin RR, Morales A. Vagus nerve stimulation for the management of seizures in children: an 8-year experience. J Pediatr Surg. 2010;45(7):1479-1483. doi:10.1016/j.jpedsurg.2010.02.066

222. Hornig GW, Murphy JV, Schallert G, Tilton C. Left vagus nerve stimulation in children with refractory epilepsy: an update. South Med J. 1997;90(5):484-488. doi:10.1097/00007611-199705000-00003

223. You SJ, Kang HC, Kim HD, et al. Vagus nerve stimulation in intractable childhood epilepsy: a Korean multicenter experience. J Korean Med Sci. 2007;22(3):442-445. doi:10.3346/jkms.2007.22.3.442

224. Murphy JV, Torkelson R, Dowler I, et al. Vagus nerve stimulation in refractory epilepsy: the first 100 patients receiving vagal nerve stimulation at a pediatric epilepsy center. Arch Pediatr Adolesc Med 2003;157:560-4.

225. Saneto RP, Sotero de Menezes MA, Ojemann JG, et al. Vagus nerve stimulation for intractable seizures in children. Pediatr Neurol 2006;35:323-6.

226. Alexopoulos AV, Kotagal P, Loddenkemper T, et al. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure 2006;15:491-503.

227. Orosz I, McCormick D, Zamponi N, Varadkar S, Feucht M, Parain D, Griens R, Vallee L, Boon P, Rittey C, Jayewardene AK, Bunker M, Arzimanoglou A, Lagae L (2014) Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 55(10):1576–1584.

228. Healy S, Lang J, Te Water Naude J, Gibbon F, Leach P. Vagal nerve stimulation in children under 12 years old with medically intractable epilepsy. Childs Nerv Syst. 2013;29(11):2095-2099. doi:10.1007/s00381-013-2143-3

229. Hauptman JS, Mathern GW. Vagal nerve stimulation for pharmacoresistant epilepsy in children. Surg Neurol Int. 2012;3(Suppl 4):S269-S274. doi:10.4103/2152-7806.103017

230. Yu C, Ramgopal S, Libenson M, et al. Outcomes of vagal nerve stimulation in a pediatric population: a single center experience. Seizure. 2014;23(2):105-111. doi:10.1016/j.seizure.2013.10.002

231. Colicchio G, Policicchio D, Barbati G, et al. Vagal nerve stimulation for drug-resistant epilepsies in different age, aetiology and duration. Childs Nerv Syst. 2010;26(6):811-819. doi:10.1007/s00381-009-1069-2

232. Soleman J, Knorr C, Datta AN, et al. Early vagal nerve stimulator implantation in children: personal experience and review of the literature. Childs Nerv Syst. 2018;34(5):893-900. doi:10.1007/s00381-017-3694-5

233. Trimble MR, Dodson WE. Epilepsy and quality of life. Ed. Raven Press, New York, 1994.

234. Boon P, D'Havé M, Van Walleghem P, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia. 2002;43(1):96-102. doi:10.1046/j.1528-1157.2002.40100.x

235. Hermann BP, Whitman S. Behavioral and personality correlates of epilepsy: a review, methodological critique, and conceptual model. Psychol Bull 1984;95:451-97.

236. Morrow JI, Bingham E, Craig JJ, et al. Vagal nerve stimulation in patients with refractory epilepsy. Effect on seizure frequency, severity and quality of life. Seizure 2000;9:442-5.

237. McLachlan RS, Sadler M, Pillay N, et al. Quality of life after vagus nerve stimulation for intractable epilepsy: is seizure control the only contributing factor? Eur Neurol. 2003;50(1):16-19.

238. Valencia I, Holder DL, Helmers SL, et al. Vagus nerve stimulation in pediatric epilepsy: a review. Pediatr Neurol 2001;25:368-76.

239. Dodrill CB, Morris GL. Effects of vagal nerve stimulation on cognition and quality of life in epilepsy. Epilepsy Behav 2001;2:46-53.

240. Qiabi M, Bouthillier A, Carmant L, Nguyen DK. Vagus nerve stimulation for epilepsy: the notre-dame hospital experience. Can J Neurol Sci. 2011;38(6):902-908. doi:10.1017/s0317167100012506

241. Salinsky MC, Uthman BM, Ristanovic RK, et al. Vagus nerve stimulation for the treatment of medically intractable seizures. Results of a 1-year open-extension trial. Vagus Nerve Stimulation Study Group. Arch Neurol 1996;53:1176-80.

242. Shahwan A, Bailey C, Maxiner W, et al. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. Epilepsia 2009;50:1220-8.

243. Kuba R, Brázdil M, Kalina M, et al. Vagus nerve stimulation: Longitudinal followup of patients treated for 5 years. Seizure 2009;18:269-74.

244. Labar D. Antiepileptic drug use during the first 12 months of vagus nerve stimulation therapy. Neurology 2002;59:38-43.

245. Arcand J, Waterhouse K, Hernandez-Ronquillo L, et al. Efficacy of Vagal Nerve Stimulation for Drug-Resistant Epilepsy: Is it the Stimulation or Medication? Can J Neurol Sci. 2017; 44: 532-537.

246. Glauser T, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16(1):48–61.

247. Hesdorffer DC, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 2012;53 (2):249–52.

248. Sierra-Marcos A, et al. Successful outcome of episodes of status epilepticus after vagus nerve stimulation: a multicenter study. Eur J Neurol 2012;19 (9):1219–23.

249. Gedelab S, Sitwata B, Welcha WP et al. The effect of vagus nerve stimulator in controlling status epilepticus in children Seizure 2018; 55: 66–69.

250. Guiraud D, Andreu D, Bonnet S, et al. Vagus nerve stimulation: state of the art of stimulation and recording strategies to address autonomic function neuromodulation. J Neural Eng. 2016;13(4):041002. doi:10.1088/1741-2560/13/4/041002

251. Sadler RM, Purdy RA, Rahey S. Vagal nerve stimulation aborts migraine in patient with intractable epilepsy. Cephalalgia. 2002;22:482– 484.

252. Hord ED, Evans MS, Mueed S, et al. The effect of vagus nerve stimulation on migraines. J Pain. 2003;4:530 –534.

253. Mauskop A. Vagus nerve stimulation relieves chronic refractory migraine and cluster headaches. Cephalalgia. 2005;25:82– 86.

254. Lenaerts ME, Oommen KJ, Couch JR, Skaggs V. Can vagus nerve stimulation help migraine? Cephalalgia. 2008;28:392–395.

255. Cecchini AP, Mea E, Tullo V, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. Neurol Sci. 2009;30 (suppl 1):S101–S104.

256. Beekwilder JP, Beems T. Overview of the clinical applications of vagus nerve stimulation. J Clin Neurophysiol. 2010; 27:130–8.

257. Frieda A. Koopmana, Sangeeta S. Chavanb, Sanda Miljkoc, Simeon Graziod, Sekib Sokolovice, et al. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. PNAS 2016; 113 (29): 8284–8289.

258. Lange G, Janal MN, Maniker A, Fitzgibbons J, Fobler M, Cook D, Natelson BH. Safety and efficacy of vagus nerve stimulation in fibromyalgia: a phase I/II proof of concept trial. Pain Med. 2011 Sep;12(9):1406-13.

259. Ben-Menachema E, Revesza D, Simonb BJ and Silbersteinc S. Surgically implanted and non-invasive vagus nerve stimulation: a review of efficacy, safety and tolerability. European Journal of Neurology 2015; 22: 1260–1268.

260. Asconapé JJ, Moore DD, Zipes DP, et al. Bradycardia and asystole with the use of vagus nerve stimulation for the treatment of epilepsy: a rare complication of intraoperative device testing. Epilepsia 1999;40:1452-4.

261. 250. Tanganelli P, Ferrero S, Colotto P, Regesta G: Vagus nerve stimulation for treatment of medically intractable seizures. Evaluation of long-term outcome. Clin Neurol Neurosurg 2002; 105:9–13.

262. Spuck S, Tronnier V, Orosz I, Schönweiler R, Sepehrnia A, Nowak G, et al: Operative and technical complications of vagus nerve stimulator implantation. Neurosurgery 201; 67 (2 Suppl Operative):489–494.

263. Kang HC, Hwang YS, Kim DS, Kim HD: Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study. Acta Neurochir 2006; Suppl 99:93–96.

264. Révész D, Rydenhag B, Ben-Menachem E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. J Neurosurg Pediatr March 2016; 25: 1-8.

265. Kahlow H, Olivecrona M: Complications of vagal nerve stimulation for drug-resistant epilepsy: a single center longitudinal study of 143 patients. Seizure 2013; 22:827–833.

266. Patel NC, Edwards MS: Vagal nerve stimulator pocket infections. Pediatr Infect Dis J 2004; 23:681–683.

267. Air EL, Ghomri YM, Tyagi R, Grande AW, Crone K, Mangano FT: Management of vagal nerve stimulator infections: do they need to be removed? J Neurosurg Pediatr 2009; 3:73–78.

268. Tronnier VM. Vagus Nerve Stimulation: Surgical Technique and Complications. Prog Neurol Surg. 2016; 29: 29–38.

269. Granbichler CA, Nashef L, Selway R, Polkey CE. Mortality and SUDEP in epilepsy patients treated with vagus nerve stimulation. Epilepsia 2015; 56(2): 291–296.

270. Zalvan C, Sulica L, Wolf S, Cohen J, Ginzalez-Yanes O, Blitzer A: Laryngopharyngeal dysfunction from the implant vagal stimulator. Laryngoscope 2003; 113: 221–225.

271. Robinson LC, Winston KR. Relationship of vocal cord paralysis to the coil diameter of vagus nerve stimulator leads. J Neurosurg 2015; 122:532–535.

272. Trout AT, Larson DB, Mangano FT, Gonsalves CH. Twiddler syndrome with a twist: a cause of vagal nerve stimulator lead fracture. Pediatr Radiol. 2013;43(12):1647-1651. doi:10.1007/s00247-013-2736-8

273. Ali II, Pirzada NA, Kanjwal Y, Wannamaker B, Medhkour A, Koltz MT, et al: Complete heart block with ventricular asystole during left vagus nerve stimulation for epilepsy. Epilepsy Behav 2004; 5:768–771.

274. Panebianco M, Zavanone C, Dupont S, Restivo DA, Pavone A. Vagus nerve stimulation therapy in partial epilepsy: a review. Acta Neurol Belg. 2016;116(3):241-248. doi:10.1007/s13760-016-0616-3

275. Clark AJ, Kuperman RA, Auguste KI, Sun PP. Intractable episodic bradycardia resulting from progressive lead traction in an epileptic child with a vagus nerve

stimulator: a delayed complication. J Neurosurg Pediatr. 2012;9(4):389-393. doi:10.3171/2011.12.PEDS11124

276. Frost M, Gates J, Helmers SL, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. Epilepsia 2001; 42: 1148–1152.

277. Liporace J, Hucko D, Morrow R, Barolat G, Nie M, Schnur J, et al. Vagal nerve stimulation: adjustments to reduce painful side effects. Neurology. 2001;11:885–6.

278. Milby AH, Halpern CH, Baltuch GH. Vagus nerve stimulation in the treatment of refractory epilepsy. Neurotherapeutics. 2009;6(2):228–37.

279. Ramsay RE, Uthman BM, Augustinsson LE, Upton ARM, Naritoku D, Willis J, et al. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. Epilepsia. 1994;35(3):627–36.

280. Cukiert A, Mariani PP, Burattini JA, et al. Parkinsonism induced by VNS in a child with double-cortex syndrome. Epilepsia. 2009;50(12):2667-2669.

281. De Herdt V, Boon P, Vonck K, Goossens L, Nieuwenhuis L, Paemeleire K, et al. Are psychotic symptoms related to vagus nerve stimulation in epilepsy patients? Acta Neurol Belg. 2003;103(3):170–5.

282. Duhaime AC, Melamed S, Clancy RR. Tonsillar pain mimicking glossopharyngeal neuralgia as a complication of vagus nerve stimulation: case report. Epilepsia. 2000;41(7):903–5.

283. Papacostas SS, Myrianthopoulou P, Dietis A, Papathanasiou ES. Induction of central-type sleep apnea by vagus nerve stimulation. Electromyogr Clin Neurophysiol. 2007;47(1):61–3.

284. Khurana DS, Reumann M, Hobdell EF, Neff S, Valencia I, Legido A et al. Vagus nerve stimulation in children with refractory epilepsy: unusual complications and relationship to sleep-disordered breathing. Childs Nerv Syst 2007; 23:1309–1312.

285. Guilfoyle MR, Fernandes H, Price S. In vivo alteration of Strata valve setting by vagus nerve stimulator-activating magnet. Br J Neurosurg. 2007;21(1):41-42.

286. Carius A, Schulze-Bonhage A. Trigeminal pain under vagus nerve stimulation. Pain. 2005;118:271–3.

287. Ackman C, Riviello JJ, Madsen JR, Bergin AM. Pharyngeal dysesthesia in refractory complex partial epilepsy: new seizure or adverse effect of vagal nerve stimulation? Epilepsia. 2003;44(6):855–8.

288. Bhat S, Lysenko L, Neiman ES, Rao GK, Chokroverty S. Increasing off-time improves sleep-disordered breathing induced by vagal nerve stimulation. Epileptic Disord. 2012;14(4):432–7

289. Hosain S, Nikalov B, Hardin C, Li M, Fraser R, Labar DJ. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. Child Neurol 2000;15:509–12.

290. Schallert G, Foster J, Lindquist N, Murphy J. Chronic stimulation of the left vagal nerve in children: effect on swallowing. Epilepsia 1998;39:113–4.

291. Mawer G, Briggs M, Baker GA, Bromley R, Coyle H, Eatock J, Kerr L et al. Pregnancy with epilepsy: Obstetric and neonatal outcome of a controlled study. Seizure 2010; 19: 112–119

292. Díaz-Güemes Martín-Portugués I, Sánchez Margallo FM, Pascual Sánchez-Gijón S, Crisóstomo Ayala V, Usón Gargallo J. Histopathologic features of the vagus nerve after electrical stimulation in swine. Histol Histopathol. 2005;20(3):851-856. doi:10.14670/HH-20.851

293. Sackeim HA, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. Neuropsychopharmacology. 2001;25(5):713-728. doi:10.1016/S0893-133X(01)00271-8

294. Dursun I, Yesildag O, Soylu K, Yilmaz O, Yasar E, Meric M. Late pacemaker twiddler syndrome. Clin Res Cardiol. 2006;95(10):547-549. doi:10.1007/s00392-006-0417-4

295. Schuurman PR, Beukers RJ. Ventricular asystole during vagal nerve stimulation. Epilepsia. 2009;50(4):967-968. doi:10.1111/j.1528-1167.2008.01907.x

296. Ficker DM, So EL, Shen WK, et al. Population-based study of the incidence of sudden unexplained death in epilepsy. Neurology. 1998;51(5):1270-1274. doi:10.1212/wnl.51.5.1270

297. Lhatoo SD, Johnson AL, Goodridge DM, et al. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a longterm, prospective, population-based cohort. Ann Neurol 2001; 49: 336–344.

298. Opeskin K, Berkovic SF. Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. Seizure 2003;12:456–464.

299. Tennis P, Cole TB, Annegers JF, et al. Cohort study of incidence of sudden unexplained death in persons with seizure disorder treated with antiepileptic drugs in Saskatchewan, Canada. Epilepsia 1995;36:29–36.

300. Annegers JF, Coan SP, Hauser WA, et al. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 2000;41:549–553.

301. Timarova G, Šteňo A. Late-onset jaw and teeth pain mimicking trigeminal neuralgia associated with chronic vagal nerve stimulation: case series and review of the literatura. BMC Neurology 2017; 17 (113): 1-6.

302. Campbell, E, Kennedy, F, Russell, A, Smithson, WH, Parsons, L, Morrison, PJ, Liggan, B, Irwin, B, Delanty, N, Hunt, SJ, Craig, J, Morrow, J. Malformation risks of antiepileptic drug monotherapies in pregnancy: updated results from the UK and Ireland Epilepsy and Pregnancy Registers. J. Neurol. Neurosurg. Psychiatry 2014; 85: 1029–1034.

303. Parry CH. On a Case of Nervous Affection Cured by Pressure of the Carotids; with Some Physiological Remarks. Med Phys J. 1811;26(154):458-461.

304. Begley CE, Annegers JF, Lairson DR, Reynolds TF, Hauser WA. Cost of epilepsy in the United States: a model based on incidence and prognosis. Epilepsia. 1994;35(6):1230-1243. doi:10.1111/j.1528-1157.1994.tb01794.x

305. Department of Health, Education, and Welfare, National Institutes of Health: Plan for nationwide action on epilepsy. Washington, DHEW, 1978. Publication No (NIH) 79-1115.

306. Silfvenius H. Economic costs of epilepsy--treatment benefits. Acta Neurol Scand Suppl. 1988;117:136-154. doi:10.1111/j.1600-0404.1988.tb08015.x

307. Halpern M, Rentz A, Murray M. Cost of illness of epilepsy in the US: comparison of patient-based and population-based estimates. Neuroepidemiology. 2000;19(2):87-99. doi:10.1159/000026243

308. Hamer HM, Spottke A, Aletsee C, et al. Direct and indirect costs of refractory epilepsy in a tertiary epilepsy center in Germany. Epilepsia. 2006;47(12):2165-2172. doi:10.1111/j.1528-1167.2006.00889.x

309. Tetto A, Manzoni P, Millul A, et al. The costs of epilepsy in Italy: a prospective cost-of-illness study in referral patients with disease of different severity. Epilepsy Res. 2002;48(3):207-216. doi:10.1016/s0920-1211(02)00013-x

310. Beghi E, Garattini L, Ricci E, Cornago D, Parazzini F; EPICOS Group. Direct cost of medical management of epilepsy among adults in Italy: a prospective cost-of-illness study (EPICOS). Epilepsia. 2004;45(2):171-178. doi:10.1111/j.0013-9580.2004.14103.x

311. Jacoby A, Buck D, Baker G, McNamee P, Graham-Jones S, Chadwick D. Uptake and costs of care for epilepsy: findings from a U.K. regional study. Epilepsia. 1998;39(7):776-786. doi:10.1111/j.1528-1157.1998.tb01164.x

312. Ben-Menachem E, Hellström K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology. 2002;59(6 Suppl 4):S44-S47. doi:10.1212/wnl.59.6_suppl_4.s44

313. Purser MF, Mladsi DM, Beckman A, Barion F, Forsey J. Expected Budget Impact and Health Outcomes of Expanded Use of Vagus Nerve Stimulation Therapy for Drug-Resistant Epilepsy [published correction appears in Adv Ther. 2018 Sep 12;:]. Adv Ther. 2018;35(10):1686-1696. doi:10.1007/s12325-018-0775-0

314. Forbes RB, Macdonald S, Eljamel S, Roberts RC. Cost-utility analysis of vagus nerve stimulators for adults with medically refractory epilepsy. Seizure. 2003;12(5):249-256. doi:10.1016/s1059-1311(02)00270-4

315. Bernstein AL, Hess T. Vagus nerve stimulation therapy for pharmacoresistant epilepsy: effect on health care utilization [published correction appears in Epilepsy Behav. 2011 Dec;22(4):819. Barkan, Howard [removed]]. Epilepsy Behav. 2007;10(1):134-137. doi:10.1016/j.yebeh.2006.09.014

316. Helmers SL, Duh MS, Guérin A, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav. 2011;22(2):370-375. doi:10.1016/j.yebeh.2011.07.020

317. Morris GL 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2013;81(16):1453-1459. doi:10.1212/WNL.0b013e3182a393d1

318. Scherrmann J, Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. J Clin Neurophysiol. 2001;18(5):408-414. doi:10.1097/00004691-200109000-00004

319. Nakken KO, Henriksen O, Røste GK, Lossius R. Vagal nerve stimulation--the Norwegian experience. Seizure. 2003;12(1):37-41. doi:10.1016/s1059131102001383

320. Janszky J, Hoppe M, Behne F, Tuxhorn I, Pannek HW, Ebner A. Vagus nerve stimulation: predictors of seizure freedom. J Neurol Neurosurg Psychiatry. 2005;76(3):384-389. doi:10.1136/jnnp.2004.037085

321. Ghaemi K, Elsharkawy AE, Schulz R, et al. Vagus nerve stimulation: outcome and predictors of seizure freedom in long-term follow-up. Seizure. 2010;19(5):264-268. doi:10.1016/j.seizure.2010.03.002

322. Ben-Menachem E, Hellström K, Waldton C, Augustinsson LE. Evaluation of refractory epilepsy treated with vagus nerve stimulation for up to 5 years. Neurology. 1999;52(6):1265-1267. doi:10.1212/wnl.52.6.1265

323. Kutlu G, Gömceli YB, Erdal A, İnan LE. The Honeymoon Effect in Adult Patients with Refractory Partial-Onset Epilepsy Under Levetiracetam Add-on Treatment. Epilepsia 2013;19(1):15-18.

324. Helmers SL, Griesemer DA, Dean JC, et al. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy: patients with seizures for six years or less. Neurologist. 2003;9(3):160-164. doi:10.1097/00127893-200305000-00004

325. Galbarriatu L, Pomposo I, Aurrecoechea J, et al. Vagus nerve stimulation therapy for treatment-resistant epilepsy: a 15-year experience at a single institution. Clin Neurol Neurosurg. 2015;137:89-93. doi:10.1016/j.clineuro.2015.06.023

326. Labar D. Vagus nerve stimulation for intractable epilepsy in children. Dev Med Child Neurol. 2000;42(7):496-499. doi:10.1017/s001216220000092x

327. Montavont A, Demarquay G, Ryvlin P, et al. Efficacité de la stimulation intermittente du nerf vague dans les épilepsies pharmaco-résistantes non chirurgicales de l'adolescent et de l'adulte [Long-term efficiency of vagus nerve stimulation (VNS) in non-surgical refractory epilepsies in adolescents and adults]. Rev Neurol (Paris). 2007;163(12):1169-1177. doi:10.1016/S0035-3787(07)78401-1

328. Pellock JM, Hunt PA. A decade of modern epilepsy therapy in institutionalized mentally retarded patients. Epilepsy Res. 1996;25(3):263-268. doi:10.1016/s0920-1211(96)00072-1

329. De Herdt V, Boon P, Ceulemans B, et al. Vagus nerve stimulation for refractory epilepsy: a Belgian multicenter study. Eur J Paediatr Neurol. 2007;11(5):261-269. doi:10.1016/j.ejpn.2007.01.008

330. Kostov H, Larsson PG, Røste GK. Is vagus nerve stimulation a treatment option for patients with drug-resistant idiopathic generalized epilepsy?. Acta Neurol Scand Suppl. 2007;187:55-58. doi:10.1111/j.1600-0404.2007.00848.x

331. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. J Neurosurg. 2011;115(6):1248-1255. doi:10.3171/2011.7.JNS11977

332. Holmes MD, Silbergeld DL, Drouhard D, Wilenskya AJ, Ojemannb LM. Effect of vagus nerve stimulation on adults with pharmacoresistant generalized epilepsy syndromes. Seizure 2004; 13: 340–345.

333. Shen Y, Constantino T, Matsuo F, Lorie B. Efficacy of vagal nerve stimulation in treating patients with medically refractory primary generalized epilepsy (abstract). Epilepsia 2004; 45(suppl.7): 149.

334. Farrag AB, Pestana EM, Kotagal P. Vagus nerve stimulation for refractory absence seizures (abstract). Epilepsia 2002; 43(suppl. 7): 79–80.

335. Parain D, Blondeau C, Peudenier S, Delangre T. Vagus nerve stimulation in refractory childhood absence epilepsy (abstract). Epilepsia 2003; 44(suppl. 9): 326.

336. Tecoma ES, Iragui VJ. Vagus nerve stimulation use and effect in epilepsy: What have we learned? Epilepsy Behav 2006;8:127-36.

337. Lhatoo SD, Sander JW. The epidemiology of epilepsy and learning disability. Epilepsia. 2001;42 Suppl 1:6-20. doi:10.1046/j.1528-1157.2001.00502.x

338. Téllez-Zenteno, J. F., Hernández Ronquillo, L., Moien-Afshari, F., 2010. Surgical outcomes in lesional and non-lesional epilepsy: A systematic review and meta-analysis. Epilepsy Res. 89, 310-318. https://doi.org/10.1016/j.eplepsyres.2010.02.007.

339. McGrother CW, Bhaumik S, Thorp CF et al. Epilepsy in adults with intellectual disabilities: prevalence, associations and service implications. Seizure. 2006 Sep; 15(6): 376-86.

340. Mariani E, Ferini-Strambi L, Sala M et al. Epilepsy in institutionalized patients with encephalopathy: clinical aspects and nosological considerations. Am J Ment Retard. 1993; 98 Suppl: 27-33.

341. McDermott S, Moran R, Platt T et al. Prevalence of epilepsy in adults with mental retardation and related disabilities in primary care. Am. J Ment Retard. 2005 Jan; 110(1): 48-56.

342. Bowley C, Kerr M. Epilepsy and intellectual disability. J Intellect Disabil Res. 2000 Oct; 44 (5): 529-43.

343. Airaksinen EM, Matilainen R, Mononen T, et al. A population-based study on epilepsy in mentally retarded children. Epilepsia. 2000;41(9):1214-1220. doi:10.1111/j.1528-1157.2000.tb00328.x

344. Endermann M. Predictors of health-related and global quality of life among young adults with difficult-to-treat epilepsy and mild intellectual disability. Epilepsy Behav. 2013;26(2):188-195. doi:10.1016/j.yebeh.2012.12.002

345. Elliott RE, Morsi A, Geller EB, Carlson CC, Devinsky O, Doyle WK. Impact of failed intracranial epilepsy surgery on the effectiveness of subsequent vagus nerve stimulation. Neurosurgery. 2011;69(6):1210-1217. doi:10.1227/NEU.0b013e3182230ae3

346. Benedetti-Isaac JC, Torres-Zambrano M, Fandiño-Franky J, Polo-Verbel LM, BolañoEsquirol M, Villa-Delgado R, Guerra-Olivares R, Alcalá-Cerra G: Vagus nerve stimulation therapy in patients with drug-resistant epilepsy and previous corpus callosotomy (in Spanish). Neurocirugia (Astur) 2012;23:244–249.

347. Schmidt D, Bourgeois B: A risk-benefit assessment of therapies for Lennox-Gastaut syndrome. Drug Saf 2000;22:467–477.

348. Helmers SL, Wheless JW, Fros M, Gates J, Levisohn P, Tardo C, Conry JA, Yalnizoglu D, Madsen JR: Vagus nerve stimulation therapy in pediatric patients with refractory epilepsy: retrospective study. J Child Neurol 2001;16: 843–848.

349. Vale FL, Ahmadian A, Youssef AS, Tatum WO, Benbadis SR: Long-term outcome of vagus nerve stimulation therapy after failed epilepsy surgery. Seizure 2011;20:244–248.

350. Guillamón E, Miró J, Gutiérrez A, Conde R, Falip M, Jaraba S, Plans G, Garcés M, Villanueva V. Combination of corpus callosotomy and vagus nerve stimulation in

the treatment of refractory epilepsy. Eur Neurol. 2014;71(1-2):65-74. doi: 10.1159/000353979. Epub 2013 Dec 5.

351. Camp C, Smithson WH, Bunker M, Burke T, Hughes D. Impact of vagus nerve stimulation on secondary care burden in children and adults with epilepsy: Review of routinely collected hospital data in England. Epilepsy Behav. 2015 Nov;52(Pt A):68-73. doi: 10.1016/j.yebeh.2015.08.026. Epub 2015 Sep 25.

352. Klinkenberg S, Majoie HJ, van der Heijden MM, et al. Vagus nerve stimulation has a positive effect on mood in patients with refractory epilepsy. Clin Neurol Neurosurg 2012;114:336–340.

353. Aaronson ST, Sears P, Ruvuna F, et al. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am J Psychiatry 2017;174:640–648.

354. Hoppe C, Helmstaedter C, Scherrmann J, et al. Self-reported mood changes following 6 months of vagus nerve stimulation in epilepsy patients. Epilepsy Behav 2001;2:335–342.

355. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia 2014;55:893–900.

356. Elger G, Hoppe C, Falkai P, et al. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res 2000;42:203–210.

357. Harden CL, Pulver MC, Ravdin LD, et al. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav 2000;1:93–99.

358. Hilderink J, Tjepkema-Cloostermans MC, Geertsema A, Glastra-Zwiers J, de Vos CC. Predicting success of vagus nerve stimulation (VNS) from EEG symmetry. Seizure. 2017 May;48:69-73. doi: 10.1016/j.seizure.2017.03.020. Epub 2017 Apr 4.

359. Mercadé Cerdá JM, Sancho Rieger J, Mauri Llerda JA, López González FJ, Salas Puig X. Guías diagnósticas y terapéuticas de al Sociedad Española de Neurología

2012. 1. Guía oficial de práctica clínica en epilepsia. Ediciones SEN 2012. ISBN: 978-84-7989-750-5.

360. Blount JP, Tubbs RS, Kankirawatana P, et al. Vagus nerve stimulation in children less than 5 years old. Childs Nerv Syst. 2006;22(9):1167-1169. doi:10.1007/s00381-006-0104-9

361. Vitale SA, Andriola MA, Gabis L et al. Vagus nerve stimulation in the toddler age group. Epilepsia 2001; 42(suppl 7).

362. Labar D. Vagus nerve stimulation for 1 year in 269 patients on unchanged antiepileptic drugs. Seizure. 2004;13(6):392-398. doi:10.1016/j.seizure.2003.09.009

363. Murphy JV. Left vagal nerve stimulation in children with medically refractory epilepsy. The Pediatric VNS Study Group. J Pediatr. 1999;134(5):563-566. doi:10.1016/s0022-3476(99)70241-6

364. Zamponi N, Rychlicki F, Corpaci L, Cesaroni E, Trignani R. Vagus nerve stimulation (VNS) is effective in treating catastrophic 1 epilepsy in very young children. Neurosurg Rev. 2008;31(3):291-297. doi:10.1007/s10143-008-0134-8

365. Elliott RE, Rodgers SD, Bassani L, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. J Neurosurg Pediatr. 2011;7(5):491-500. doi:10.3171/2011.2.PEDS10505

366. Levy ML, Levy KM, Hoff D, et al. Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. J Neurosurg Pediatr. 2010;5(6):595-602. doi:10.3171/2010.3.PEDS09153

367. Bodin E, Le Moing AG, Bourel-Ponchel E, et al. Vagus nerve stimulation in the treatment of drug-resistant epilepsy in 29 children. European Journal of Paediatric Neurology : EJPN : Official Journal of the European Paediatric Neurology Society. 2016 May;20(3):346-351. DOI: 10.1016/j.ejpn.2016.01.011

368. Englot DJ, Hassnain KH, Rolston JD, Harward SC, Sinha SR, Haglund MM. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav. 2017;66:4-9. doi:10.1016/j.yebeh.2016.10.005

369. Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. Epilepsia. 2006;47(1):115-122. doi:10.1111/j.1528-1167.2006.00377.x

370. Cersósimo RO, Bartuluchi M, Fortini S, Soraru A, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. Epileptic Disord. 2011;13(4):382-388. doi:10.1684/epd.2011.0479

371. Majoie HJ, Berfelo MW, Aldenkamp AP, Evers SM, Kessels AG, Renier WO. Vagus nerve stimulation in children with therapy-resistant epilepsy diagnosed as Lennox-Gastaut syndrome: clinical results, neuropsychological effects, and cost-effectiveness. J Clin Neurophysiol. 2001;18(5):419-428. doi:10.1097/00004691-200109000-00006

372. Kostov K, Kostov H, Taubøll E. Long-term vagus nerve stimulation in the treatment of Lennox-Gastaut syndrome. Epilepsy Behav. 2009;16(2):321-324. doi:10.1016/j.yebeh.2009.07.038

373. Yamamoto T. Vagus nerve stimulation in the treatment of intractable epilepsy—knacks in programming and results of long-term follow-up. Neurological Medicine 2014; 80: 223–230.

374. Suller Marti A, Mirsattari SM, MacDougall K, et al. Vagus nerve stimulation in patients with therapy-resistant generalized epilepsy. Epilepsy Behav. 2020;111:107253. doi:10.1016/j.yebeh.2020.107253

375. Kalayjian L, Heck CN.Vagal nerve stimulation and pregnancy. Epilepsia 2005; 46 (suppl 9): 1209. Abstract.

376. Husain MM, Stegman D, Trevino K. Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: a case report. Ann Gen Psychiatry. 2005;4:16. Published 2005 Sep 16. doi:10.1186/1744-859X-4-16

377. Suller Marti A, Mirsattari SM, Steven DA, et al. Experience on the use of Vagus Nerve Stimulation during pregnancy. Epilepsy Res. 2019;156:106186. doi:10.1016/j.eplepsyres.2019.106186

378. The North American Pregnancy and Epilepsy Registry, 2005. A North American Registry for Epilepsy and Pregnancy, a unique public/ private partnership of health surveillance. Epilepsia. 39: 793-798.

379. Kelly S, Sprague A, Fell DB, et al., 2013. Examining Caesarean Section Rates in Canada Using the Robson Classification System. J Obstet Gynaecol Can. 35: 206–214. https:// doi: 10.1016/S1701-2163(15)30992-0.

380. Komisaruk BR, Whipple B, Crawford A, et al., 2004. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the vagus nerves. Brain Res. 1024: 77-88.

381. Judkins A, Johnson RL, Murray ST, Yellon SM, Wilson CG. Vagus nerve stimulation in pregnant rats and effects on inflammatory markers in the brainstem of neonates. Pediatr Res. 2018;83(2):514-519. doi:10.1038/pr.2017.265

382. Danielsson I, Lister L. A pilot study of the teratogenicity of vagus nerve stimulation in a rabbit model. Brain Stimul. 2009;2(1):41-49. doi:10.1016/j.brs.2008.06.008

383. O'Keane V, Dinan TG, Scott L, Corcoran C. Changes in hypothalamic-pituitary-adrenal axis measures after vagus nerve stimulation therapy in chronic depression. Biol Psychiatry. 2005;58(12):963-968. doi:10.1016/j.biopsych.2005.04.049

384. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J. 2013;34(29):2281-2329. doi:10.1093/eurheartj/eht150

385. Scelzo E, Mehrkens JH, Bötzel K, et al. Deep Brain Stimulation during Pregnancy and Delivery: Experience from a Series of "DBS Babies". Front Neurol. 2015;6:191. Published 2015 Sep 1. doi:10.3389/fneur.2015.00191

8- SUMMARY IN SPANISH

1. Introducción

La epilepsia es una enfermedad neurológica muy frecuente que afecta 1% de la población. La epilepsia se caracteriza por la predisposición de sufrir crisis epilépticas recurrentes así como las consecuencias neurobiológicas, psicosociales, cognitivas y sociales. Además, los pacientes con epilepsia tienen un riesgo mayor de mortalidad prematura, incluyendo las muerte súbita asociada al paciente con epilepsia (sudden unexpected death in epilepsy, SUDEP). Las crisis epilépticas son la expresión de una actividad neuronal asincrónica, anormal y excesiva. La epilepsia puede estar causada por muchas etiologías distintas, lo que hacen que la epilepsia sea una enfermedad muy heterogénea que puede afectar a cualquier edad, desde recién nacidos hasta los más ancianos. Otra importante peculiaridad de la epilepsia son los distinto tipos de crisis que puede ser asociada. La Liga Internacional de la Epilepsia (ILAE) creó una clasificación de las distintas tipos de crisis epilépticas, incluyendo focales, generalizadas, de inicio incierto, con las subvariantes de cada una de ellas. El hecho de clasificar las crisis en estos tres subgrupos permite dividir las epilepsia en focales, generalizadas y las que son de dudoso tipo (normalmente pendientes de ser evaluadas). La epilepsia requiere de pruebas complementarias fundamentales para poder entender esta entidad y clasificar adecuadamente el tipo de epilepsia. Las más importantes son electroencefalograma (EEG) y resonancia magnética nuclear (RMN).

Desafortunadamente no existe un tratamiento curativo para la epilepsia. El tratamiento de la epilepsia se base en la prevención de sufrir futuras crisis epilépticas. Los fármacos utilizados se llaman fármacos anticrisis, previamente llamados fármacos antiepilépticos. Existe una larga lista de fármacos anticrisis pero al menos un tercio de los pacientes seguirán teniendo crisis a pesar de probar múltiples fármacos y diferentes combinaciones de fármacos. Aquellos pacientes que prueben dos o más fármacos anticrisis y siguen teniendo crisis epilépticas, se consideran que sufren epilepsia fármaco-resistente. En estos casos es cuando se les debe considerar candidatos para

cirugía de la epilepsia. Para determinar si los pacientes son candidatos a cirugía de la epilepsia, deben someterse a una investigación muy detallada. Esta investigación pre-quirúrgica incluye pruebas de neuroimagen, capturar crisis epilépticas con monitorización electroencefalográfica, test neuropsicológicos y otras pruebas de neuroimagen funcional. Sin embargo, un gran porcentaje de los pacientes que se someten a esa investigación no serán candidatos a cirugía. Frecuentemente el foco es extenso, bilateral o tienen múltiples focos, en otros casos el foco epileptogénico se superpone con un área elocuente. En estos casos es cuando otras alternativas terapéuticas deben ser propuestas, incluyendo neuromodulación, dieta cetogénica, cirugías paliativas o tratamientos con fármacos experimentales.

La neuromodualación es un tipo de tratamiento que se caracteriza por la aplicación de corrientes eléctricas a una parte del sistema nervioso, central o periférico, con el fin de controlara las crisis epilépticas. La neuromodulación es un tratamiento menos efectivo que la cirugía, que pretende reducir el número de crisis así como su severidad. Aunque la neuromodualación fue empleada ya por los romanos para tratar distintas dolencias, incluyendo cefaleas y la epilepsia, no fue has mediados del siglo pasado cuando evolucionó significativamente. Existen varios dispositivos de neuromodulación, pero los más empleados para tratar la epilepsia son el estimulador del nervio vago (vagus nerve stimulator, VNS), el estimulador profundo cerebral bilateral del tálamo (deep brain stimulator thalamus, DBS) y el neuroestimulador con respuesta (responsive neurostimulation, RNS). El dispositivo más comúnmente utilizado del que tenemos más experiencia a nivel mundial es el VNS.

El VNS fue aprobado para el tratamiento de la epilepsia fármaco resistente por la Unión Europea en 1994. El VNS se implanta en el nervio vago izquierdo a nivel del cuello y el generador se implanta en la parte alta de la zona intercostal (cerca de la zona clavicular). A pesar de todos los años de uso de este dispositivo, el mecanismo de acción sigue sin saberse con seguridad. Del mismo modo, se desconoce los pacientes que

tendrán más beneficio de él tras su implantación. El estudio más importante donde se revisaba su efecto fue publicado por Englot et al. En este estudio se mostró que la tasa de estar libre de crisis, se alcanzó en el 8% de los implantados. La tasa de respondedores (reducción de crisis del 50% o más) fue 49% en los primeros meses y 63% a los 24-48 meses de seguimiento. Respecto a los factores de buen pronóstico se mencionó edad de inicio temprana, crisis generalizadas y epilepsia no lesionales. Sin embargo no existe un criterio de selección de los pacientes que van a obtener más beneficio tras su implantación.

2. Objetivos

El objetivo principal de este estudio es definir la reducción de crisis y el impacto sobre las crisis epilépticas en pacientes implantados con el VNS.

Los objetivos secundarios son:

- Describir las características de los pacientes incluidos en la muestra, desde tipo de epilepsias, los hallazgos en sus EEG y RMN, y tipo de crisis epilépticas.
- Definir los posibles factores predictores de buen pronóstico en los pacientes respondedores al VNS.
- Analizar los factores relacionados con VNS en los pacientes implantados con VNS con mejor respuesta.
- Definir otros posibles beneficios asociados con la terapia del VNS.
- Evaluar la eficacia del VNS en una subplación con epilepsia generalizada refractaria, población pediátrica.
- Describir la seguridad obtenida con el dispositivo, incluyendo complicaciones, efectos adversos y tolerabilidad durante el embarazo.

3. Metodología

3.1. Población

La población incluida en este estudio son pacientes con epilepsia fármaco resistente, según la definición de la ILAE, que fueron implantados con VNS en nuestra institución, London Health Science Centre- Western University, y que fueron seguidos en nuestro centro. El periodo de inclusión fue desde 1997 hasta julio del 2018.

3.2. Diseño del Estudio

Este estudio es un estudio retrospectivo, observacional y descriptivo, que incluyó pacientes con epilepsia fármaco resistente implantados con el VNS, tanto de edad pediátrica como de edad adulta.
Este estudio fue aprobado por el comité de ética de nuestro centro y ha seguido el código ético estipulado por la Declaración de Helsinki.

3.3. Criterios de Inclusión y exclusión

Los criterios de inclusión fueron:

- Pacientes con epilepsia fármaco resistente.
- VNS fue implantado con el fin de controlar las crisis epilépticas.
- Los pacientes incluidos no eran candidatos a epilepsia resectiva o habían fallado previamente a una cirugía para controlar su epilepsia.
- No eran candidatos para otro tratamiento para el control de la frecuencia de sus crisis.
- Los pacientes fueron implantados con un VNS en el London Health Science Centre-Western University, London, Ontario.

- La frecuencia de las crisis tenía un impacto negativo en la calidad de vida de los pacientes.
- Los pacientes fueron seguidos por un mínimo de tres meses tras la implantación del VNS en nuestro centro.

Los criterios de exclusión fueron:

- Los pacientes fueron implantados con un VNS fuera de London Health Science Centre-Western University, London, Ontario.
- Los pacientes fueron implantados con VNS por una motivo médico distinto del control de la epilepsia.
- Los pacientes no fueron seguidos por un mínimo de tres meses tras la implantación del VNS en nuestro centro.

3.4 Análisis estadístico

Los resultados postimplantación se calculó en base a la frecuencia de crisis por mes, en el último seguimiento antes del análisis. La frecuencia de crisis después de la implantación fue la media del total de crisis (todos los tipos de crisis) por mes en el último seguimiento. El otro análisis fue el ratio de reducción de la frecuencia de crisis, la cual fue calculada como el resultado de la frecuencia de crisis por mes antes de la implantación, menos la frecuencia de crisis por mes tras la implantación del VNS, dividido por la frecuencia de crisis por mes antes de la implantación, expresado en porcentaje. Se consideró respondedores cuando la reducción de la frecuencia de crisis tras la implantación fue del 50% o más. Los resultados negativos significan que los pacientes tuvieron una reducción de crisis respecto a la frecuencia der crisis inicial.

Se realizaron tres subanálisis:

- Pacientes con epilepsia generalizada fármaco resistente.

Para este subanalálisis se incluyeron dos poblaciones. Los pacientes con el diagnóstico de síndrome de Lennox-Gastaut (SLG) y los pacientes con epilepsia genética generalizada (EGG). Los SLG seleccionados debían de cumplir los criterios diagnósticos de SLG (diferentes tipos de crisis epilépticas, retraso intelectual y punta-onda generalizada lenta en el EEG). Y los pacientes con EGG también sufrían los síndromes clásicos (epilepsia de ausencia infantil, epilepsia de ausencias de la adolescencia, epilepsia mioclónica juvenil, crisis generalizadas solamente) además de los alteraciones electrográficas típicas (punta-onda generalizada a más de 2.5 Hz con intelecto normal.

- Pacientes de edad pediátrica implantados con VNS.

- Pacientes mujeres implantadas con VNS y que posteriormente se quedaron embarazadas.

El análisis estadístico se llevó a cabo usando SAS versión 9.4 y el límite de significación utilizado fue <0.05. Las variables continuas se expresaron como mediana y rango intercuartil (IQR) y las variables categóricas como frecuencias absolutas y porcentajes.

En el análisis de variables continuas, se usó el test Wilcoxon Signed Rang o t-test, dependiendo de si las variables seguían distribución normal o no. Se usó el test de Kolmogorov-Smirnov para verificar la distribución normal de las variables. Respecto a las variables categóricas, se aplicó el test de Fisher's Exact test. En el análisis de eficacia del VNS a largo plazo, se usó el ordinary least squares (OLS) regresión linear.
En los otros subanálisis se completó usando el SPSS versión 22.0. En el subanálisis de los pacientes pediátricos, las variables categóricas se analizaron usando el test de Chi-cuadrado y cuando el número fue inferior a cinco, el Fisher's exact test. En el caso de variables continuas, se empleó el test de T-Student cuando seguían distribución normal y U-Mann-Whitney test cuando no seguían distribución normal. En el caso de las epilepsias generalizadas refractarias, se utilizó para las variables continuas el Wilcoxon

Rank-Sum Test o Mann-Whitney-Wilcoxon test. Para las variables categóricas se empleó el Fisher's Exact Test.

4. Resultados

4.1 VNS En Epilepsia

Un total de 114 pacientes fueron implantados en nuestro centro con historia de epilepsia fármaco resistente. 56,1% (n=64) fueron hombres y 43,9% (n=50) fueron mujeres. Un total de 72,8% (n=83) eran diestros. La mediana de la edad de la población incluida en este estudio era 35,4 años (IQR= 28,1-44,0) y la edad de implantación fue 26,5 años (IQR=20-34).

El número total de s fármacos anticrisis previos fuer 5 (IQR=3-6). El fármaco más frecuentemente administrado anticrisis era el ácido valproico y la fenitoína, en un 52,6% de los casos (n=60), seguido del clobazam en el 44,7% (n=51), y la carbamacepina y el topiramato en el 42,1% (n=48). En el momento de la implantación la mediana de fármacos anticrisis utilizados era 3 (IQR=2-3). El más utilizado en ese momento era la lamotrigina en el 36% (n=41) de los casos con una media de 300 mg por día (IQR=200-400 mg/día), seguido por el topiramato en el 33,3% (n=38) con 225 mg por día (IQR=200-381,3), la fenitoína en 28,9% (n=33) con 300 mg por día (IQR=200-474) y finalmente el levetiracetam en el 26,5% (n=30) con 2000 mg por día (IQR= 1000-3000 por día).

El 38,7% (n=43) tenía historia de estatus epiléptico. El 91,9% (n=102) habían sido hospitalizados en algún momento para el manejo de sus crisis y el 94,7% (n=108) fueron hospitalizados en la unidad de monitorización de epilepsia con fines diagnósticos o para la optimización de su tratamiento, con una mediana de días de hospitalización de 7 días

(IQR=5-11). Del grupo de pacientes con epilepsia refractaria, un 29,8% (n=34) fueron sometidos a cirugía de la epilepsia en algún momento para la optimización del tratamiento previo a la implantación del VNS. El tipo más frecuente de cirugía a la que fueron sometidos fue callosotomía en el 55% (n=21), seguida de lobectomía temporal derecha en el 13% de los casos (n=5) y lobectomía temporal izquierda en el 11% (n=4).

El tipo de epilepsia más común fue el tipo generalizada en un 27% (n=31) y la etiología más frecuente fue la de causa desconocida en un 25% (n=38) de los casos. La mediana de tipo de crisis fue 3 (IQR=2.75-4), siendo las crisis focales con pérdida de conciencia las más frecuentes. La mediana de número de crisis por mes fue 25 (IQR=8,7-60 por mes). Un 38,6% (n=44) tenían algún tipo de retraso intelectual.

Los resultados del VNS se midieron tras la implantación en el último seguimiento antes del cierre del estudio. La mediana de meses tras la implantación fue 46 (IQR=21,5-79,3), con un máximo de 268 meses, que representa unos 22,3 años. La libertad de crisis se obtuvo en 21,1% (n=24), pero con una duración muy corta de sólo 3 meses (IQR=1-7,8 meses). Cuando se evaluó únicamente las crisis generalizadas, el 14,1% (n=16) estuvieron libres de crisis por 9 meses (IQR=6,5-11,5). Lo que representa que el 29% de los pacientes con crisis generalizadas estuvieron libres de crisis por varios meses.

La mediana de ratio de reducción de crisis fue de -67,75% (IQR= (-92,55%)- (-37,17%). La reducción de crisis se clasificó en grupos: 50% o más reducción, menos de 50%, y no respuesta. Se encontró que el 55,6% (n=41= tuvieron un 50% o más en reducción de crisis, un 21,2% (n=24) menos del 50%, y 23% (n=26%) no tuvieron ningún tipo de respuesta positiva. En el grupo de 50% o más de reducción, el 17,5% (n=11) sufrió una reducción entre el 50-60%, el 17.5% (n=11) entre un 60% y menos del 75%, y el 34,9% (n=22) un 75% o más de reducción. Un modelo de regresión fue aplicado y no se vio una mejoría a lo largo del tiempo, con una p=0,26. El VNS mostró que fue más

efectivo en la reducción de crisis generalizadas tónico-clónicas (p=0,0037), focales con progresión a bilateral tónico-clónica (p=0,0007) y focales con pérdida de conciencia (p=0,00013). En el lado opuesto, se observó que en 11,4% (n=13) de los casos el VNS se apagó por falta de eficacia y en 6,1% se explantó por falta de resultados. En el análisis multivalente no se vio un subgroupo que resultara más efectivo.

Respecto otros posibles beneficios del VNS, no se vio diferencias significativas en el número de fármacos anticrisis antes y después de la implantación, así como de las dosis utilizadas de medicaciones anticrisis antes y después del VNS. Sin embargo, el número total de hospitalizaciones bajó del 89.5% (n=102) al 45.6% (n=52) tras la implantación, cuya reducción fue estadísticamente significativa.

La duración de la batería fue 43,5 meses de mediana (IQR=20-73,24). Respecto a la seguridad del dispositivo se clasificaron los efectos adversos relacionados con la implantación y los relacionados con la estimulación. Un total de 5,3% (n=6) tuvieron algún tipo de complicación relacionada con la implantación, ninguna mortal, y siendo de las más severo la infección en el área de la implantación en dos casos. Por otro lado, los efectos relacionados con la estimulación fueron más frecuentemente reportados, en un 63,16% (n=72). El más comúnmente detectado fue ronquera en un 26,4% (n=19), cambios en la voz en 19,4% (n=14) y dolor de garganta en 16,7% (n=12).

4.2 VNS En La Edad Pediátrica

En este subanálisis se incluyeron 22 niños implantados con el VNS, los cuales tenían 17 o menos años en el momento de la cirugía. La mediana de edad era 15,8 años (IQR=6-24,3) y 13 a la edad de implantación (IQR=9.5-15). El 72,7% (n=16) eran chicos y el 40,9% (n=9) eran diestros. La edad de inicio fue a los 3 años de mediana (IQR= 1.6-5), con una duración de epilepsia de 9 años al momento de la implantación (IQR=6.2-13.2). Un total

de 86,4% (n=19) tenían algún tipo de retraso intelectual. Además, todos los pacientes de este subgrupo habían sido hospitalizados en algún momento para el manejo de su epilepsia y el 72,7% (n=16) tenían historia de estatus epiléptico. Un 95,5% (n=21) habían sido investigados en unidad de monitorización de epilepsia. La etiología más frecuente de este subgrupo era SLG en un 45,5% (n=10). El tipo de crisis epiléptica más frecuente era crisis generalizada tónico-clónica en un 68,2% (n=15) y crisis mioclónicas en un 45,5% (n=10). El número total de crisis por mes era de 108 (IQR= 16-216,5). Estos pacientes habían probado, de mediana, un total de 3,5 fármacos (IQR= 2-6) y en el momento de la implantación del VNS estaban usando dos fármacos anticrisis (IQR=2-3). El más utilizado era el levetiracetam en 45,5% (n=10), seguido de la lamotrigina en 31,8% (n=7) y el topiramato en un 27,3% (n=6).

Los pacientes pediátricos fueron seguidos por unos 35,5 meses post-implantación (IQR=6,75-151). La reducción de crisis del 50% o más fue observado en un 50% (n=11) de los implantados. En un 9,1% (n=2) las crisis se redujeron entre el 50-60% y en el 40,9% (n=9) en una reducción superior o igual al 75%. Los padres y/o los pacientes describieron una reducción en la intensidad de las crisis en el 31,8% (n=7). La mediana en la reducción el número de crisis fue del -75% (IQR= (-95,3%) – (44,3%)). Las crisis epilépticas con una reducción significativa comparando antes y después del VNS, fueron las crisis focales con pérdida de conciencia (p=0,022), las crisis focales con progresión a bilateral tónico-clónicas (p=0,022) y las generalizadas tónico-clónicas (p=0,022).

Las hospitalizaciones ser redujeron tras el uso del VNS, y solamente el 36,4% (n=8) las necesitó post implantación. Sin embargo, esta reducción no fue estadísticamente significativa. No se detectó cambios significativos en el número de fármacos tras el VNS.

En relación a la seguridad del dispositivo, un paciente refirió dolor y rigidez de cuello tras la implantación, que mejoró con el tiempo. Respecto los efectos adversos de la estimulación, 54,5% (n=3) describieron, los pacientes o los padres de los pacientes,

efectos adversos, y el más frecuente era la tos, en un 25% (n=3) de todos los casos. La duración de la batería fue de 35,5 meses (IQR=7-63).

4.3. VNS En Epilepsia Generalizada

46 pacientes fueron incluidos en el subanálisis de epilepsia generalizada. La mediana de edad de los pacientes era 35,8 (IQR= 24,8-43,4) años y el 50% (n=23) eran mujeres. 24 años (IQR=17,8-31) fue la mediana de edad de implantación del VNS. El 39,2% (n=11) tenían historia de estatus epiléptico y cinco eran los fármacos anticrisis probados antes de la implantación (IQR=2,8-7). En el momento de la implantación estaban tomando tres fármacos (IQR=2-3) y el fármaco más frecuentemente usado era el ácido valproico (41,3% , n=19), seguido de la fenitoína (37%, n=17) y el levetiracetam (30%, n=14). La muestra se dividió en dos subgroupos, los que tenía SLG (63%, n=23) y los que sufrían EGG (37%, n=17).

En este subanalisis se observó una mediana de seguimiento de 63 meses (IQR=31-112,8). El 41,4% (n=12) del grupo de SLG fueron respondedores y el 64,7% (n=11) de los EGG, en el último seguimiento (p=0,048). El ratio de reducción de crisis fue de un 59% (IQR= 92,5-38,8) en el SLG grupo y del 86% (IQR= 97,9-44,9) en el grupo EGG, en el último seguimiento, con una diferencia no estadísticamente significativa. Del grupo del EGG, un 35,3% (n=6) estuvo libre de crisis con una mediana de duración de diez meses (IQR=6-21,5). En referencia a la reducción del tipo de crisis, en el grupo de SLG se vio que la reducción de crisis generalizadas tónico-clónicas pasó de 14,3 por mes (IQR=14,5-98,3) a 10 por mes (IQR=7,5-15) (p=0,46). En el caso del grupo de EGG, las crisis generalizadas tónico clónicas pasaron de 3,4 por mes (IQR=1,5-6) a 0,3 (IQR=0,2-2,3). La ratio de respuesta no se incrementó a lo largo del tiempo cuando se usó un modelos de regresión linear (p=0,27).

De la misma manera que en el grupo general, se vio una reducción en las hospitalizaciones relacionadas con las crisis epilépticas incontroladas, pasando del 92,3% (n=42) antes del VNS, al 43,5% (n=20) tras el VNS. En ambos grupos la reducción fue significativa (SLG p<0,001, y en EGG p=0,003). El número de fármacos anticrisis no cambió tras la implantación del VNS.

Respecto efectos del VNS, un paciente sufrió infección en el área de implantación y dos pacientes desarrollaron dolor en el área tras implantación. Efectos adversos asociados con la estimulación fueron reportados por el 63% (n=29). Los efectos más frecuentes eran tos en el 37,9% (n=11), cambios en la voz en el 20,7% (n=6) y dolor de garganta en el 13,8% (n=4). No hubo diferencias entre ambos grupos. La duración media de la batería fue 60 meses (IQR=37,5-113) en el grupo de SLG y 43 meses para el EGG (IQR=14-59,9).

4.4. VNS Durante el Embarazo

Un total de cuatro pacientes se quedaron embarazadas después de haber sido implantadas con el VNS, y tuvieron siete bebés entre todas. Una de las mujeres tubo tres bebés y otra mujer tuvo dos bebés estando implantadas con el VNS.

El primer caso era un mujer de 24 años, diestra, con epilepsia genética generalizada fármaco resistente que tenías ausencias diarias y crisis generalizadas tónico-clónicas infrecuentemente. Esta paciente había probado tres fármacos anticrisis. Su RMN era normal y tenía antecedentes familiares de epilepsia. El primer embarazo ocurrió más de un año después de la implantación de su VNS. No hubo cambios en los parámetros del VNS durante el embarazo. El bebé nació a las 38 semanas vía cesárea debido a un fallo de progresión en el momento del parto. El bebé estaba sano. Su segundo embarazo ocurrió a la edad de 27 años, sin cambios en su medicación o en los parámetros del VNS.

El segundo bebé nació con una cesárea electiva a las 38 semanas. No hubo complicaciones en el parto y ambos bebés, en último control, estaban sanos.

El segundo caso era una mujer de 31 años, diestra, con heterotopias nodulares periventriculares bilaterales y con epilepsia bitemporal. Ella fue tratada con cuatro fármacos anticrisis y en el momento del embarazo estaba tomando dos. Durante el embarazo no se cambiaron los fármacos o los parámetros de estimulación. El bebé nació a las 40 semanas con un parto vaginal sin complicaciones obstétricas o perinatales.

El tercer caso era el de una joven de 18 años, diestra, con historia de epilepsia genética generalizada. Probó seis fármacos anticrisis previamente y dos fármacos y el VNS durante su embarazo. En relación al tipo de crisis, ella tenía ausencias diarias y dos crisis generalizadas tónico-clónicas por mes. En su primer embarazo, nueve meses tras la implantación del VNS, requirió una cesárea urgente por pre-eclampsia a las 37 de gestación. El bebé nació sin complicaciones. Su segundo embarazo ocurrió tres años después de la implantación del VNS, y el bebé nació por vía vaginal a las 39 semanas. En el tercer embarazo la paciente tenía 22 años, cuatro años tras iniciar la terapia de VNS. El bebé nació a las 38 semanas con un parto vaginal sin complicaciones para el recién nacido o para la madre.

El último paciente incluido fue una mujer de 22 años, que se quedó embarazada más de tres años después de la implantación del VNS. Ella sufría epilepsia generalizada refractaria y había probado ocho fármacos anticrisis. Como comorbilidad destacaba retraso intelectual leve. Su epilepsia se caracterizaba por crisis generalizadas tónico-clónicas cada dos o tres meses. En su caso, el VNS se apagó a las 26 semanas de gestación. Pero debido al aumento de crisis, el VNS se encendió de nuevo un mes más tarde. Ella requirió a cesárea debido a la ruptura espontánea del saco amniótico. En el último control se mencionó que el bebé presentaba rasgos dismórficos y un posible

murmuro cardiaco. Lamentablemente se perdió su seguimiento y no se pudo obtener más información del bebé.

5. Conclusiones

5.1. VNS en Epilepsia

- Los resultados des este estudio apoyan la eficacia del VNS en pacientes con epilepsia fármaco resistente, con una reducción del número de crisis del 50% o más, en un total del 56% de los pacientes implantados con el VNS.
- Hay una probabilidad baja de quedar libre de crisis tras la implantación del VNS, sin embargo en casi un tercio de los pacientes con crisis generalizadas tónico-clónicas estarán libres de este tipo de crisis por casi un año.
- Con este estudio hemos encontrado factores de buena respuesta tras la implantación del VNS: pacientes con historia de crisis generalizadas tónico-clónicas, crisis focales que progresan a bilatearal tónico-clónicas, crisis focales con pérdida de conciencia, hallazgos de multifocalidad en el EEG así como de generalizada, historia de epilepsia genética generalizada, mayor tiempo de tiempo 'On' de la estimulación, y los modelos 102, 103, 105 y 106.
- El VNS mostró una reducción significativa de hospitalizaciones relacionadas con la falta de control de la epilepsia, tras la implantación del VNS.
- Hay menos de un 2% de complicación severa tras la implantación, y un 63% der riesgo de efectos adversos relacionados con la estimulación, siendo la tos y ronquera los más frecuentes. Estos efectos adversos mejoran con el tiempo en la mayoría de casos.

5.2. VNS en la Edad Pediátrica

- En pacientes menores de 15 años, el VNS mostró una reducción significativa de crisis en pacientes implantados.
- No se vio diferencias en la respuesta en pacientes implantados con edades mayores de 6 años comparados con los menores de 6 años.
- No se vio complicaciones severas en este grupo de edad, y los efectos adversos leves mejoraban con el tiempo.

5.3. VNS en Epilepsia Generalizada

- Pacientes con epilepsia generalizada que no responden a fármacos anticrisis deben ser considerados para la implantación con el VNS. Este estudio muestras la reducción significativa de crisis que experimentan este grupo de pacientes con epilepsia generalizada fármaco resistente.
- El ratio de respondedores fue particularmente alto en el grupo de pacientes con epilepsia genética generalizada, siendo un 64,7% respondedores en el grupo de EGG, y el 41,7% en el grupo de SLG.
- El VNS se vio más efectivo en la reducción de crisis generalizadas tónico-clónicas en ambos grupos.
- La mejoría en el control de las crisis tiene un efecto en la calidad de vida así como la reducción de los costes de salud asociados a la reducción de hospitalizaciones debido a la epilepsia mal controlada.

5.4. VNS Durante el Embarazo.

- Aunque la muestra analizada es pequeña, los resultados obtenidos en este análisis del VNS durante el embarazo sugieren que el VNS está bien tolerado durante el embarazo, puede ayudar a reducir politerapia y parece ser seguro para el feto.
- Las complicaciones obstétricas parecen más frecuentes, pero el VNS parece que tiene un bajo riesgo de malformaciones congénitas.
- Estudios prospectivos o muestras de tamaños mayores son necesarias para determinar las seguridad y el potencial teratogénico del VNS.