UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA"

BUCHAREST

DOCTORAL SCHOOL

MEDICINE FIELD

ABSTRACT OF THE DOCTORAL THESIS

The importance of vagus nerve stimulation in the therapeutic management of drug-resistant epilepsy

Scientific coordinator:

Acad. Prof. Univ. Dr. Alexandru Vlad Ciurea

Phd student:

Dr. Urian Flavius Iuliu

BUCHAREST

-2025-

Contents

INTRODUCTION

The research explores innovative ways to optimize vagus nerve stimulation (VNS) therapy in drug-resistant epilepsy, with a focus on developing IRES and 5-SENSE scores for patient stratification and monitoring treatment effectiveness. The IRES score, validated in this study, provides a detailed assessment of the therapeutic response, integrating the reduction of the frequency, intensity and duration of seizures, along with the improvement of quality of life. The results demonstrated that higher IRES score values are correlated with significant clinical improvements, making this tool an essential guide for longitudinal patient monitoring.

In addition, the 5-SENSE score, originally used for SEEG guidance, was adapted to predict response to VNS, based on variables such as the presence of structural lesions, bilateral EEG activity, and locator semiology. Patients with low scores showed a significant reduction in seizure frequency, while those with high scores benefited less from therapy, suggesting the usefulness of this score in selecting candidates for VNS or alternative interventions.

The analysis of the differences between the types of seizures showed a higher efficiency of the VNS in the case of major seizures, such as tonic-clonic seizures, compared to minor seizures, emphasizing the importance of personalizing the treatment according to their semiology. The integration of IRES and 5-SENSE scores contributes to more accurate patient selection and optimization of interventions, making VNS a first-choice therapeutic solution for drug-resistant epilepsy and paving the way for personalized medicine.

I. GENERAL PART

1. Fundamentals of drug-resistant epilepsy – from diagnosis to treatment

Epilepsy is a chronic neurological disorder that affects more than 70 million people worldwide. Despite the availability of more than 20 antiepileptic drugs (AEDs) for the symptomatic treatment of epileptic seizures, approximately one third of patients with epilepsy have seizures refractory to pharmacotherapy [1].

Patients with drug-resistant epilepsy face significant challenges, including an increased risk of premature death, injury, and psychosocial problems, requiring the development of more effective therapies. Understanding the mechanisms of epilepsy and developing experimental models are essential for progress in this field. Recent efforts have led to the identification of promising new therapies, including etiology-specific drugs and multi-target therapeutic approaches [2].

Non-pharmacological treatment options include vagus nerve stimulation (VNS), deep brain stimulation, and cortical stimulation, which offer valuable alternatives for improving epileptic seizure control [3].

In particular, VNS, involving the application of electrical impulses to the vagus nerve through an implantable device, has demonstrated benefits in reducing the frequency and intensity of seizures in patients with drug-refractory epilepsy [4].

Epilepsy surgery may also provide long-term seizure freedom in selected cases of drug-resistant focal epilepsy [2,5].

Evaluating patients in tertiary epilepsy centers is crucial for discussing their eligibility for these innovative therapies. In addition to seizure control, it is important to address the psychological impact and social integration through comprehensive care, in order to improve the quality of life of patients with drug-resistant epilepsy [6].

1.1 Definitions and concepts

Treatment-resistant epilepsy (ERT) is defined as the consecutive failure of two correctly administered antiepileptic drugs, regardless of their type, according to clinical observations and standards [7][8]. Despite technological advances and new drugs, 20-30% of patients remain refractory to treatment [9]. The ILAE definition ("Kwan et al., 2010") considers a patient to be drug-refractory if, after 2 years, he does not maintain seizure freedom following the use of two tolerated and appropriate drug regimens [10]. Other definitions, such as that of "Camfield and Camfield" [11], emphasize the persistence of frequent seizures despite multiple treatments. A Canadian study identified first-drug response failure as a risk factor for ERT [10][12].

1.1.1 Evaluation of patients with drug-refractory epilepsy

The evaluation of patients with drug-resistant epilepsy involves a multidisciplinary approach, including detailed anamnesis, clinical examination, structural and functional imaging investigations, video-EEG monitoring and neuropsychological tests. These steps are essential for locating the epileptogenic area and for determining eligibility for surgery [13].

1.1.2 Anamnesis and clinical examination

The anamnesis should include details about the history of seizures, their types and frequency, triggers, response to treatments, and the medical history of the patient and family [14-18]. The clinical examination should assess neurological, cognitive, and psychosocial functions, using tools such as MMSE and MoCA for cognitive dysfunction and QOLIE-31 for quality of life [14][19-22].

Documenting paroxysmal episodes through seizure diaries and video recordings is essential for their classification and evaluation. The impact on social and professional functioning, the ability to lead and the needs for psychosocial support complete the assessment process [14][23][24]

1.1.3 EEG and Video-EEG

A 2022 study by Zorgör et al. demonstrated the superiority of video-EEG over routine EEG, with a detection rate of 52% for epileptiform discharges, compared to 21% via simple EEG ($p < 0.001$) [25]. Video-EEG is more effective in identifying focal and generalized epileptiform discharges, especially during sleep, supporting its status as the gold standard in diagnosing epilepsy [25,26]. Its use prevents inadequate management of patients and is indicated for the differential diagnosis of seizures, classification of electroclinical syndromes, presurgical evaluation and quantification of seizures [27]. The National Center for Pre-surgical Evaluation of Epilepsy, founded by Dr. Ioana Mîndruță, introduced this technology in Romania.

1.1.4 Current imaging explorations

Classical computed tomography (CT) and MRI are used for structural diagnosis, but many pathological substrates remain undetectable [28]. Advanced technologies such as PET-CT, SPECT, and magnetoencephalography (MEG) provide accurate localization of epileptogenic foci in difficult cases [29-30]. PET, using tracers such as 18F-FDG or TSPO, explores brain metabolism and neuroinflammation [31-34]. SPECT highlights cerebral blood flow during seizures, using radiotracers such as Tc-99m [35,36-37]. MEG detects magnetic fields associated with neural activity with a higher temporal resolution [38].

1.1.5 Invazive diagnostic method

Intracranial electrodes, such as depth (stereo-EEG) or subdural electrodes, are essential in the evaluation of epileptogenic areas in patients with intractable focal epilepsy [39-41]. They allow the precise delimitation of epileptogenic areas and the mapping of brain functions by electrical stimulation [42-43]. The placement is performed under general anesthesia, and the data obtained are correlated with clinical signs and imaging. Functional mapping identifies eloquent areas of the brain, which are essential for planning interventions. Cortical stimulation and CCEP studies reveal pathological connectivity and optimization of surgical strategies [44-45]

1.2 5-SENSE score

The 5-SENSE score is a valuable tool developed for predicting the focality of the seizure onset area in patients investigated by stereoelectroencephalography (SEEG), based on five predictive variables: focal lesion on MRI, absence of bilateral discharge on scalp EEG, neuropsychological lateralization deficits, strongly localizing semiology and regional ictal onset on EEG [46]. With validated sensitivity and specificity, this free tool, accessible online at https://lab-frauscher.github.io/Sense_calc/, supports patient selection for invasive explorations, reducing unnecessary investigations and excessive use of surgical resources [46-47].

The therapeutic arsenal of drug-resistant epilepsy (EFR) involves pharmacological and non-pharmacological strategies:

- **Pharmacological management** through polytherapy with antiepileptic drugs (AEDs), adapted to each patient [48].
- **Epilepsy surgery** may provide seizure freedom for patients with drug-resistant focal epilepsy [49,50].
- **Stimulation therapies** (VNS, DBS, RNS) complement the options for complex cases [51-52].
- **The ketogenic diet** is effective, especially in children, requiring medication adjustments to avoid interactions [53-54].

Comprehensive management of EFR goes beyond crisis management, including multidisciplinary support (neurologists, psychiatrists, psychologists, dietitians) to address the impact of the disease on patients' quality of life [55]. Contemporary and innovative strategies require a personalized approach to optimize patient outcomes and condition [56-59].

2 Neurostimulator models and their indications

Vagus nerve stimulation (VNS) therapy has evolved significantly over the decades, with each generation of devices bringing improvements and expanding therapeutic indications. The first model, NCP M100 (1997), was approved by the FDA for the treatment of drug-refractory epilepsy and introduced programmed stimulation parameters and a battery life [60-62]. Subsequent models, such as the PulseTM M102 and AspireHC® M105, maintained the indications for epilepsy and introduced improvements such as longer battery life and more effective stimulation [63-65]. The SenTiva® M1000 expanded applications for epilepsy and depression, including in pediatrics [60].

2.1. Indications of VNS in drug-resistant epilepsy

Indications for VNS in refractory epilepsy include forms of epilepsy with multiple foci, cryptogenic generalized epilepsy, and treatment-refractory idiopathic epilepsies. The therapy is also used for patients who do not benefit from successful epilepsy surgery and for those who cannot undergo surgery for health reasons [66-72].

2.2 Surgical technique

The implantation of the vagus nerve stimulator involves several essential steps: positioning the patient, making incisions, dissecting the vagus nerve and placing the electrodes. The procedure is performed with great care to avoid nerve damage and to ensure proper functioning of the device [73-75].

2.2.1 Peri and post-operative complications of VNS

Studies on complications associated with VNS implantation indicate risks such as infections, vocal cord paralysis, and device failure, but these events are relatively rare and can be treated with corrective surgery [75-77].

2.3 Other methods of vagal stimulation

Right cervical VNS and transcutaneous stimulation (t-VNS) are non-invasive approaches used for treatments such as migraines and headaches. These methods are effective and safe, and are also applicable in the treatment of epilepsy and depression [78-80].

2.4 Future prospects of VNS

The future of VNS is promising, with the expansion of clinical applications in various conditions and the use of closed-loop technologies that allow the personalization of treatment according to the patient's physiological responses. Future research is also aimed at validating VNS in treatments for treatment-resistant depression, as seen in the RECOVER trial [81,82].

II. SPECIAL PART

3. Working hypothesis and objectives of the study

General objectives

Determination of the effectiveness of VNS according to the types of seizures Identification of differences in the therapeutic response to major seizures (generalized tonic-clonic, focal with bilateralization) and minor seizures (focal without alteration of consciousness, absent seizures), in order to personalize the treatment.

Validation of the 5-SENSE score as a pre-therapeutic predictor. Use of the 5-SENSE score as a predictive tool for patient selection, analyzing its correlation with reducing the frequency, duration, intensity of seizures and improving quality of life.

Longitudinal assessment of treatment response. Monitoring of changes in response to treatment by VNS at 6, 12 and 18 months post-implantation assessed by the cumulative IRES score.

Analysis of clinical, paraclinical and imaging factors. Identification of the role of clinical variables (onset of epilepsy, frequency of seizures, type of seizures, history of treatments, neuropsychiatric status), paraclinical (video-EEG) and imaging variables (structural lesions on CT, MRI or PET-CT), in influencing the therapeutic response.

Secondary objectives

Characterization of the response according to the 5-SENSE score. Comparative analysis of the results obtained in patients with low (0–1 points), moderate (2–3 points) and high (4–5 points) focicity.

Determination of predictive factors of suboptimal response. Evaluation of clinical and imaging characteristics of patients who do not achieve a ≥50% reduction in seizure frequency, in order to optimize therapeutic protocols.

Impact of structural lesions on response. Analysis of the influence of lesions observed on structural imaging on treatment effectiveness.

Analysis of response parameters and variables such as:

- Determination of age, sex and onset of epilepsy as predictive factors for treatment effectiveness.
- The frequency of annual seizures before and after stimulation.
- Classification of crises according to ILAE-2017 (types of major and minor crises).
- The number of antiepileptic drugs administered.
- Average monthly number of seizures before and after stimulation.
- The presence of post-operative complications and side effects following stimulation.
- Stimulation current parameters (OC-current, mA, magnet use, wavelength).
- Etiology of epilepsy and associated genetic abnormalities.
- The circadian preponderance of seizures.
- Improvement of post-ictal status.
- Evaluation of psychomotor development in relation to the response to VNS.

4. General research methodology

Introduction

This retrospective study looks at the effectiveness of vagus nerve stimulation (VNS) in the treatment of drug-resistant epilepsy. The primary goal is to assess clinical response through 5-SENSE and IRES scores before and after device implantation, focusing on optimal patient selection and improvement of therapeutic outcomes. The methodology integrates clinical, imaging, electrophysiological data and predictive analysis.

Study design

The study is retrospective, descriptive and exploratory, based on data from patients with treatment-resistant epilepsy, treated at the Epileptology Center of the Bucharest University Emergency Hospital. The implantation of the Aspire SR 106 device took place between 2021 and 2024. Preoperative evaluations included imaging (MRI, CT, PET-CT), electroencephalographic monitoring and clinical scores to establish the typology of epilepsy and the location of epileptogenic lesions. The postoperative evaluation was performed using the IRES score, which reflects the frequency, duration and intensity of seizures, but also the improvement of quality of life.

Study population

The study included 76 patients (59.2% women and 40.8% men), with an average age of 36 years, diagnosed with treatment-resistant epilepsy.

Preoperative evaluation

Patient selection was carried out based on detailed assessments, including medical imaging (MRI, CT, PET-CT) and electrophysiological analysis (EEG), to identify epileptogenic areas. Classification of seizure types according to ILAE-2017 standards and calculation of the 5-SENSE score were essential for stratifying patients according to epilepsy focality.

Adjusting VNS Parameters and Monitoring

The Aspire SR 106 was initially set to a current of 0.25 mA, frequency of 30 Hz and pulse duration of 500 µs. The adjustments were made bi-weekly, based on the clinical response of the patients.

Postoperative evaluation

The postoperative evaluation was performed using the IRES score, which analyzes the reduction in the frequency and intensity of seizures, their duration and the improvement of quality of life. The total score ranges from 0 to 8, indicating a lack of response or a significant improvement in the patient's condition.

Statistical analysis

Statistical tests were used to analyse differences between patient groups, such as Kruskal-Wallis and ANOVA tests, logistic regression and machine learning techniques. These methods allowed the identification of factors influencing the response to VNS and their correlation with the patient's characteristics.

Ethical aspects

The study complies with international medical research standards, and patients provided informed consent. The data used has been anonymized, according to the General Data Protection Regulation (GDPR), and has been used exclusively for research purposes.

Limitations and prospects

The retrospective study imposes limitations related to data variability and incomplete information, but offers insights for improving the efficiency of VNS through more accurate patient selection. Additional, prospective studies with a larger number of patients and a longer follow-up period are needed to validate these results.

5. 5-SENSE Score

5.1. Introduction

The 5-SENSE score represents a significant advance in the management of epilepsy, providing a more accurate stratification of patients eligible for SEEG and having real potential in the selection of candidates for vagal stimulation therapy (VNS). It uses a refined method for analyzing the focus of the onset of seizures, filling in the gaps where non-invasive assessments do not provide clarity. The score is based on five fundamental predictive variables: focal lesions on MRI, absence of independent bilateral waves on EEG, localized neurological deficit, localizing semiology, and regional ictal onset detected by video-EEG. These variables are essential for assessing the focus and stratifying patients for appropriate therapeutic interventions. Recent studies also highlight the effectiveness of machine learning techniques in predicting seizures and optimizing VNS therapy. Also, technological innovations allow the development of non-invasive systems for initiating VNS stimulation, highlighting the importance of accurate crisis prediction and appropriate patient selection.

5.2. Working hypothesis

The main hypothesis is that the 5-SENSE score, through its predictive variables (focal lesions, absence of independent bilateral EEG waves, localizing semiology, regional ictal onset, and neurological deficits), can predict the efficacy of vagus nerve stimulation (VNS). Thus, it could become possible to select patients for VNS without resorting to invasive SEEG, the invasive procedure being reserved only for cases where the benefits outweigh the risks. Validating the 5-SENSE score for this purpose could improve treatment personalization and optimize clinical safety and resources.

5.3. Methodologies

The retrospective study evaluated 76 patients with drug-resistant epilepsy, treated between 2021 and 2024 at the Bucharest University Emergency Hospital. The main goal was to correlate the 5-SENSE score with the reduction in seizure frequency after VNS. Patients were evaluated preoperatively by advanced imaging and video EEG, and the semiology of seizures was documented according to ILAE-2017 guidelines. After VNS therapy, the results were tracked to assess the effectiveness of the treatment. The 5-SENSE score was used to classify patients into three groups of focus: low (0-1 points), moderate (2-3 points), and high (4-5 points). The reduction in seizure frequency was assessed based on the percentage change in monthly seizure frequency. The Kruskal-Wallis test and the t-pair tests were used for statistical analysis.

5.4. Results

Most of the patients were in the group with low focus, with a significant reduction in seizures (50.69%). The group with moderate focus had a reduction of 34.71%, and the group with high focus recorded an increase in the frequency of seizures by 72.98%. These results emphasize an inverse relationship between focicity and the effectiveness of VNS therapy. Statistical tests showed significant differences between the low and high focus groups. The 5-SENSE score demonstrated the ability to stratify patients and guide their selection for VNS therapy or for further investigation through SEEG, promoting a personalized approach in the treatment of drug-resistant epilepsy.

5.5. Discussions

High-intensity stimulation via VNS appears to be more effective in reducing the frequency of epileptic seizures, even in focal lesions, compared to low-intensity stimulation. The analysis showed a hazard ratio (RR) of 1.73 for a 50% or greater reduction in seizure frequency (95% confidence interval: 1.13–2.64), providing evidence of moderate certainty [83].

The results of VNS therapy in structural versus non-structural epilepsies showed that generalized seizures had the most significant response to this form of treatment. Among patients with a history of status epilepticus (SE) prior to VNS implantation, 67% had no recurrence of ES after treatment [84].

Post-surgical outcomes in epilepsy varied by histopathology, highlighting significant differences in success rates. Tumors associated with epilepsy, vascular malformations and hippocampal sclerosis showed the best results in terms of seizure control two years after surgery. The percentage of patients who remained without debilitating seizures was 77.5% for low-grade tumors, 74.0% for vascular malformations, and 71.5% for hippocampal sclerosis [85].

The perspective on epilepsy language and surgery shows that current advanced surgical techniques, such as stereotactic laser ablation and radiofrequency ablation, play a crucial role in both the effective treatment of epilepsy and the understanding of language networks. These modern methods allow for highly precise intervention on focal lesions, contributing not only to seizure control, but also to exploring the relationship between brain regions involved in language and epileptiform activity [86].

A 2021 study by Zhu et al. showed a higher average reduction in seizure frequency in follow-up intervals for patients undergoing deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS), compared to those treated with vagus nerve stimulation (VNS). These results suggest that ANT-DBS may be more effective in certain cases, paving the way for the integration of patient-specific clinical features in the personalization of treatment strategies [87].

Advanced imaging techniques and personalized modeling have made it possible to map epileptogenic networks, providing crucial support in surgical planning. These methods not only allow for more precise localization of epileptogenic areas, but also have the potential to significantly improve treatment outcomes in patients with drug-resistant epilepsy [88].

5.6 Conclusions

The 5-SENSE score allows for more precise identification of patients for whom VNS may be less effective due to an extremely marked focality of the seizure onset area, redirecting them to more appropriate therapeutic strategies.

Our study not only validated the use of the 5-SENSE score beyond its original, SEEG-dedicated context, but also stimulated a rethinking of how diagnostic tools can be integrated to improve decision-making in epilepsy management. This underscores the potential of the 5-SENSE score to become a central tool in personalizing vagal stimulation treatments, optimizing clinical outcomes, SEEG complications, and surgical procedures, thereby improving patients' quality of life.

At the same time, the explanation for the significant heterogeneity of treatment responses observed in the high-focus group has not yet been fully elucidated. These preliminary results suggest that the 5-SENSE score should be used with caution and with particular finesse for prognostic purposes. They draw attention to the fact that the treatment of epilepsy must be individualized for each case.

Future studies will need to investigate the reasons for this heterogeneity in more detail in order to refine the predictive value of the 5-SENSE score and tailor treatments accordingly. Thus, it will be possible to develop increasingly personalized approaches in standard treatments. Extensive investigations, such as those involving the 5-SENSE score, will become essential in identifying the best treatment modality for each individual patient.

This direction will help optimize standard care and lead to a better quality of life for patients with drug-resistant epilepsy. Personalizing treatment will not only improve clinical outcomes, but will also provide an approach tailored to patients' individual needs.

6. IRES SCORE

6.1. Introduction

Advances in technology have improved treatments for drug-resistant epilepsy, and vagus nerve stimulation (VNS) therapy has become a viable therapeutic option [89,90]. Post-implantation outcomes of VNS devices vary, highlighting the need for robust monitoring methodologies, including seizure reduction and quality of life improvement [91-94]. Studies have shown that VNS can lead to significant long-term improvements, but the effectiveness of this therapy depends on factors such as lesional etiology and age at implantation[90,95]. The therapy can also induce changes in heart rhythm, suggesting their use for treatment monitoring[91,96]. The variability of VNS results reflects the complexity of drug-refractory epilepsy and the benefits of neurostimulation[97,98]. VNS not only reduces seizures, but also improves quality of life[93,99-103], and genetic analysis becomes essential for personalization of treatment[96,103,104-107].

6.2. Working hypothesis

The paper investigates the effectiveness of VNS in the treatment of drug-resistant epilepsy using a new assessment tool, the Stimulation Response Index (IRES). The hypothesis is that the IRES score reflects the therapeutic response through clinical, imaging, electrophysiological, genetic, neuropsychiatric and demographic parameters. The response to VNS varies significantly depending on seizure characteristics, age, sex, etiology of epilepsy, and other factors. The general objectives are to evaluate the effectiveness of VNS based on the IRES score and to explore the pre-operative factors influencing the response to treatment. Secondary objectives include assessing response dynamics and correlating the IRES score with other stratification measures, such as the 5-SENSE score.

6.3. Methodologies

The study, conducted between January 2021 and May 2024 at the Bucharest University Emergency Hospital, included 76 patients with drug-resistant epilepsy, treated with VNS (ASPIRE SR 106 device). The IRES score was used to assess response to treatment, including four components: reducing the duration, intensity and frequency of seizures, and improving quality of life. Evaluations took place at 6, 12 and 18 months post-implantation. The parameters of the device have been adjusted to optimize the therapeutic response. The IRES score was interpreted on a scale from 0 to 8, indicating the variability of the response to treatment, from minimal to significant. IRES scores between 0 and 2 reflect a minimal response, between 3 and 6 suggest moderate improvements, and above 6 indicate a significant response.

6.4. Results

A total of 76 patients with drug-resistant epilepsy who underwent VNS implantation at the Bucharest University Emergency Hospital were followed retrospectively over a period of 18 months (January 2021-May 2024) by interpreting the IRES score (Table 6.1.) Patient characteristics, clinical data, epilepsy classifications and follow-up information are presented in.

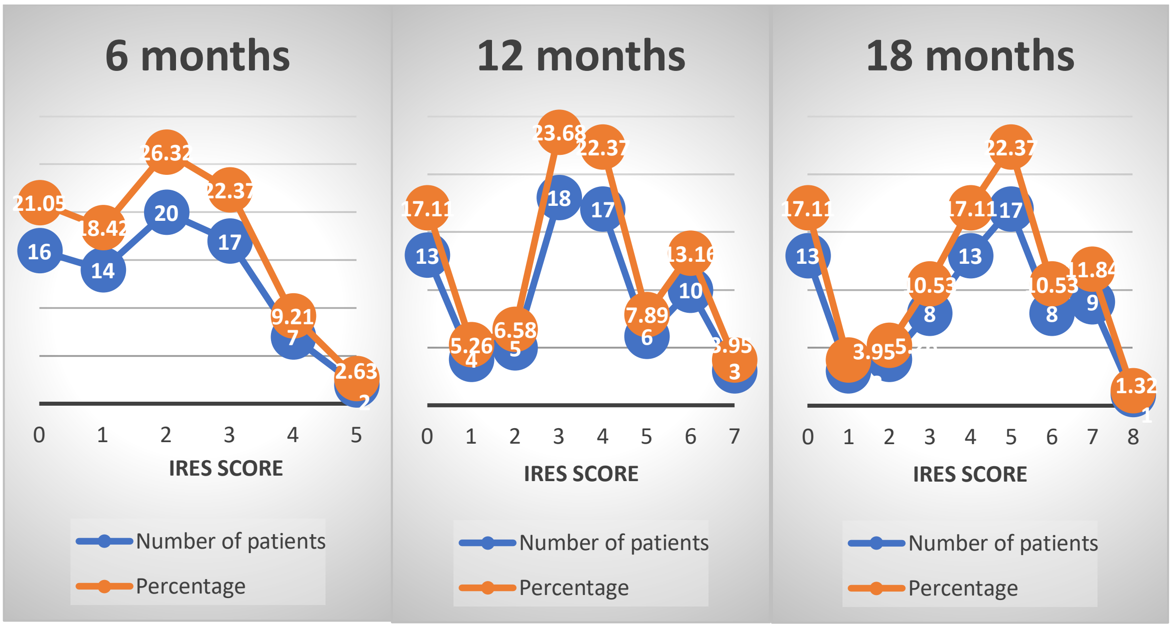
Table 6.1. Evaluation of IRES score after vagal stimulation.

Component	0 Points	1 Point	2 Points
Decrease in the duration of crises	0-25% improvement	25-50% improvement	>50% improvement
Decrease in the intensity of crises	0-25% improvement	25-50% improvement	>50% improvement
Improving quality of life	No changes in your daily routine No improvements in quality of life (sleep, depressive symptoms, functional capacity, cognitive improvement)	Feels a little better **Slight improvement in carrying out daily activities**	Observed **improvement Significant decreases in depressive symptoms and an overall improvement in mood and functionality.**
Decrease in the frequency of seizures	0-25% improvement	25-50% improvement	>50% improvement
Total IRES:	**0-2 points**	**3-6 points**	**>6 points**
Interpret:	***Minimal or no response***	***Partial answer***	***Significant or complete response***

The study included patients with a median age of 36 years, most of whom had the onset of epilepsy at 10 years of age. The most common EEG abnormalities were multifocal (52.6%), and most patients had no lesions on brain imaging. The crises were predominantly bilateralized (46.1%) and mixed (26.3%). VNS therapy had a favorable response for 65.8%

of patients, with a significant decrease in seizure frequency (from 19.29 to 8.79 per month). Most patients used 3-5 medications, and magnet seizure capture was reported in 18.4%.

The IRES score increased over the course of the study, reaching mean values of 1.88 at 6 months, 3.25 at 12 months, and 3.83 at 18 months. At 6 months, most patients had scores between 0 and 2, and 34.21% had scores between 3 and 6. At 12 months, 67.11% of patients had scores between 3 and 6, and at 18 months, 60.53% had similar scores, and 13.16% had scores between 7 and 8, indicating a significant or complete response Figure 6.1.



A **B** **C**

Figure 6.1 Distribution of IRES scores after VNS therapy: ***A.*** at 6 months, ***B.*** at 12 months, ***C.*** at 18 months.

The t- and p-values are the results of statistical tests used to compare average IRES scores between two time points. A negative t-value indicates that the mean IRES score at the later time is higher than at the previous time, reflecting an improvement in therapeutic response over time (Table 6.2.)

Table 6.2. Mean IRES scores at 6, 12, and 18 months for each age group and sex, along with corresponding t- and p-values, indicate the significance of changes over time in response to VNS therapy.

Category	**IRES 6 Months Mean**	**IRES 12 Months Mean**	**IRES 18 Months Mean**	**6-12 Months T-Value**	**6-12 Months P-Value**	**12-18 Months T-Value**	**12-18 Months P-Value**
19-29	2.08	3.33	3.92	-5.23945	<0.05	-4.98573	<0.05
30-40	1.80	3.17	3.83	-7.69827	<0.05	-4.99831	<0.05
>40	1.93	3.32	3.82	-7.43701	<0.05	-4.52522	<0.05
Sex F	1.88	3.18	3.70	-9.00464	<0.05	-5.87516	<0.05
Sex M	1.90	3.35	4.03	-7.21193	<0.05	-4.7678	<0.05

By analyzing the frequency distribution of the IRES components, varying degrees of effectiveness over time for each score variable can be highlighted. The components of the system include SDC (Decreased Seizure Duration), SIC (Decreased Seizure Intensity), LCI (Increased Quality of Life), and SFC (Decreased Seizure Frequency). This assessment highlights the contribution of each component to the overall performance of the system, shedding light on changes and impact trends over different time frames Figure 6.2.

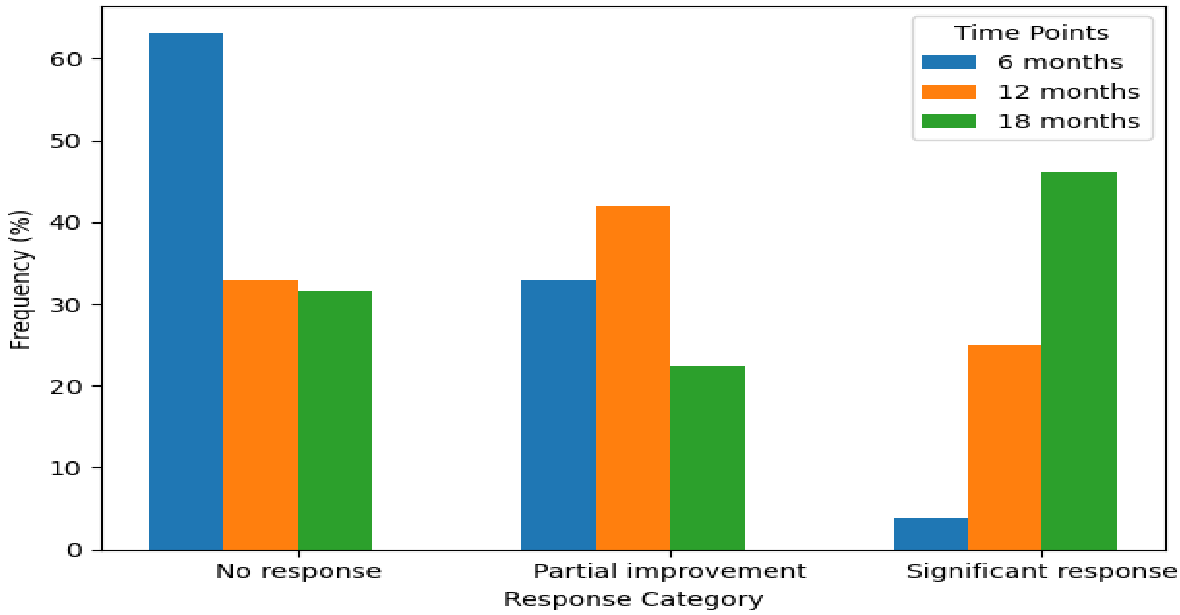


Figure 6.2. Distribution of response categories for CFS (Decreased Seizure Frequency) over time, at intervals of 6, 12 and 18 months.

At 6 months, most patients (63.2%) had no response to therapy, 32.9% had partial improvements, and 3.9% showed a significant response. At 12 months, the proportion of those without response decreased to 32.9%, and the categories of partial improvement and significant response increased to 42.1% and 25%, respectively. At 18 months, 46.1% of patients had a significant response, while the no-response category decreased to 31.6%.

In terms of decreasing the duration of seizures, 55.3% of patients had no response at 6 months, and 6.6% had a significant response. At 12 months, the significant response increased to 21.1%, and at 18 months it reached 30.3%. For improving quality of life, most patients had a partial improvement at 6 months (71.1%), and the percentage of those with a significant response increased to 35.5% at 18 months. In terms of decreasing the intensity of crises, 77.6% had no response at 6 months, and the significant response increased to 9.2% at 18 months.

A decrease in unresponsive cases and an increase in partially improving cases are observed over time, with a reduced number of patients with significant or complete response Figure 6.3.

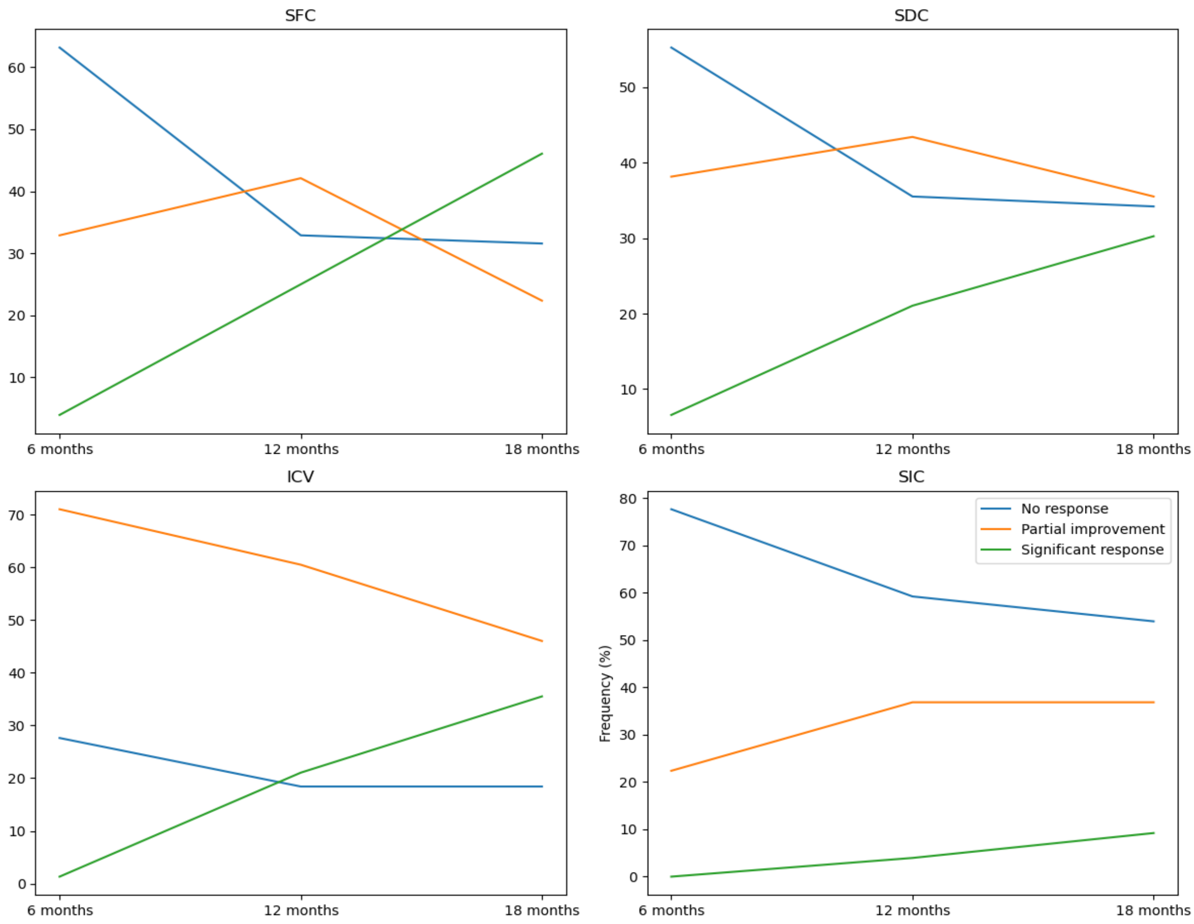


Figure 6.3. Complete perspective on the four components of the IRES (SFC - Decrease in the Frequency of Seizures, SDC - Decrease in the Duration of Seizures, ICV - Improvement of Quality of Life and SIC - Decrease in the Intensity of Seizures).

At first, most cases were unresponsive, but this proportion decreased over time, and cases with partial improvement and significant response gradually increased. IRES scores, which measure treatment effectiveness, were statistically analyzed at 6, 12, and 18 months, and their distribution was normal, validating the use of statistical tests to compare treatment effectiveness.

The results showed that the presence of lesions on imaging had a significant impact on IRES scores, with higher values in their absence. Magnet use was also associated with lower IRES scores, and patients with favorable clinical responses had significantly better scores. The presence of genetic abnormalities was correlated with lower scores, and post-hoc analysis identified significant differences between groups.

Tests for variables such as seizure classification and circadian seizure prevalence showed significant differences, especially at 12 and 18 months. The frequency of seizures before treatment showed significant differences over time. Significant variations were also observed between groups based on the 5-SENSE score and the onset of epilepsy.

Comparisons of the number of pre- and post-VNS seizures showed significant changes after treatment, with a reduction in symptoms and increased efficacy, confirmed by statistical tests appropriate for non-normal data.

The results of the correlation tests between IRES scores and numerical variables prior to VNS treatment are shown in Table 6.3.

Table 6.3. Correlation of IRES score with numerical variables

	IRES - 6 luni	IRES - 12 luni	IRES - 18 luni
% decrease in crises	0.773 (0.000)**	0.747 (0.000)	0.789 (0.000)
Average number of monthly seizures before stimulation	-0.267 (0.020)*	-0.219 (0.057)	-0.207 (0.073)
Days off without seizures before VNS	0.462 (0.000)*	0.388 (0.001)	0.360 (0.001)

* Spearman's Correlation test. Correlation coefficient (P value)

** Pearson's Correlation test

The results of the statistical analysis show a significant positive correlation between IRES scores and the reduction of epileptic seizures at 6, 12 and 18 months (p=0.000, correlations of 0.773, 0.747 and 0.789). The tests also indicated a moderate negative correlation at 6 months between the average monthly number of seizures before stimulation and IRES scores (-0.267, p=0.020), suggesting that a higher IRES score is associated with fewer seizures, although at 12 and 18 months this correlation is no longer statistically significant.

Significant positive correlations between the number of seizure-free days before stimulation and IRES scores were observed at all time intervals, indicating that longer seizure-free periods are associated with higher scores. Multinomial logistic regression was used to assess the impact of predictive factors on outcomes, and the analysis showed statistical significance in all cases, with the Nagelkerke value R^2 indicating that predictors explain much of the variation in IRES scores (53.7% at 6 months, 71.1% at 12 months, and 81.8% at 18 months).

Among the significant predictors identified in the logistic regression models, the mean number of seizures and the number of seizure-free days before stimulation had a major influence on treatment response, both in the short and long term. At 12 months, a significant impact was also observed for etiology and genetic abnormalities, and at 18 months, the age of onset of epilepsy had a major effect on treatment effectiveness.

The model was also used to classify patients into three groups based on response to treatment: those who do not benefit significantly from treatment, those with moderate improvement, and those with substantial therapeutic benefits. Factors such as age, gender, etiology of epilepsy, the presence of genetic abnormalities and other clinical and demographic variables were included in the logistic regression, and their analysis allowed the personalization of treatment and the optimization of patient care.

The model was refined in three stages to optimize the accuracy of the predictions, eliminating features that did not have a significant impact on the results at 6, 12 and 18 months. Following the adjustments, a robust model was obtained, which allowed the identification of key factors influencing treatment success and contributed to improving the management of epilepsy patients treated with vagal stimulation (VNS).

Table 6.4 presents the assessment metrics for the classification model used to predict IRES scores at three distinct time points: 6 months, 12 months and 18 months.

Table 6.4. Evaluation of the performance of classification models				
	Accuracy	Sensibility	Specificitate	P-value*
6 luni IRES, Model (1)	0.75	[0.75, 0.75]	[0.9, 0.5]	<0.001
12 luni IRES, Model (2)	0.875	[0.667, 1]	[1.0, 0.833]	<0.001
18 luni IRES, Model (3)	0.75	[0.667, 0.875, 0.5]	[1.0, 0.833, 0.75]	<0.001

* P-value calculat utilizand test one-sample multinomial.

At 6 months, the model demonstrated 75% accuracy, meaning that three-quarters of the predictions were correct. This performance suggests that, from the early stages, the model is able to identify patients who benefit from treatment or not.

After one year, the model's accuracy increased significantly to 87.5%, highlighting the improvement in predictions with data accumulation and longer follow-up time. This increase reflects a better understanding of predictive factors and how they influence treatment effectiveness over time.

At 18 months, accuracy returned to 75%, indicating long-term pattern consistency. Although the 12-month performance has not been maintained, the model continues to be robust and provide relevant predictions.

6.5. Discussions

The effectiveness of VNS therapy has been increasingly explored lately, with numerous studies reporting various methods of monitoring patients and the results obtained in the management of drug-resistant epilepsy [89-107]. Although the use of a personalized score, such as IRES, provides a nuanced approach in assessing the progress of patients after VNS therapy, the literature indicates a variety of metrics and methodologies available for evaluating the effectiveness of VNS therapy within diverse populations.

6.6. Conclusions

The IRES score represents a solid platform for assessing long-term NSV therapy outcomes, with strong correlations between the score components (SFC, SDC, SIC, ICV) and the overall score, demonstrating its ability to detect the subtle effects of therapy on seizure control and quality of life. The study highlights the increased effectiveness of VNS in the management of drug-resistant epilepsy, with significant improvements in IRES scores at 6, 12 and 18 months, as well as a reduction in the frequency of major seizures and an increase in seizure-free intervals. The main predictors of a positive response to VNS are the circadian preponderance of seizures, the frequency of annual seizures before treatment, and seizure-free days before treatment.

7. Evaluation of the effectiveness of vagus nerve stimulation in relation to "minor" and "major" epileptic seizures

7.1. Introduce

The response to vagal stimulation (VNS) in drug-resistant epilepsy varies significantly between different seizure types. Studies show that VNS has a greater impact on major seizures, such as tonic-clonic seizures, compared to minor seizures, such as auras or focal seizures without impaired consciousness [108-110]. There is also evidence that VNS can improve cognitive and behavioral functions, even in minor seizures [111–114]. The effectiveness of the treatment depends on the therapeutic parameters, which must be adjusted for each individual patient [115, 116].

7.2. Working hypothesis

It is assumed that VNS therapy is more effective in major seizures than in minor seizures, and that patients who have both types of seizures will experience a more variable therapeutic response. Thus, a personalized approach to treatment is necessary to optimize results.

Main objectives

- To assess differences in clinical response to VNS between patients with major and minor crises.
- Investigation of the effectiveness of VNS in patients with both types of seizures.
- To determine the overall effectiveness of VNS in reducing crises, depending on their type.

Secondary objectives

- Analysis of the influence of seizure severity on therapeutic response.
- Investigate the interaction between major and minor seizures and the impact on the effectiveness of therapy.
- Exploring differences in the effects of VNS in the first 12 months of treatment.

7.3. Methodologies

The retrospective study included 76 patients with drug-resistant epilepsy treated with VNS in the Bucharest University Emergency Hospital between 2021 and 2024. Patients were classified according to the type of seizures into 'minor' and 'major' to assess the different response to VNS. The therapy was adjusted at two-week intervals and the analysis was performed after 12 months of treatment. Reducing crises by more than 50% was considered a favorable response.

7.4. Results

In the cohort studied, 51.32% of patients had major seizures, 21.05% minor seizures, and 27.63% had both types of seizures. The response to VNS therapy was:

- 25% of patients with minor seizures got a favorable response, while 75% did not.
- 82.05% of patients with major crises had a favorable response.
- 38.10% of patients with combined seizures responded favorably, and 61.90% did not.

The Chi-square test showed a significant difference between seizure types and response to VNS (Chi-square = 19.82, $p = 0.00005$). In the case of major seizures, the Chi-square value was 7.37 ($p = 0.0066$), indicating a significant association with a favorable response to treatment. Minor seizures had a Chi-squared value of 17.20 ($p = 0.000034$), signifying a strong association between them and unfavorable responses Figure 7.1.

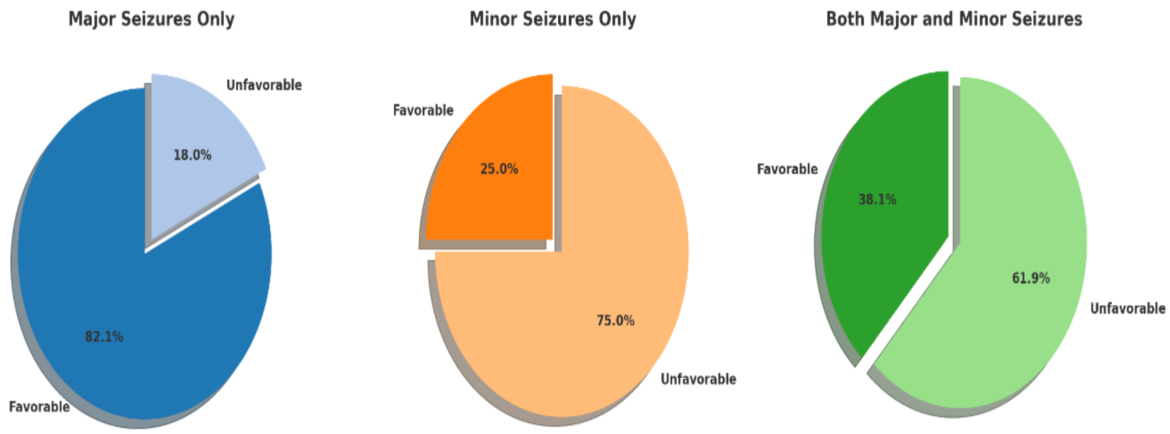


Figure 7.1. Distribution of clinical responses to VNS therapy according to the type of seizure. A favorable response is defined as a reduction in seizure frequency by more than 50% after 12 months of VNS therapy, while an unfavorable response refers to a reduction of less than 50% over the same period.

7.5. Discussion

The results support that VNS is more effective in treating major seizures compared to minor seizures, which is consistent with previous studies [108, 110, 111]. Also, patients with combined seizures have a mixed therapeutic response, and personalized therapy adjustments are essential to achieve favorable outcomes [112, 113]. In conclusion, VNS therapy can provide significant benefits, but careful and personalized monitoring of treatment is necessary for patients with mixed seizures.

7.6. Conclusions

The results of the study showed that VNS therapy is highly effective in treating major seizures, such as focal seizures that become bilateral tonic-clonic or generalized motor seizures, with a response rate of 82.05%. This indicates that VNS counteracts the serious effects of drug-resistant epilepsy. On the other hand, patients with less intense seizures, such as focal conscious or non-motor seizures (absences), had a more modest response, with only 25% achieving favorable results. Patients who have both types of seizures have shown mixed responses, requiring an individualized approach for appropriate treatment management.

These differences underscore the importance of personalized adjustment of VNS therapy, as the interaction of major and minor seizures can influence overall effectiveness.

8. General conclusions and personal contributions

This doctoral research explores in depth VNS therapy in drug-resistant epilepsy, with a focus on three major directions: integration of the 5-SENSE score for patient stratification, development of the IRES score for longitudinal monitoring of therapeutic response, and differentiated analysis of seizure types (major and minor). The study contributes significantly to the refinement of selection criteria and to the optimization of treatment, promoting a personalized approach in epileptology.

The 5-SENSE score is an essential methodological innovation, being adapted from SEEG procedures for stratifying patients according to the focality of epileptogenic areas and response to VNS. Based on five predictive factors – structural injury (MRI), bilateral EEG activity, neurological signs of laterality, localizing semiology and ictal EEG onset – the 5-SENSE score allows the characterization of patients before treatment. The analyses showed that patients with low scores (0-1 points) experienced an average reduction of 50.69% in seizure frequency and a favorable response rate of 86.67%, while patients with high scores (4-5 points) experienced increases in seizure frequency (72.98%). These results ($p < 0.001$) validate the 5-SENSE score as an essential tool for patient selection and guidance for alternative interventions, such as surgical resection.

The IRES score (stimulation response index) was created to assess the longitudinal effectiveness of VNS, quantifying the reduction in the frequency, intensity and duration of seizures, along with the improvement in quality of life. It was calculated at 6, 12 and 18 months, highlighting a significant increase in scores for patients with favorable responses (1.93 at 6 months vs. 5.14 at 18 months). Preoperative factors, such as seizure-free interval before VNS, were associated with higher scores, highlighting the importance of pre-treatment control of epileptic activity. The IRES score not only monitors therapeutic progress, but also identifies patients who can benefit the most from VNS. The analysis of the response to VNS according to the types of seizures highlighted the higher efficacy of the therapy in the case of major seizures (generalized tonic-clonic and focal with bilateralization), with a favorable response rate of 82.05%. Patients with minor seizures (absences, focal conscious seizures) had a more modest response rate (25%), and those with mixed seizures had additional complexity (favorable response 38.10%). These results (Chi-square = 19.82, $p < 0.001$) support the need to adjust the stimulation parameters according to the semiology of the seizures in order to optimize the treatment.

This doctoral work fundamentally contributes to the personalization of VNS therapy, setting new standards for patient selection, progress monitoring and adjustment of therapeutic interventions in drug-resistant epilepsy.

BIBLIOGRAPHY

1. Löscher W, Potschka H, Sisodiya SM, et al. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacol Rev. 2020 Jul; 72(3):606-638.

2. Guery D, Rheims S. Clinical Management of Drug Resistant Epilepsy: A Review on Current Strategies. Neuropsychiatr Dis Treat. 2021 Jul 12;17:2229-2242.

3.Alqahtani F, Imran I, Pervaiz H, et al. Non-pharmacological Interventions for Intractable Epilepsy. Saudi Pharm J. 2020; 28(8):951-962.

4. Batson S, Shankar R, Conry J, et al. Efficacy and safety of VNS therapy or continued medication management for treatment of adults with drug-resistant epilepsy: systematic review and meta-analysis. J Neurol. 2022 Jun; 269(6):2874-2891.

5. Brodie MJ, Barry SJE, Bamagous GA, et al. Patterns of treatment response in newly diagnosed epilepsy. Neurology. 2012; 78(20):1548–1554.

6. Schiller Y, Najjar Y. Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology. 2008; 70(1):54–65.

7. Assenza G. Diagnosis and Treatment of Drug-Resistant Epilepsy: Present and Future Perspectives. Brain Sci. 2020 Oct 26; 10(11):779.

8. Kwan P., Arzimanoglou A., Berg A.T., et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010; 51:1069–1077.

9. Fattorusso A, Matricardi S, Mencaroni E, et al. The Pharmacoresistant Epilepsy(2021): An Overview on Existant and New Emerging Therapies.

10. Kwan P. Early identification of refractory epilepsy. N Engl J Med. (2000) 342:314–9.

11.Camfield PR, Camfield CS, Gordon KE, et al. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr. (1997) 131:821–4.

12. Blond BN, Hirsch LJ, Mattson RH. Misperceptions on the chance of seizure freedom with antiseizure medications after two failed trials. Epilepsia. (2020) 61:1789–90.

13. Rathore C, Radhakrishnan K. Concept of epilepsy surgery and presurgical evaluation. Epileptic Disord. 2015 Mar; 17(1):19-31; quiz 31.

14.Panayiotopoulos CP. The Epilepsies: Seizures, Syndromes and Management. Oxfordshire (UK): Bladon Medical Publishing; 2005. Chapter 1, Clinical Aspects of the Diagnosis of Epileptic Seizures and Epileptic Syndromes.

15. Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. Epilepsia. 2001; 42:796–803

16. Gates JR. Nonepileptic seizures:Classification, coexistence with epilepsy, diagnosis, therapeutic approaches, and consensus. Epilepsy Behav. 2002; 3:28–33.

17. Murtagh J. Fits, faints and funny turns. A general diagnostic approach. Aust Fam Physician. 2003; 32:203–6

18. Gates JR. Nonepileptic seizures:Classification, coexistence with epilepsy, diagnosis, therapeutic approaches, and consensus. Epilepsy Behav. 2002; 3:28–33.

19. Saadi A, Patenaude B, Mateen FJ. Quality of life in epilepsy-31 inventory (QOLIE-31) scores: A global comparison. Epilepsy Behav. 2016 Dec;65:13-17.22.

20. Souza MC, de Paulo CO, Miyashiro L, et al. Comparison of screening tests in the evaluation of cognitive status of patients with epilepsy. Dement Neuropsychol. 2021 Jan-Mar; 15(1):145-152.

21. Montaño-Lozada JM, López N, Espejo-Zapata LM, et al. Cognitive changes in patients with epilepsy identified through the MoCA test during neurology outpatient consultation. Epilepsy Behav. 2021;122:108158.

22. Lin F, Han J, Xue T, et al. Predicting cognitive impairment in outpatients with epilepsy using machine learning techniques. Sci Rep. 2021 Oct 8; 11(1):20002.

23. Ricci L, Boscarino M, Assenza G, et al. Clinical utility of home videos for diagnosing epileptic seizures: a systematic review and practical recommendations for optimal and safe recording. Neurol Sci. 2021 Apr; 42(4):1301-1309.

24. Patel P, Moshé SL. The evolution of the concepts of seizures and epilepsy: What's in a name? Epilepsia Open. 2020 Jan 10; 5(1):22-35.

25. Zorgör G, Eren F, Gül G, Baştuğ Gül Z. A comparison of video EEG monitoring and routine EEG for diagnosis of epilepsy. Arch Epilepsy. 2022; 28(2):85-88.

26. Jules Fidele N. Additional overnight video EEG for the diagnosis of epilepsy: Experiences from Western Kenya. Clin Neurophysiol Pract. 2023 Aug 7;8:164-168. .

27. Baumgartner C, Pirker S. Video-EEG. Handb Clin Neurol. 2019;160:171-183.

28. Yassin A, El-Salem K, Al-Mistarehi AH., et al. Use of Innovative SPECT Techniques in the Presurgical Evaluation of Patients with Nonlesional Extratemporal Drug-Resistant Epilepsy. Mol Imaging. 2021 Mar 2;2021:6614356.

29. Rathore C., Dickson J. C., Teotonio R, et al. The utility of 18F-fluorodeoxyglucose PET (FDG PET) in epilepsy surgery. Epilepsy Research. 2014; 108(8):1306–1314.

30. Ray A, Bowyer SM. Clinical applications of magnetoencephalography in epilepsy. Ann Indian Acad Neurol. 2010 Jan; 13(1):14-22.

31. Sarikaya I. PET studies in epilepsy. Am J Nucl Med Mol Imaging. 2015; 5:416–430.

32. Turkheimer FE, Rizzo G, Bloomfield PS, et al. The methodology of TSPO imaging with positron emission tomography. Biochem Soc Trans. 2015; 43(4):586–592.

33. Gershen LD, Zanotti-Fregonara P, Dustin et al. Neuroinflammation in Temporal Lobe Epilepsy Measured Using Positron Emission Tomographic Imaging of Translocator Protein. JAMA Neurol. 2015; 72:882–888.

34. Hirvonen J, Kreisl WC, Fujita M, et al. Increased in vivo expression of an inflammatory marker in temporal lobe epilepsy. J Nucl Med. 2012; 53:234–240.

35. Kim S, Mountz JM. SPECT Imaging of Epilepsy: An Overview and Comparison with F-18 FDG PET. Int J Mol Imaging. 2011;2011:813028.

36. Walovitch RC, Hill TC, Garrity ST, et al. Characterization of technetium-99m-L,L-ECD for brain perfusion imaging, part 1: pharmacology of technetium-99m ECD in nonhuman primates. Journal of Nuclear Medicine. 1989; 30(11):1892–1901

37. Cikrit DF, Dalsing MC, Harting PS, et al. Cerebral vascular reactivity assessed with acetazolamide single photon emission computer tomography scans before and after carotid endarterectomy. American Journal of Surgery. 1997; 174(2):193–197

38. Proudfoot M, Woolrich MW, Nobre AC, et al. Magnetoencephalography. Practical Neurology. 2014; 14:336–343.

39. Nair DR, Burgess R, McIntyre CC, et all. Chronic subdural electrodes in the management of epilepsy. Clin Neurophysiol 119: 11– 28, 2008.

40. Zumsteg D, Wieser HG: Presurgical evaluation: current role of invasive EEG. Epilepsia 41 (Suppl 3): S55– S60, 2000

41. Kahane P, Francione S: Stereoelectroencephalography, in Lüders HO. (ed): Textbook of Epilepsy Surgery. London, Informa Healthcare, Taylor & Francis distributor, 2008, pp 649– 658

42. Watts AD, Herrick IA, McLachlan RS, et al. The effect of sevoflurane and isoflurane anesthesia on interictal spike activity among patients with refractory epilepsy. Anesth Analg 89: 1275– 1281, 1999.

43. Adrian ED: The spread of activity in the cerebral cortex. J Physiol (Lond) 88: 127– 161, 1936.

44. Barth DS, Sutherling W: Current source-density and neuromagnetic analysis of the direct cortical response in rat cortex. Brain Res 450: 280– 294, 1988.

45. Enatsu R, Jin K, Elwan S, et al. Correlations between ictal propagation and response to electrical cortical stimulation: a cortico-cortical evoked potential study. Epilepsy Res 101: 76– 87, 2012.

46. Astner-Rohracher A, Zimmermann G, Avigdor T, et al. Development and Validation of the 5-SENSE Score to Predict Focality of the Seizure-Onset Zone as Assessed by Stereoelectroencephalography. JAMA Neurol. 2022; 79(1):70–79.

47. Gallagher RS, Sinha N, Pattnaik AR, et al. Quantifying interictal intracranial EEG to predict focal epilepsy. 2023;1:9-10.

48. Callaghan B, Schlesinger M, Rodemer W, et al. Remission and relapse in a drug-resistant epilepsy population followed prospectively: drug-resistant epilepsy population. *Epilepsia*. 2011;**52**(3):619–626.

49. Perucca E, French J, Bialer M. Development of new antiepileptic drugs: challenges, incentives, and recent advances. *Lancet Neurol*. 2007;**6**(9):793–804.

50. Thieffry S, Klein P, Baulac M, et al. Understanding the challenge of comparative effectiveness research in focal epilepsy: a review of network meta-analyses and real-world evidence on antiepileptic drugs. *Epilepsia*. 2020;**61**(4):595–609.

51. Guery D, Rheims S. Is the mechanism of action of antiseizure drugs a key element in the choice of treatment? *Fundam Clin Pharmacol*. 2020; fcp.12614.

52. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. *Lancet Neurol*. 2014;**13**(11):1114–1126.

53. Lambrechts DAJE, de Kinderen RJA, Vles JSH, et al. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurol Scand*. 2017;**135**(2):231–239.

54. Kverneland M, Taubøll E, Molteberg E, et al. Pharmacokinetic interaction between modified Atkins diet and antiepileptic drugs in adults with drug-resistant epilepsy. *Epilepsia*. 2019;**60**(11):2235–2244.

55. Leidy NK, Elixhauser A, Vickrey B, et al.. Seizure frequency and the health-related quality of life of adults with epilepsy. *Neurology*. 1999;**53**(1):162.

56. Jacoby A, Baker GA, Steen N, et al. The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community Study. *Epilepsia*. 1996;**37**(2):148–161.

57. Ramos-Perdigués S, Baillés E, Mané A, et al. A prospective study contrasting the psychiatric outcome in drug-resistant epilepsy between patients who underwent surgery and a control group. *Epilepsia*. 2016;**57**(10):1680–1690.

58. Mehdizadeh, A., Barzegar, M., Negargar, S. *et al.* The current and emerging therapeutic approaches in drug-resistant epilepsy management. *Acta Neurol Belg* **119**, 155–162 (2019).

59. Devinsky O, Marsh E, Friedman De, et.al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol. 2016 Mar; 15(3):270-8.

60. LivaNova Inc. *VNS Therapy Physician's Manual*. LivaNova, Inc., 26-0009-7600/6 (U.S.) (2020).

61. Cyberonics Inc. *NeuroCybernetic Prothesis System Physician's Manual*. Cyberonics, Inc., 26-0006-0900/1 U.S. Domestic Version (2002).

62. Terry R, Tarver B, Zabara J. An implantable neurocybernetic prothesis system. *Epilepsia.* (1990) 31(Suppl.2):S33–7.

63. Cyberonics Inc. *VNS Therapy® System Physician's Manual*. Cyberonics, Inc., 76-0006-4400/0 (U.S.). (2015).

64. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: the head-heart connection. *Seizure.* (2014) 23:496–505.

65. 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

66. 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;20:57-63.

67. 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;7:491-500.

68. Lancman G, Virk M, Shao H, et al. Vagus nerve stimulation vs. corpus callosotomy in the treatment of Lennox-Gastaut syndrome: a meta-analysis. Seizure. 2013;22:3-8.

69. Musselman ED, Pelot NA, Grill WM. Empirically Based Guidelines for Selecting Vagus Nerve Stimulation Parameters in Epilepsy and Heart Failure. Cold Spring Harb Perspect Med. 2019 Jul 1; 9(7):a034264.

70. Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. Seizure. 2004;13:176-178.

71. Amar AP, Apuzzo MLJ, Liu CY. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. Neurosurgery. 2004;55:1086-1093.

72. Valencia I, Holder DL, Helmers SL, Madsen JR, Riviello JJ. Vagus nerve stimulation in pediatric epilepsy: a review. Pediatr Neurol. 2001;25:368-376.

73. Yang J, Phi JH. The Present and Future of Vagus Nerve Stimulation. J Korean Neurosurg Soc. 2019 May; 62(3):344-352.

74. Samala R, Agrawal M, Doddamani RS, et al. Pearls and Nuances in Vagal Nerve Stimulator Implantation Surgery. 2021 Nov 3;5:19-23.

75. Giordano F, Zicca A, Barba C, Guerrini R, Genitori L. Vagus nerve stimulation: surgical technique of implantation and revision and related morbidity. Epilepsia. 2017;58 Suppl 1:85–90.

76. 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. 2016 Jul; 18(1):97-104.

77. Kahlow H, Olivecrona M. Complications of vagal nerve stimulation for drug-resistant epilepsy: A single center longitudinal study of 143 patients. Department of Pharmacology and Clinical Neuroscience, Umeå University, Section of Neurosurgery, Umeå University Hospital, Umeå, Sweden. 15 July 2013.

78. Dietrich S, Smith J, Scherzinger C, et al. A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. Biomed Tech (Berlin). 2008; 53:104–11.

79. Ventureyra EC. Transcutaneous vagus nerve stimulation for partial onset seizure therapy. A new concept. Childs Nerv Syst. 2000; 16:101

80. Kraus T, Hosl K, Kiess O, et al. BOLD fMRI deactivation of limbic and temporal brain structures and mood enhancing effect by transcutaneous vagus nerve stimulation. J Neural Transm. 2007; 114:1485–93.

81. Peuker ET, Filler TJ: The nerve supply of the human auricle. **Clin Anat** 2002; 15:35–37

82. Badran BW, Austelle CW. The Future Is Noninvasive: A Brief Review of the Evolution and Clinical Utility of Vagus Nerve Stimulation. Novel Neurotherapeutics. Winter 2022; 20(1):3-7.

83. Panebianco M, Rigby A, Marson A, et al. - Vagus nerve stimulation for focal seizures. The Cochrane Database of Systematic Reviews. 2022, 7

84. Limura Y, Suzuki H, Mitsuhashi T, et al. - Effect of vagus nerve stimulation against generalized seizure and status epilepticus recurrence, Frontiers in Neurology, 2023, 14

85. Lamberink HJ, Otte WM, Blümcke I, et al. - Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. The Lancet Neurology. 2020, 19(9), 748-757

86. Drane DL, Pedersen NP. - Knowledge of language function and underlying neural networks gained from focal seizures and epilepsy surgery. Brain and Language. 2019, 189, 20-33

87. Zhu J, Wang X, Xu C, et al. - Comparison of efficiency between VNS and ANT-DBS therapy in drug-resistant epilepsy: A one year follow-up study. J Clin Neurosci. 2021, 90, 112-117

88. Wang HE, Woodman M, Triebkorn P, et al. - Delineating epileptogenic networks using brain imaging data and personalized modeling in drug-resistant epilepsy. Sci Transl Med. 2023, 15

89. Kawai K, Tanaka T, Baba H, et al. - Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord. 2017; 19(3):327-38

90. Colicchio G, Montano N, Fuggetta F, et al. - Vagus nerve stimulation in drug-resistant epilepsies. Analysis of potential prognostic factors in a cohort of patients with long-term follow-up. Acta Neurochir (Wien). 2012; 154:2237-40

91. Liu H, Yang Z, Meng F, et al. - Chronic vagus nerve stimulation reverses heart rhythm complexity in patients with drug-resistant epilepsy: An assessment with multiscale entropy analysis. Epilepsy Behav. 2018; 83:168-74

92. Wang H, Tan G, Zhu L, et al. - Predictors of seizure reduction outcome after vagus nerve stimulation in drug-resistant epilepsy. Seizure. 2019; 66:53-60

93. 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

94. Rong P, Liu A, Zhang J, et al. - An alternative therapy for drug-resistant epilepsy: transcutaneous auricular vagus nerve stimulation. Chin Med J. 2014; 127(2):300-4

95. Hajtovic S, LoPresti M, Zhang L, et al. - The role of vagus nerve stimulation in genetic etiologies of drug-resistant epilepsy: a meta-analysis. J Neurosurg Pediatr. 2022;1-14.8. Constantinescu V, Matei D,

96. Constantinescu V, Matei D, Constantinescu I, Cuciureanu DI. Cardiac autonomic modulation in drug-resistant epilepsy patients after vagus nerve stimulation therapy. Neurol Neurochir Pol. 2020; 54(4):329-336.

97. Sen A, Verner R, Valeriano J, et al. - Vagus nerve stimulation therapy in people with drug-resistant epilepsy (CORE-VNS): rationale and design of a real-world post-market comprehensive outcomes registry. BMJ Neurol Open. 2021; 3:e000218

98. Liu HY, Yang Z, Meng F, et al. - Preoperative heart rate variability as predictors of vagus nerve stimulation outcome in patients with drug-resistant epilepsy. Sci Rep. 2018; 8:1-11

99. Bauer S, Baier H, Baumgartner C, et al. - Transcutaneous Vagus Nerve Stimulation (tVNS) for treatment of drug-resistant epilepsy: A randomized, double-blind clinical trial (cMPsE02). Brain Stimul. 2016; 9(3):356-63

100. Zhang Y, Qian R, Fu XM, et al. - Efficacy analysis of vagus nerve stimulation for the treatment of drug-resistant epilepsy: A report of 110 cases. Chin J Neurosurg. 2019; 35:1059-63

101. Lagae L, Verstrepen A, Nada A, et al. - Vagus nerve stimulation in children with drug-resistant epilepsy: age at implantation and shorter duration of epilepsy as predictors of better efficacy? Epileptic Disord. 2015; 17(3):308-14

102. Benedetti-Isaac JC, Torres-Zambrano M, Fandiño-Franky J, et al. - Vagus nerve stimulation therapy in patients with drug-resistant epilepsy and previous corpus callosotomy, Neurocirugia (Astur). 2012; 23(6):244-9

103. Nalbantoğlu M, Ozkara C, Yeni N, et al. - Efficacy of Vagus Nerve Stimulation in Patients with Drug Resistant Epilepsy. J Turk Epilepsi Soc. 2014; 20:23-2

104. Verrier RL, Nearing BD, Olin B, et al. - T-wave alternans levels and cardiac electrical stability response to vagus nerve stimulation: a heart rhythm study. Heart Rhythm. 2016; 13(4):982-7.

105. Shan H, Zhang X, Zhao X, et al. - Clinical outcome and safety of vagus nerve stimulation in drug resistant epilepsy: a single center experience. Front Neurol. 2022;13:716487.

106. Bao EL, Chao LY, Ni P, et al. - Vagus Nerve Stimulation for Epilepsy: Long-term therapy outcomes in a Chinese population. Chin Med J. 2011; 124(15):2336-40.

107. Tanaka M, Toda K, Hayashida Y, et al. - Efficacy and safety of transcutaneous vagus nerve stimulation in drug-resistant epilepsy: a randomized clinical trial. Clin Neurophysiol. 2017; 128(6):992-9.

108. Danielsson, S., Viggedal, G., Gillberg, C., et al. (2008). Lack of effects of vagus nerve stimulation on drug-resistant epilepsy in eight pediatric patients with autism spectrum disorders: A prospective 2-year follow-up study. Epilepsy & Behavior, 12(3), 298-304.

109. Borghetti, D., Pizzanelli, C., Maritato, P., et al. (2007). Mismatch negativity analysis in drug-resistant epileptic patients implanted with a vagus nerve stimulator. Brain Research Bulletin, 73(1), 81-85.

110. Alshahrani, A., Eriksson, A., Røste, G. K., et al. (2020). Vagal nerve stimulation in children with drug-resistant epilepsy, 126(7), 896-898.

111. Manca, C., Coa, R., Murru, E., et al. (2023). Identification of Metabolic Biomarkers of Chronic Vagus Nerve Stimulation (VNS) in Subjects with Drug-Resistant Epilepsy (DRE). Epilepsia Open.

112. Panebianco, M., Rigby, A., Weston, J., et al. (2015). Vagus nerve stimulation for partial seizures. The Cochrane Database of Systematic Reviews, 4, CD002896.

113. Elliott, R. E., Rodgers, S. D., Bassani, L., et al. (2011). Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. Journal of Neurosurgery: Pediatrics, 7(5), 491-500.

114. Fisher, B., Desmarteau, J. A., Koontz, E. H., et al. (2021). Responsive Vagus Nerve Stimulation for Drug Resistant Epilepsy: A Review of New Features and Practical Guidance for Advanced Practice Providers. Frontiers in Neurology, 11.

115. Lattanzi, S., Cagnetti, C., Matricardi, S., et al. (2018). Palliative non-respective surgery for drug-resistant epilepsy. Brain and Development, 40, 512-513.

116. Müller K, Fabó D, Entz L, et al. Outcome of vagus nerve stimulation for epilepsy in Budapest. Epilepsia. 2010 Jul; 51(Special Issue: 10th Workshop on the Neurobiology of Epilepsy):98-101.

List of published scientific papers

1. Urian FI, Rizea RE, Costin HP, Corlatescu AD, Iacob G, Ciurea AV. "INTEGRATING THE 5-SENSE SCORE FOR PATIENT SELECTION IN VAGUS NERVE STIMULATION FOR DRUG-RESISTANT EPILEPSY" *Cureus.* 2024 Aug 28; 16(8):e68003.

2. Urian, FI., Corneliu Toader, Razvan-Adrian Covache Busuioc, Antonio-Daniel Corlatescu, Costin, H. P., Iacob, G., Alexadru Vlad Ciurea. . INTRODUCING THE INDEX OF RESPONSE TO STIMULATION (IRES): A NOVEL METRIC FOR ASSESSING VAGUS NERVE STIMULATION OUTCOMES IN DRUG-RESISTANT EPILEPSY. Medicina. 2025

3. Urian FI, Toader C, Busuioc R-AC, Glavan L-A, Corlatescu AD, Iacob G, Ciurea AV. "EVALUATING THE EFFICACY OF VAGUS NERVE STIMULATION ACROSS ‘MINOR’ AND ‘MAJOR’ SEIZURE TYPES: A RETROSPECTIVE ANALYSIS OF CLINICAL OUTCOMES IN PHARMACORESISTANT EPILEPSY" *Journal of Clinical Medicine*. 2024; 13(14):4114.