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NEUROMODULATION IN EPILEPSY: AN UPDATED REVIEW AND FUTURE PERSPECTIVES

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Abstract: Objective: Evaluate and synthesize the most recent scientific evidence on neuromodulation techniques used in the treatment of epilepsy, focusing on recent advances and future perspectives. **Methodology:** Narrative bibliographic review using the PubMed database, using the search terms "Neuromodulation", "Transcutaneous Electric Nerve Stimulation", "Deep Brain Stimulation", "Vagal Nerve Stimulation", "Epilepsy", associated with the Boolean operators "OR" and "AND", resulting in 982 articles, of which only 18 became official sources of the study after applying the inclusion and exclusion criteria. **Discussion:** Studies demonstrate that neuromodulation techniques are effective and safe in reducing the number of seizures in patients with epilepsy. Furthermore, it has direct effects on quality of life and a greater probability of survival of patients, especially those with epilepsy refractory to drug treatment **Final Considerations:** The lack of specific guidelines, such as intensity and frequency of stimulation, results in heterogeneous long-term effects. Therefore, studies are needed to understand the factors that influence these effects to develop even more effective stimulation protocols.

Keywords: Epilepsy, Neuromodulation, Deep Brain Stimulation, Vagus Nerve Stimulation.

INTRODUCTION

Epilepsy is a chronic neurological condition that affects around 50 million individuals globally, according to data from the World Health Organization (WHO). It is characterized by the occurrence of recurrent seizures, with a third of these individuals demonstrating resistance to conventional antiepileptic pharmacological treatments. Furthermore, a portion of these patients do not present themselves as suitable candidates for ablative surgical interventions (KUSYK D.

et al., 2022). In this scenario, neuromodulation techniques, such as deep brain stimulation and vagus nerve stimulation, emerge as emerging strategies for a more effective therapeutic response.

In recent years, studies have evaluated the impact of these techniques on the survival and quality of life of patients with epilepsy. Although the literature is still scarce regarding the psychological impact of these interventions (KUSYK D. et al., 2022), there is growing evidence of their beneficial effect on the survival of patients with epilepsy refractory to pharmacological treatments (ZHANG L. et al., 2023).

Research into neuromodulation for epilepsy has revealed promising results. Both an increase in response to pharmacological treatments and a reduction in the frequency of epileptic seizures are observed in patients undergoing neuromodulation (KUSYK D. et al., 2022). Additionally, an increase in the survival of these individuals was reported, with a probability of surviving beyond 10 years estimated at 98.45% (ZHANG L. et al., 2023). Therefore, the need for more in-depth studies on neuromodulation, covering the investigation of the affected brain areas, the necessary stimuli and intensities, among other pertinent variables, becomes evident (CAO, P. et al., 2023).

The application of neuromodulation in the management of epilepsy demonstrated significant rates of seizure reduction and response to treatment, superior to other neurostimulation modalities (KUSYK D. et al., 2022). Specifically, for patients with resistance to pharmacological treatments, vagus nerve stimulation (VNS), in conjunction with best medical practices, has been shown to be superior in improving health-related quality of life in patients aged 16 to 75 years with resistant epilepsy. to medications, compared to best medical practice alone (ZHANG L. et. al., 2023). Other investigations corroborate the combined effectiveness of pharmacological treatment and neuromodulation.

The central purpose of this review was to evaluate and condense the most recent scientific evidence regarding neuromodulation techniques used in the management of epilepsy, with a particular emphasis on recent advances and future perspectives in this field. This objective was based on the emerging need to explore effective therapeutic alternatives, especially for those patients who demonstrate resistance to conventional antiepileptic treatments or who are not ideal candidates for surgical interventions. Neuromodulation techniques, including deep brain stimulation and vagus nerve stimulation, have shown promising improvements in the quality and life expectancy of patients with epilepsy. However, there is still a significant gap in understanding the impact of these techniques on patients' psyches, as well as the specificities related to the affected brain areas, the necessary stimuli, intensities and other pertinent variables.

METHODOLOGY

This is a narrative-type literary review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "What are the recent advances and future perspectives of neuromodulation techniques in the treatment of epilepsy, and how have these approaches impacted the effectiveness of the treatment and the quality of life of patients?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients diagnosed with epilepsy who are being treated or are candidates for treatment with neuromodulation techniques, including deep brain stimulation, vagus nerve stimulation and other emerging approaches

with the aim of evaluating the effectiveness of such techniques in controlling epileptic seizures and improving patients' quality of life, as well as the future perspectives of these approaches.

The searches were carried out by searching the PubMed Central (PMC) database. The search terms were used in combination with the Boolean term "AND" and "OR" through the search strategy: ((Neuromodulation) OR (Transcutaneous Electric Nerve Stimulation) OR (Deep Brain Stimulation) OR (Vagal Nerve Stimulation)) AND (Epilepsy). From this search, 982 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in English published between October 2022 and October 2023 that addressed the themes proposed for this research, review and meta-analysis studies, observational studies, clinical trials, and made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. After thorough analysis, a total of 48 potentially relevant articles were selected and, after a secondary analysis, were reduced to a total of 18 articles to compose the present study.

DISCUSSION

Epilepsy is one of the most prevalent chronic neurological diseases, affecting millions of people around the world (SHAN M. et al., 2022). Epileptic seizures can lead to neuronal death, promoting epileptogenesis and the subsequent occurrence of seizures. The proposed mechanisms for epileptogenesis involve changes in synapses, neurotransmitters, receptors, oxidative stress, mitochondrial dysfunction, cytokine signaling and apoptosis. There is a growing association between the development of epilepsy and the presence of oxidative stress and the overproduction of reactive oxygen species (ROS). Oxidative stress induces neurological changes such as inflammation, neurodegeneration and lowering the seizure threshold, resulting in epileptogenesis. Oxidative stress, by altering calcium homeostasis, accelerates the onset of seizures, neurodegeneration and neuronal excitability. Experimental evidence also indicates that brain inflammation is associated with epilepsy, being observed in both animal models of epilepsy and humans (MADIREDDY S.; MADIREDDY S., 2023)

According to Shan, M. et al. (2022), drug-resistant epilepsy (DRE) is characterized by the therapeutic failure of at least two anticonvulsant drugs selected and administered appropriately and tolerated by the patient. Surgery is considered effective for DRE, encompassing resection, disconnection and neuromodulation techniques. When resection is not feasible or is not efficient, neuromodulation is indicated.

The use of neuromodulation in the treatment of refractory epilepsy, especially when considering vagus nerve stimulation therapy, is widely recognized for promoting significant improvements in the control of seizures. (BAGIĆ A. et al., 2023). A study conducted by Shan M. et al. (2022), demonstrated the effectiveness of vagus nerve stimulation, revealing that 26 patients undergoing this technique showed a reduction in the number of seizures per month, in contrast to 9 patients who had an increase and 10 who did not exhibit changes in the frequency of episodes monthly seizures. Additionally, using McHugh's classification at the end of the study, the researchers showed that, from the group with reduced seizure frequency, 11 patients achieved a reduction of 80-100%, 11 of 50-79% and 4 of less than 50%.

According to Zhang L. et al. (2023), an analysis of a cohort of patients aged 0 to 17 years with refractory epilepsy indicated that

the survival of those undergoing vagus nerve stimulation therapy, in addition to treatment with anticonvulsant medications, showed a greater probability of survival (92, 65%) over 10 years, compared to the exclusive use of drug therapy (89.27%). However, the survival of patients who underwent brain surgery for epilepsy, associated with the use of anticonvulsants, was even higher (98.45%) in the same time window, compared to vagus nerve stimulation.

Although studies have proven the efficacy and safety of vagus nerve stimulation therapy in patients with resistant epilepsy, as reported by Bagić A. et al. (2023), there remains a gap regarding the existence of specific guidelines for implementing this technique that maximize results. Consequently, several patients may be receiving treatment without achieving maximum possible effectiveness. In an effort to fill this gap, Bagić A. et al. (2023) conducted a randomized, double-blind clinical trial with patients treated for refractory epilepsy. The results indicated the possibility of achieving an ideal dose of vagus nerve stimulation (1.5 mA, 500 μs, 20 Hz and 10% duty cycle - 30 seconds on and 5 minutes off) to obtain the best therapeutic response in 3 months. or less. It has been observed that patients who receive regular increments in the intensity of vagus nerve stimulation, with increased output current and stable pulse width, compared to other stimulation parameters held constant, are more likely to achieve this target dose.

Deep brain stimulation (DBS), developed between the 1970s and 1980s, also presents itself as an innovative approach for the treatment of refractory epilepsy, through the stimulation of specific brain targets. Although the exact antiepileptic mechanism of ECP has not yet been fully elucidated, several clinical reports attest to its effectiveness in the management of epilepsy (YAN H. et al., 2023). According to an editorial by Cao P. et al. (2023), neuromodulation of specific regions in the epileptogenic network may confer therapeutic benefits to patients with refractory epilepsy.

Different targets have been investigated, including the anterior nucleus of the thalamus (NAT), the hippocampus, the subthalamic nucleus (STN), the cerebellum, among others; Each of these sites has unique connections with cortical and subcortical structures, which makes them relevant for the propagation of seizures. Furthermore, it is recognized that neuromodulation can induce a 30–40% reduction in seizure incidence after 3 months of treatment, and the majority of patients experience a greater than 50% decrease in seizure frequency (MADIREDDY S.; MADIREDDY, 2023).

In agreement, Dague KO et al. (2023) mention that DBS at the NAT level is a therapeutic option for patients with difficult-to-control epilepsy. A cohort study, published by the same authors in 2023 with 13 patients, evaluated the anticonvulsant efficacy of ANT ECP, with pre- and post-implantation analyzes of the device, measuring the frequency of seizures at 6, 12 months and during the last follow-up, where the average number of crises throughout the study was calculated. The results revealed that approximately 54.5% of participants experienced a decrease in seizures. In three patients, a greater than 50% reduction in seizure frequency was observed, while only one patient showed a significant decline in executive functions, a cognitive effect attributed to DBS.

Similarly, Tran TPY et al. (2023) noted that NTA ECP was approved for the treatment of refractory focal epilepsy following a large randomized, double-blind, placebo-controlled, parallel-group clinical trial. Considering that the NTA is a crucial node in the Papez circuit, ECP in this region may decrease cortical excitability or stop

the spread of focal seizures to cortical areas. Furthermore, Tran TPY et al. (2023) evaluated the acute effects of high-frequency insular stimulation on interictal epileptiform discharge rates in patients with refractory epilepsy, concluding that the short-term effects of high-frequency insular radiation and ECP on interictal epileptiform discharge rates in patients with refractory epilepsy were not uniform, highlighting the need for additional studies to examine factors that influence these heterogeneous effects, such as stimulation frequency.

Heart rate variability (HRV) is a biomarker that reflects the balance between the sympathetic and parasympathetic nervous systems and is capable of assessing general well-being, physical and mental resilience, and life expectancy in individuals with epilepsy. In epileptic patients, a dysregulation of this balance is observed, which increases the risk of morbidity and mortality. Thus, reduced HRV values are associated with inadequate responses to physical and mental stress. Lorincz K. et al. (2023) demonstrated that patients with epilepsy resistant to pharmacological treatments and undergoing DBS of the anterior thalamic nucleus may experience an increase in HRV, indicating a positive influence on autonomic regulation.

In this context, Lorincz K. et al. (2023) performed a retrospective analysis of medical records and electrocardiographic data from 30 patients with drug-resistant epilepsy, collected during video-electroencephalography monitoring sessions at two epilepsy centers in Hungary, between 2011 and 2019. The authors concluded that ECP -NTA is a safe treatment for patients with drug-resistant epilepsy ineligible for resective surgery, as the improvement in HRV suggests that NTA stimulation may have direct neuromodulatory effects on the autonomic centers of the nervous system.

The study reported by Schulze-Bonhage A. et. al (2023), emphasizes the effectiveness of epicranial focal cortex (FCS) stimulation using the EASEE System, an implantable device developed for patients with a predominant seizure focus. This method demonstrated a significant reduction in seizure frequency, marking a promising direction for treatment. The study results reveal a heterogeneous response to FCS, suggesting the need for personalized stimulation protocols considering individual patient characteristics and crisis foci. Despite the limitations of being non-randomized and uncontrolled studies, the promising results invite additional research to refine these techniques and explore their long-term efficacy and safety.

Responsive neural stimulation (RNS) may also be a valuable neuromodulation technique in the treatment of epilepsy. The RNS system operates a unique "closed" system of electrocorticography-triggered stimulation for seizure control. In contrast to other neuromodulation devices such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS), the RNS system is a "closed" system that includes a cranially fixed neurostimulator connected to one or two depth electrodes. or cortical rowing electrodes. Kusyk D. et al., (2022) showed a success rate comparable to other neuromodulation modalities. The meta-analysis suggests that despite limitations such as publication bias, RNS offers a significant therapeutic option for a group of patients with few alternatives, where resective or ablative surgery is not an option. Advances in this area include the improvement of detection and stimulation algorithms, as well as the integration of more adaptive and personalized systems for seizure control.

Oxidative stress is both a cause and a consequence of the progression of epilepsy. Clinical and experimental studies have demonstrated an association between levels

of oxidative stress biomarkers and neuronal damage, which can lead to the development of subsequent seizures in a chain reaction. Therefore, antioxidant therapies aimed at mitigating oxidative stress may be beneficial in controlling seizures in patients with drug-resistant epilepsy. Several studies highlight antioxidant agents, including the ketogenic diet and the intake of vitamins, polyphenols and flavonoids, which act to reduce levels of oxidants, contributing to the reduction of seizures and epileptic damage.

FINAL CONSIDERATIONS

This study highlights the growing role of neuromodulation techniques in the treatment of epilepsy, a complex neurological condition characterized by recurrent seizures. Recent advances in neuromodulation, including vagus nerve stimulation (VNS) and deep brain stimulation (DBS), have demonstrated significant benefits in reducing the frequency and severity of seizures, thereby improving the quality of life and prognosis of patients with epilepsy. In addition to these established techniques, emerging responsive neural stimulation (RNS) have shown promising results. This technique represents an important advance in personalizing epilepsy treatment by adapting to the patient's brain activity to provide precise therapeutic stimulation. The efficacy and safety of these new neuromodulation modalities, especially long-term, are areas of active and critical research. However, the variability of short-term neuromodulation effects points to the need for more specific and standardized guidelines. The intensity, frequency and duration of stimulation need to be optimized for each patient, which requires a deeper understanding of the factors that contribute to the heterogeneous effects observed. Future studies must focus on identifying these factors and developing more effective stimulation protocols, aiming to maximize the therapeutic benefits of neuromodulation for patients with epilepsy. The importance of continuing research in neuromodulation is highlighted, with the aim of improving existing techniques and developing new approaches that can offer better results for patients. Integrating these techniques into standard epilepsy treatment has the potential to significantly transform the management of the condition, offering new hope and a better quality of life for affected patients.

REFERENCES

BAGIĆ, Anto I. et al. ASCEND: A randomized controlled trial of titration strategies for vagus nerve stimulation in drug-resistant epilepsy. **Epilepsy & Behavior**, v. 145, p. 109333, 2023.

CAO, Peng et al. Network-guided neuromodulation for epilepsy: Unveiling the pathway to personalized therapy. **Journal of Translational Internal Medicine**, v. 11, n. 3, p. 203-205, 2023.

DAGUE, Karmele Olaciregui et al. DBS of the ANT for refractory epilepsy: A single center experience of seizure reduction, side e effects and neuropsychological outcomes. **Frontiers in Neurology**. v.14, p. 1106511, 2023.

DO PRADO, Henrique Jannuzzelli Pires et al. Predictive factors for successful vagus nerve stimulation in patients with refractory epilepsy: real-life insights from a multicenter study. **Frontiers in Neuroscience**, v. 17, e1210221, 2023.

IIMURA, Yasushi et al. Effect of vagus nerve stimulation against generalized seizure and status epilepticus recurrence. **Frontiers in Neurology**, v. 14, e1258854, 2023.

ILYAS, Adeel et al. Optimal targeting of the anterior nucleus of the thalamus for epilepsy: a meta-analysis. **Journal of Neurosurgery**, v. 137, n. 6, p. 1582-1590, 2022.

KUSYK, Dorian et al. Systematic Review and Meta-Analysis of Responsive Neurostimulation in Epilepsy. **World Neurosurg**, v.167, p. 70-78, 2022.

LORINCZ, Katalin et al. Effects of anterior thalamic nucleus **DBS on interictal heart rate variability in patients with refractory epilepsy.** Clin Neurophysiol, v. 147 p. 17-30, 2023

MADIREDDY, Sahithi; MADIREDDY, Samskruthi. Therapeutic Strategies to Ameliorate Neuronal Damage in Epilepsy by Regulating Oxidative Stress, Mitochondrial Dysfunction, and Neuroinflammation. **Brain Sciences**, v. 13, n. 5, p. 784, 2023.

OOI, Qian Yi et al. Alteration of Excitation/Inhibition Imbalance in the Hippocampus and Amygdala of Drug-Resistant Epilepsy Patients Treated with Acute Vagus Nerve Stimulation. **Brain Sciences**, v. 13, n. 7, p. 976, 2023.

RASPIN, Christopher et al. An economic evaluation of vagus nerve stimulation as an adjunctive treatment to anti-seizure medications for the treatment of drug resistant epilepsy in the United States. **Journal of Medical Economics**. v. 26 n. 1 p. 189-199, 2023

ROUHANI, Ehsan et al. Suppression of seizure in childhood absence epilepsy using robust control of deep brain stimulation: a simulation study. **Scientific Reports**, v. 13, n. 1, p. 461, 2023.

SCHULZE-BONHAGE, Andreas et al. Focal cortex stimulation with a novel implantable device and antiseizure outcomes in 2 prospective multicenter single-arm trials. **JAMA Neurology**, v. 80, n. 6, p. 588 - 5986, 2023.

SHAN, Ming et al. Vagus nerve stimulation for drug resistant epilepsy: clinical outcome, adverse events, and potential prognostic factors in a single center experience. **Journal of Clinical Medicine**, v. 11, n. 24, p. 7536, 2022.

STAVROPOULOS, Ioannis et al., Neuromodulation in new-onset refractory status epilepticus. **Frontiers in Neurology**, v. 14, n. 14, p. 1195844, 2023.

TRAN, Thi Phuoc Yen et al. Acute Effects of High-Frequency Insular Stimulation on Interictal Epileptiform Discharge Rates in Patients with Refractory Epilepsy. **Brain Sciences**, v. 12, n. 12, p. 1616, 2022.

YAN, Hao et al. Deep brain stimulation for patients with refractory epilepsy: nuclei selection and surgical outcome. **Frontiers in Neurology**, v. 14, p. 1169105, 2023.

ZHANG, Lu et al. Comparison of long-term survival with continued medical therapy, vagus nerve stimulation, and cranial epilepsy surgery in paediatric patients with drug-resistant epilepsy in the USA: an observational cohort study. **The Lancet Child & Adolescent Health**, v. 7, n. 7, p. 455 - 462, 2023.