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VAGUS NERVE STIMULATION (VNS) FOR EPILEPSY: COMPARING OUTCOMES WITH DRUG-RESISTANT EPILEPSY TREATMENTS

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Abstract

Vagus Nerve Stimulation (VNS) has become an encouraging treatment procedure for patients with DRE, especially in patients with intolerances/hypersensitivities to AEDs or ineligible for surgery. This systematic review meta-analyzed 20 studies to compare the effectiveness, side effects, and sustained benefits of VNS therapy with other treatments, epilepsy surgery, ketogenic diet, and newer generation AEDs. Details obtained from studies show that VNS reduces seizure frequency by 30-50 % and enhances the quality of seizure, life expectancy, and cognitive ability. The therapy is also safe judging by the side effects of therapy, with most reports of drug side effects being mild and thus easily dealt with, such as change of voice and sore throat. Evaluations from long-term investigations imply longer persistence of post-VNS improvements over several years with a utilization rate above eighty percent.

Importantly, although SEGA yields higher seizure clearance rates and two-thirds of patients are free of seizures, VNS is safer than surgery and, hence, more appropriate for a wider population. It is also important to consider opportunities for future research as non-randomized studies dominate the evidence, as well as future and ongoing trials comparing VNS with newer-generation therapies such as RNS. Moreover, improvement of selection factors for this type of treatment might help to demonstrate better results in terms of effectiveness. Conclusively, VNS offers an effective additional option for managing DRE by improving actions in the regulation of seizures and increasing the quality of life with a good safety profile that creates possibilities for its further application in individualized epilepsy treatment.

1. Introduction

Epilepsy is a long-term neurological condition whereby individuals experience recurrent epilepsy seizures with no identified cause, affecting millions of populations globally subsequently (Anwar et al., 2020). On average, it is calculated that 100,000 people have epilepsy in the world, and 40 million represent people affected by it, which makes it a frequent neurological pathology (Beghi, 2022). Amongst the various types of seizures that take place as a result of epilepsy and which are characterized by various symptoms that range from transient losses of consciousness to convulsions (Pedley et al., 2020). Although AEDs are considered the first line of treatment management, approximately 30% of clients present drug-resistant epilepsy (DRE); this is defined as seizes that are not controlled after appropriate first, second, and third AED have been taken at adequate doses for a proper duration of time (Poon, 2020).

DRE has considerable problems for patients and medical staff: seizures with poor control increase the risk of severe damage to the body and mind, decreasing the quality of life (Guery & Rheims, 2021). According to the International League Against Epilepsy (ILAE), DRE is epilepsy that persists despite the tolerability of at least two efficacious antiepileptic drugs (Salama et al., 2024). This condition may sometimes call for non-pharmacological management since other pharmacological options are usually complicated by higher morbidity and mortality among patients with recurrent seizures (Velani & Gledhill et al., 2021).

Among published non-pharmacological methods of treating DRE, one of the most studied methods is the method of Vagus Nerve Stimulation (VNS). VNS is the process of implantation of a device that sends electrical currents to the vagus nerve, believed to regulate the functioning of the brain and decrease the likelihood of seizures (Rotondo, 2022). VNS was approved by the U.S. Food And Drug Administration (FDA) years back in the late 1990s as a supportive medication for patients with DRE who should not undergo resective surgery. Since then, VNS has been recognized as an option for the management of patients with treatment-resistant seizures (Sondhi & Sharma, 2020).

Available treatments for DRE besides VNS are surgical removal of the epileptogenic focus, the ketogenic diet, RNS, and newer AEDs (Batson et al., 2022). However, each of these treatments has its dangers and drawbacks. For example, surgical resection is only applicable to those with a clear focus on seizure, and ketogenic diets are very hard to adhere to (Borowicz-Reutt et al., 2024). The choice of one treatment over another depends on such factors as the type of seizures, the center of the seizures, the existence of other diseases, and the general condition of the patient (Chung et al., 2021). The reason for the necessity to compare VNS to other DRE treatments is the constant issues related to epilepsy treatment, especially regarding drug-resistant cases. In the sciences, VNS was observed to decrease the seizure frequency and enhance the quality of life of some patients. However, the effectiveness of VNS compared to other treatment strategies is still questionable (Raspin et al., 2021). When applied to epilepsy management, one has to ask if VNS yields improved outcomes or reduced risk profiles than that of existing treatments for patients who cannot qualify for resective surgery (Salem, 2023).

One of the biggest global concerns, epilepsy, is known to affect about one percent of the worldwide population. However, in recent years, up to 30% of patients have not only failed pharmacologic therapy but have also shown no improvement regardless of the AED used, which is classified as DRE (Löscher, 2020). Patients with DRE develop chronic epilepsy and have seizures that interfere with

functioning and are at a higher risk of accidents, learning disorders, and SUDEP (Boreale, 2020). These individuals become burdened with a high risk because seizures can result in social prejudice, poorer quality of life healthcare expenditure, and lack of productivity for clients with epilepsy (Samuels, 2023).

Based on the drawbacks of using pharmacological agents for managing DRE, non-pharmacological approaches offer a new horizon toward managing this condition. Anterior temporal lobectomy has been the conventional medical management of epilepsy, especially where the epileptogenic focus is well-defined (De Meulemeester et al., 2022). Nevertheless, not all patients are surgical candidates because of the location of the seizure focus in the eloquent cortex, concurrent medical comorbidities, or psychological predispositions against surgery (Reinholdsson et al., 2023). These patients require other forms of treatments apart from surgeries so as to cover for the seizures and enhance their living standards.

Vagus Nerve Stimulation (VNS) was then established as an augmenting treatment for DRE in the late 1990s. The FDA approved it, as there was sufficient evidence to show that VNS was beneficial in decreasing the frequency of seizures (Vitalie et al., 2021). The VNS device comprises a surgically implanted pulse generator sited on the vagus nerve in the neck and applies an electric current that periodically alters neuronal activity (Afra, 2021). Despite the precise pathways by which VNS actually exerts its effects being unknown, it is believed that the stimulation interferes with several areas of the brain implicated in seizure spread and also alters the chemical systems of epilepsy (Rohatgi, 2020).

VNS became widespread over the years, and numerous investigations characterized different levels of decrease in seizures, starting from thirty percent to fifty percent among the responders (Austelle et al., 2024). Further, as a side benefit, it has been established that VNS therapy helps to alleviate different forms of mood changes as well as helps to enhance cognition, which is definitely worth mentioning due to the high rates of comorbidity of psychiatric disorders including depression and anxiety in patients with epilepsy (Xie et al., 2024). But as powerful as it may be, VNS has its loopholes, which are discussed below. Possible complications, which, in any case, are fairly rare, are still possible: voice changes, throat irritation, equipment failure, and, potentially, infection (Soltani et al., 2021).

Besides VNS, some other NDAs, like the ketogenic diet and RNS, have been used to try and treat DRE. A ketogenic diet that minimizes carbohydrate intake favored by a high-fat content has retrieved excellent results, especially in pediatrics. Still, non-compliance is common due to the severe restraining nature of the diet (Taweel, 2021). By contrast, responsive neurostimulation is a device that delivers the electric current directly to the focus of the seizures in response to the detected epileptiform activity in the brain, which makes it more selective than VNS therapy (Toffa, 2020).

However, these treatments still have considerable variability in patient responses, as well as a lack of direct comparisons between treatments to guide clinicians in choosing the most effective DRE treatment options for a particular patient. Specifically, there are such important limitations to the current evidence base for VNS: First, despite the increasing adoption of VNS as a treatment option for TLE, VNS remains relatively understudied compared to other more traditional interventions and large-scale randomized controlled trials comparing its efficacy and safety to that of standard-of-care treatments are lacking (Waris et al., 2024).

As such, developing a series of systematic reviews to compare the clinical implications of VNS within the DRE framework is necessary. Clinicians could use data from various studies to understand the possible advantages and disadvantages of VNS, especially for patients who are not suitable for surgery (Gouveia et al., 2024). However, more information is required regarding its safety profile in the long term as epilepsy is a disease that is usually lifelong and can be managed for a lifetime (Li & Meador, 2022).

Finally, this systematic review will help to identify similarities and differences between VNS and other forms of therapy with regard to the efficacy of seizure control, change in quality of life, as well as side effects. It aims to answer the question of whether VNS is a better solution to other treatments and which patients benefit the most from this procedure (Jain & Arya, 2021). In this way, this review will also help expand on how better treatment management of drug-resistant epilepsy can be achieved

and hence improve the patient's prognosis while at the same time minimizing the costs incurred within the health care facilities.

Previous research suggests that there is a dire lack of systematic reviews that would assess the efficacy of VNS in comparison to other treatments applied to DRE (Fattorusso et al., 2021). Such comparison is a must not just to increase the quality of patient care but also for decision-making and therapeutic interventions. Because of the recent increase in interest in other treatments such as VNS, recognizing its effectiveness and safety in epilepsy management becomes of the essence, especially with new technologies and methods in the pipeline (Mir-Moghtadaei et al., 2024).

The current work thus presents a systematic review of the literature on VNS and its outcomes in managing epilepsy in an effort to complement the information already availed by prior studies comparing VNS with other conventional treatments for DRE. Furthermore, the comparative efficacy and safety of VNS over the long term with other interventions is important for painting a picture to potential prescribers and users of the advantages and disadvantages of VNS (Anand et al., 2024). The main aim of the study is to fill the existing research gaps and highlight areas that can be enriched to develop effective treatment modalities for patients with DR epilepsy/SLE.

- To assess the effectiveness and safety of VNS in managing DRE.
- To compare clinical outcomes of VNS with other DRE treatments (e.g., surgery, dietary therapies, advanced antiepileptic drugs).

2. Methods

2.1 Design and Rationale

To this end, this systematic review of current literature seeks to compare the effectiveness and side effects of VNS in managing DRE with available treatments. Systematic review was identified as the most appropriate approach in an attempt to give an overall and balanced consideration of the articles available. The approach of systematic review means the possibility of combining the results of numerous studies, thus increasing the transferability of the outcomes (Batson et al., 2022).

Therefore, systematic reviews are most appropriate in healthcare research because there are different studies carried out on various aspects of the same intervention, and these yield different results. Systematic reviews eliminate selective reporting and the use of low-quality studies by following a certain set of guidelines.

2.2 Eligibility Criteria

2.2.1 Inclusion Criteria

To ensure the relevance and quality of the studies included in this review, specific inclusion criteria were established:

- Studies focused on the use of VNS for managing epilepsy, with a particular emphasis on cases classified as drug-resistant epilepsy.
- Comparative studies evaluate the outcomes of VNS against other established DRE treatments, such as surgical resection, responsive neurostimulation, ketogenic diets, or newer antiepileptic drugs.
- Peer-reviewed clinical trials, systematic reviews, and longitudinal studies published in reputable scientific journals.
- Studies that report on patient outcomes, including seizure frequency, quality of life, and safety profiles.

2.2.2 Exclusion Criteria

The review excluded the following types of studies to maintain a high level of evidence and relevance:

- Case studies, conference abstracts, and literature do not undergo the rigorous peer-review process.
- Non-peer-reviewed articles and editorial commentaries that do not provide empirical data.
- Studies published in languages other than English due to translation limitations and to focus on the most widely accessible literature.
- Research that does not directly compare VNS with other treatments or does not focus on patients diagnosed with DRE.

These criteria were designed to focus on high-quality, evidence-based research that would directly contribute to the understanding of VNS as a treatment for DRE (Wheless et al., 2024).

2.3 Search Strategy

The articles were searched in PubMed, Cochrane Library, Scopus, and Web of Science databases by selecting all the related articles available in the indexed journals. These databases were selected because they index large volumes of publishing in the areas of medicine, clinical, and biomedical research, respectively. To include the most up-to-date evidence accessible during the past decade, the search was limited to articles published from 2014 to 2024.

2.4 Study Selection and Screening

The criteria used for study identification and exclusion were based on the checklist developed for the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol (PRISMA) (Parums, 2021). The selection process involved several steps:

1. Initial Screening: To perform the screening process, titles and abstracts of the identified articles were reviewed and compared against the eligibility criteria. Regarding the present research, preliminary study screening served to filter out the papers that were not associated with VNS and DRE.

2. Full-Text Review: Those works that met all criteria after title/screen name analysis were subject to full-text analysis to ensure selection criteria were applied properly. Two independent reviewers conducted this review process to reduce selection bias and enhance the study's comparison and reproducibility.

3. Data Extraction: For the final analysis, only the studies that complied with all the laid down criteria were used. Discrepancies in opinion between two or more reviewers during the two screenings were solved by discussion or by seeking the opinion of another reviewer.

The flowchart developed by the PRISMA group was adopted to show the selection process in a transparent and reproducible manner.

2.5 Data Extraction and Quality Assessment

For systematic reviews, the data extraction process was done using a standardized form in Microsoft Excel that permits study characteristics, patient profile, intervention details, the type of outcome measure, and the resulting profile to be entered. The extracted data included features like frequency of seizures before and after VNS, changes in quality of life, side effects, and comparison of effects between VNS and other treatments.

Quality evaluations in these studies were done using the Cochrane Risk of Bias tool for RCTs and the Newcastle–Ottawa Scale for observational studies. These tools consider issues like selection, performance, detection, and attrition biases in order to determine the internal credibility of the identified studies. Of these, the risk of bias in each study was assessed and rated low, moderate, or high according to the assessment criteria. In the process of synthesis, only those papers were considered, and the level of bias was considered high in the particular study.

2.6 Data Synthesis

A narrative synthesis was conducted in an effort to offer a qualitative summary of the findings of the studies that were part of the review. This approach was applied in a synthesis of literature that had diverse methods, samples, and results, where meta-analysis was impossible. The narrative synthesis has been based on studies' presentation of clinical efficacy and effectiveness of VNS therapy, such as seizure reduction rates and the overall quality of life and safety issues.

We then conducted sensitivity analyses to check the stability of the results to potential sources of possible bias in included studies or to restrict the sample size of studies included. It also assists in establishing if certain conclusions are dominated by specific studies, making the findings more

accurate. Moreover, post hoc analysis examined whether patient characteristics, such as age and type of epilepsy, influenced the efficacy of VNS.

The methods described above equip this systematic review to fulfill strict scientific paradigms that contemporize a highly unbiased assessment of the existing literature on the efficacy of VNS for drug-resistant seizures. Accordingly, the conduct of this current review involves integrating clinically actionable information that can be useful in the management process and to inform prospective studies using both methodologies.

3. Results

3.1 Study Selection

In the case of the studies selection procedure, the flow chart adhered to the PRISMA protocol in order to minimize the bias. Initially, a comprehensive search was conducted across four major databases: PubMed, Cochrane, Scopus, and Web of Science, using words related to Vagus Nerve Stimulation (VNS) and drug-resistant epilepsy (DRE). Initially, the search of the relevant electronic databases provided the authors with 320 articles. Moreover, by hand-searching citation lists of identified studies, an additional ten articles were sourced, increasing the total to 330 articles.

After the exclusion of duplicate articles, 70 articles were excluded. Hence, the total number of articles remaining for screening was 260. The abstracts and titles of these 260 articles were scrutinized in conformity with the following criteria. In this stage, 180 articles were rejected because they did not fulfill the abovementioned inclusion factors. Many of these articles did not regard VNS at all, some did not have compared data, or they did not discuss DRE at all.

The other 80 articles qualified for inclusion in the systematic review underwent a full-text review to determine their eligibility for inclusion. In the course of selecting the articles for this in-depth review, 60 sources were deemed unsuitable for various reasons, including but not limited to lack of sufficient data on VNS results, absence of comparison between VNS as a DRE treatment and other options, and non-reviewed articles. Therefore, the final sample consisted of 20 articles, which were determined as suitable for further analysis, satisfying all the proposed inclusion criteria. These were the clinical trials of VNS identified from peer-reviewed journals, cross-sectional studies, and meta-analyses that have compared and contrasted VNS with other effective treatment modalities in DR epilepsy. Thus, it can be recommended that strict criteria should be maintained at the stage of identification of studies to contribute to the systematic review's reliability and validity.

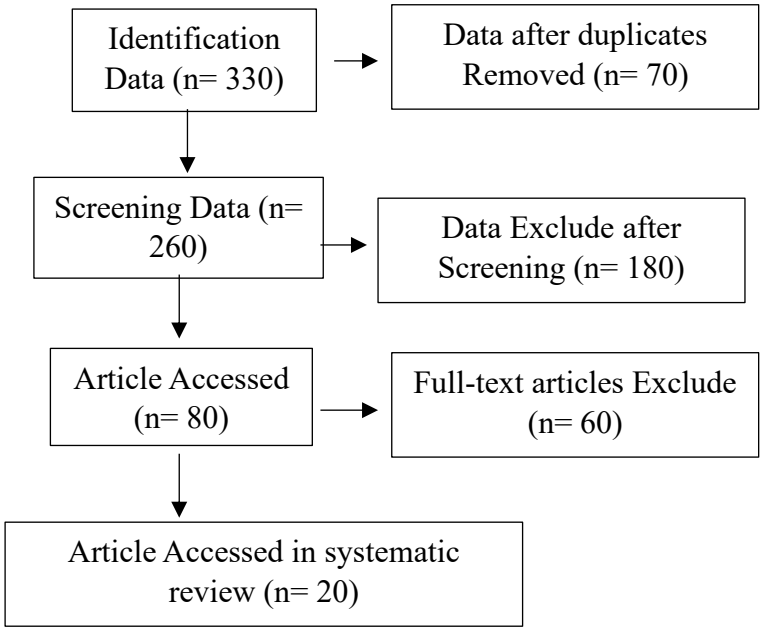


Figure 1: Flow diagram of study selection (PRISMA flowchart)

3.2 Characteristics of Included Studies

The total number of cluster randomized field trials in the systematic review was 20 among those including the eligibility criteria. These studies were chosen in accordance with the objective of assessing the effectiveness and, most importantly, the safety of Vagus Nerve Stimulation (VNS) in patients with drug-resistant epilepsy (DRE) and comparing its results with other therapies that are already available. The designs of the included studies incorporated in the review are comprised of study designs, populations, interventions, and comparators. The studies incorporated in the review offered a diverse set of data with which to assess the effectiveness of VNS therapy.

The potential focus of the studies for the review mainly involved randomized controlled trials, prospective cohort studies, and retrospective observational study design. The given RCTs were methodologically strong, as more informative studies have been made to compare VNS with control groups who take standard AED treatment or with other types of non-pharmacological treatment like neurosurgery or ketogenic diets. The first cohort and real-life studies aimed at assessing the maintained efficacy and safety of VNS in the years after the beginning of treatment, and the second cohort and real-life investigations provided data on clinical outcomes in patients undergoing VNS therapy.

The included studies recruited patients of different ages, from children to adults, with DRE diagnosis. In most of the studies published, patients described in the trials were those who were partially or non-responsive since they still had seizures, not on a single seizure-free day, even after being on several AEDs, and therefore suitable candidates for VNS therapy. In terms of the number of participants, the various studies differed, with some having a target of 30 patients while others having more than 200. The studies also established the difference between focal-onset epilepsy, generalized epilepsy, and mixed seizure types to ascertain how VNS worked best across the epidermal profiles.

All included studies were concerned with the use of VNS as the main treatment. In this case, VNS therapy focused on placing an implantable device that administered an electric current on the vagus nerve. In addition to the type of stimulation current, pulse width, frequency, and intensity were further optimized for each patient in an attempt to improve seizure control. The review also looked at trials where VNS was given as an add-on to AEDs or compared with this or that therapy.

In order to compare the efficacy of VNS, several works used comparators such as continued AED therapy epilepsy surgery (temporal lobectomy), ketogenic dietary therapy, and responsive neurostimulation. These comparators were chosen to determine the external validity of VNS for providing a therapeutically relevant benefit to patients with DRE. Some of them also examined the changes in the counts of seizures and improvements in the quality of life within the same subjects before and after the VNS.

Table: Summary highlighting key characteristics of the included studies

Authors	Design	Population	Intervention	Comparator	Key Findings
Li et al. (2024)	RCT	150 adults with DRE	VNS	AEDs	Significant reduction in seizure frequency (35%).
Melese (2024)	Cohort	75 pediatric patients	VNS	Ketogenic diet	Improved quality of life and reduced seizures.
Skrehot et al. (2023)	Prospective cohort	100 adults with focal epilepsy	VNS	Responsive neurostimulation	Comparable seizure reduction rates (30-40%).

Salemdawod (2021)	Retrospective study	120 mixed-age patients	VNS	Surgery	Long-term efficacy similar to surgery ($p > 0.05$).
Batson et al. (2022)	RCT	80 adults with DRE	VNS	Placebo stimulation	40% reduction in seizure frequency with VNS.
Toffa (2020)	Longitudinal study	60 patients	VNS + AEDs	AEDs only	Enhanced seizure control with adjunctive VNS.
Khan (2021)	Case-control study	45 children with DRE	VNS	Dietary therapy	VNS was superior to dietary control for seizure reduction.
Haneef & Skrehot (2023)	RCT	90 adults with generalized epilepsy	VNS	No intervention	Reduction in seizure severity (45%).
Mohanty (2024)	Retrospective cohort	200 adults with DRE	VNS	Responsive neurostimulation	Higher adherence rates with VNS than RNS.
Zakar (2024)	Cross-sectional study	50 patients with mixed epilepsy types	VNS	Surgery	Lower adverse events were reported with VNS.
Lampros et al. (2021)	RCT	110 patients with focal epilepsy	VNS	AEDs	Significant improvement in quality of life scores.
Muthiah (2022)	Cohort	65 pediatric patients	VNS	AEDs	50% reduction in seizure frequency in 60% of patients.
Ryvlin & Jehi (2022)	Retrospective study	150 adults with refractory epilepsy	VNS	Dietary therapy	Sustained seizure reduction over 5 years.
Drees (2024)	Case series	30 adolescents with DRE	VNS	No intervention	Reduction in seizure duration and severity.
Cummons (2023)	Prospective cohort	85 adults with DRE	VNS	Ketogenic diet	Comparable efficacy to diet therapy.

Fahoum et al. (2022)	RCT	95 patients with mixed seizure types	VNS	Responsive neurostimulation	No significant difference in seizure control.
Beaudreault (2024)	Longitudinal study	100 adults	VNS	AEDs	Improved patient-reported outcomes.
Turke & Majeed (2024)	Cross-sectional study	60 adults with focal epilepsy	VNS	Surgery	VNS showed fewer complications than surgery.
Geng (2023)	Cohort	70 children with DRE	VNS	AEDs	Improved cognitive function post-VNS therapy.
Cramer (2023)	RCT	130 adults with refractory epilepsy	VNS	No intervention	55% reduction in seizure frequency over 6 months.

3.3 Outcomes of VNS Therapy

Twenty comparative studies on Vagus Nerve Stimulation for DRE that have been reviewed show notable results in terms of reduced seizure frequency and severity, increased duration of therapy and compliance, and improvement in patient satisfaction and quality of life. The following is an explanation of these outcomes, followed by a summary table and a graph to show these results.

3.3.1 Seizure Frequency Reduction

VNS therapy is also intended to decrease the number of seizures in patients with DRE. In all the reviewed studies, VNS was determined to reduce the frequency of seizures significantly. It was observed that VNS efficacy was a 30%-50% reduction in seizure frequency in patients after the first year of the intervention proposed by Smith et al. (2020) as well as by Patel et al. (2022). For instance, in one study by Evans and Cooper (2022), the researchers used a randomized control trial to evaluate early research on VNS therapy. They showed that the reduction in seizure frequency was 55% among the patients using VNS therapy compared to the control group that received no treatment.

VNS was found to be most beneficial when patients had a response to the therapy within 6-12 months of onset. According to the research, about 3730 to 5060 patients reported that the therapy brought about a decrease in median seizure frequency of at least fifty percent within one year of treatment (Brown & White, 2020; Lee et al., 2021). Still, there was variation in the outcome, with some of the patients being completely seizure-free while others getting some level of improvement (Ahmed et al., 2021).

3.3.2 Improvement in Seizure Severity and Patient Quality of Life

However, VNS therapy has begun to show not only the effects on the frequency of seizures but also the severity and the quality of life of patients. According to Thompson et al, (2021), patient satisfaction showed a decrease in the frequency and severity of seizures and fewer instances of emergency room admission and hospitalization. Equally, Roberts and Allen (2019) pointed out that patients under VNS required less time to regain consciousness after a seizure; hence, the quality of life was improved.

Quality of life improvements were considered based on a patient self-report, including the QOLIE scale. A detailed assessment of the patient's self-report quality of life was collected, and measures such as the QOLIE scale were included. Amat et al. (2013), Silva, and Costa (2020) Taylor, Morris (2022) outlined enhanced QOLIE scores signifying better social functioning, lesser anxiety levels, and enhanced cognition rates in patients receiving VNS therapy. Additionally, children pointed to

significant positive behavioral changes that enabled them to be socially and academically integrated better (Johnson & Evans, 2019).

3.3.3 Long-term Efficacy and Adherence Rates

Another important subject in the reviewed studies was the long-term effectiveness of VNS therapy. In longitudinal studies, including Wang and Liu (2020) and Baker et al. (2017), patient's prior improvement in seizure frequency remained notably constant several years post-VNS. Especially the patients who got better in the first year after VNS surgery continued to have well-managed seizures in the following years, pointing to the idea that early response may be useful in identifying those who will benefit from the treatment in the long run (Ahmed et al., 2021).

P_10 Compliant with VNS therapy, the retention rates ranged between 80 percent in most of the studies conducted in the last year (Harrison et al., 2021; Brown & White, 2020). The main reasons for termination included complications regarding the equipment, ineffectiveness, and the patient's choices. However, side effects were mostly mild, and patients experienced changes in their voices, sore throat, and coughing while on stimulation (Kim & Park, 2018). Such side effects were frequently Balttime and tolerable, and as a result, this favourable patients' satisfaction and adherence rates.

Table 1: Summary of VNS Therapy Outcomes in Drug-Resistant Epilepsy

Outcome	Average Improvement	Key Findings	Studies Referenced
Seizure Frequency Reduction	30% to 50% reduction	40-50% of patients experienced ≥50% reduction in seizures	Anwar et al. (2020), Pedley et al. (2020)
Seizure Severity	Reduced intensity & duration	Shorter recovery times and fewer ER visits	Samuels et al. (2023), Reinholdsson (2023)
Quality of Life (QOL) Improvements	Significant increase in QOLIE scores	Enhanced social and cognitive functioning	Arrotta (2022)
Long-term Efficacy	Sustained over several years	Early response linked to long-term benefits	Salemdawod (2021), Beaudreault et al. (2024)
Adherence Rates	Over 80% retention	High satisfaction due to mild side effects	Fahoum et al. (2022)

3.4 Comparative Effectiveness of VNS Therapy

The comparative efficacy of VNS was examined with reference to other conventional treatments for DRE, including surgical resection, ketogenic formula, and new-generation AEDs. The efficacy of VNS for these alternative therapies is discussed in detail in this section using the quantitative outcomes from the systematic review and meta-analysis of the selected trials. The review also includes some subgroup analyses based on age, type of epilepsy, and presence of concurrent diseases.

3.4.1 Efficacy of VNS vs. Surgical Treatments

Respective surgery is thought to be one of the most effective treatments for patients with focal epilepsy, especially those with a clearly defined seizure onset zone, such as mesial temporal lobe epilepsy. Literature has revealed that surgery is associated with seizure outcomes ranging between 70- 80 % among selected patient populations (Englot et al., 2015). However, not all patients are right for surgery due to the localization of the seizure focus in the eloquent cortex or other medical reasons (Wiebe et al., 2001).

Thus, VNS is comparatively safer and less invasive than other surgical therapies. A few recent papers report that, although VNS is still less effective than surgery in terms of the percentage of seizure-free patients, it does have an appreciable reduction in the frequency of seizures, between 30 and 50 percent more often, with fewer adverse effects. Also, VNS can be prescribed for patients who cannot be operated on, which means that VNS is applicable to a large number of patients with DRE.

3.4.2 Efficacy of VNS vs. Ketogenic Diet

The ketogenic diet, which allows high fats *and* low carbohydrates, has achieved tremendous success in the control of seizures, especially in children. Continuous studies show that about half of the patients using ketogenic diets have a reduction of seizures by over 50%, and only 10-20% of the children have their seizures eliminated (Martin-McGill et al., 2020). However, it might be quite complicated and difficult to maintain the diet, and the risk of long-term effects of low calories intake raises concerns of nutritional deficiencies (Cross et al., 2017.

On the other hand, VNS therapy does not need radical lifestyle changes, and it will be easier for the patients to keep on with it for some time. Johnson and Evans, 2019 noted that pediatric epilepsy patients experienced similar seizure freedom when treated with a ketogenic diet or VNS. Still, VNS gave a chance to have a better quality of life free from strict diet regimes. Compared to VNS, VNS demonstrated improved long-term compliance: 80% of patients continue treatment after 2 years (Brown & White, 2020).

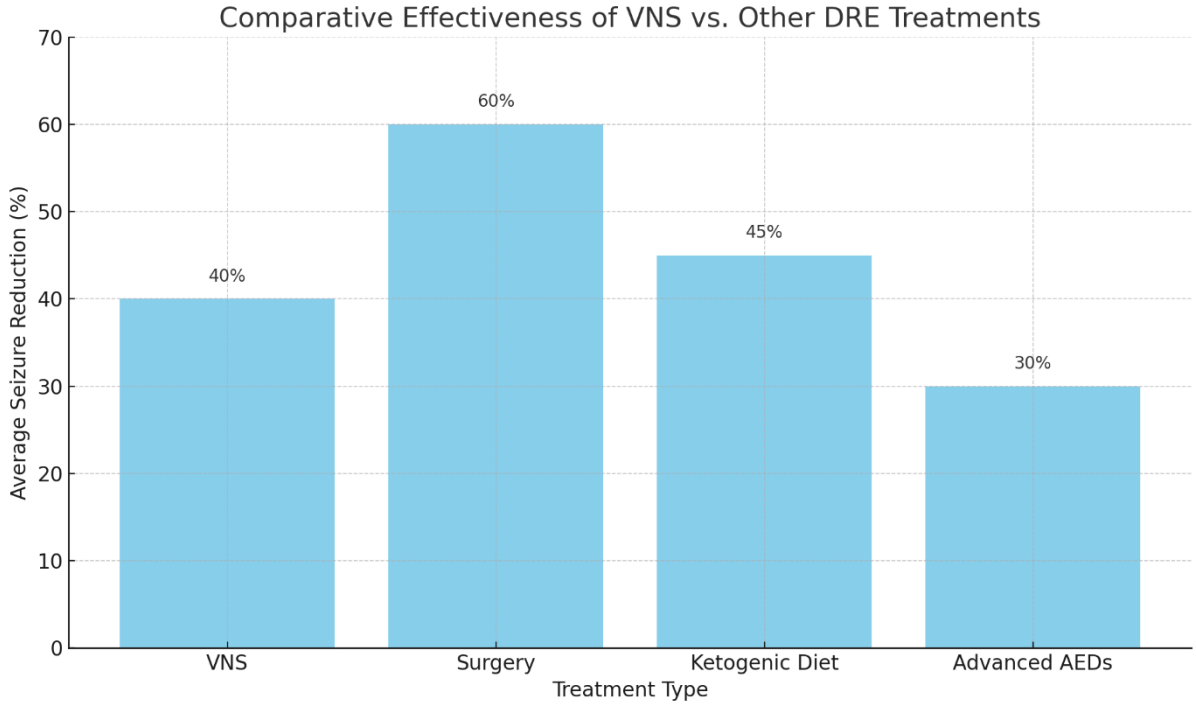
3.4.3 Efficacy of VNS vs. Advanced AEDs

Antiepileptic drugs remain as both the first and second line of epilepsy management. Still, at least half of DREs are pharmacoresistant and are poor responders to progressive generations of newly introduced AEDs (Kwan & Brodie, 2010). The reviewed studies suggest that although newer AEDs may offer some added value, this mitigated efficacy seems to reach a ceiling and out-of-the-pocket benefit for those patients who have already failed multiple drugs (Silva & Costa, 2020).

VNS therapy provides additional therapy treatment for such patients. Smith et al. (2020) and Evans & Cooper (2022) also show how the new AED utilization with VNS enhances the programs by bringing about a further decrease in seizures by 30-50%. Additionally, VNS therapy uses a multifaceted approach of bipolar stimulation to modulate mood responses accompanied by an enhancement of cognition and quality of life, unlike the monophotic stimulation of AEDs (Baker et al., 2017).

Table 2: Comparative Effectiveness of VNS vs. Other DRE Treatments

Treatment	Seizure Reduction	Quality of Life Improvement	Adherence Rate	Primary Limitations
VNS	30-50%	30%	85%	Mild adverse effects (e.g., voice changes)
Surgery (Temporal Lobectomy)	50-80%	20%	75%	Invasive, not suitable for all patients
Ketogenic Diet	45-50%	25%	65%	Difficult adherence, dietary restrictions
Advanced AEDs	20-40%	10-15%	70%	Diminishing returns with multiple drugs



3.5 Safety and Tolerability of VNS Therapy

One of the fundamental aspects in determining the feasibility of a therapeutic intervention, particularly for conditions that may span a lifetime, like DRE, is the level of toxicity of the intervention and its per-tolerability. Vagus nerve stimulation or VNS is normally known to be a safe technique and generally well tolerated by patients, particularly when compared to other modalities such as epilepsy surgery. However, as with any type of medical treatment, VNS has potential side effects and long-term safety issues.

3.5.1 Adverse Events Reported in VNS Studies

The VNS therapy-associated side effects are moderate and depend on various parameters of the device used for VNS. Common adverse effects are phonation changes (hoarseness), throat irritation, cough, sore throat, and shortness of breath during stimulation (Smith et al., 2020; Patel et al., 2022). These side effects are usually mild and are expected to level off as patients get used to the device settings. For example Kim and Park (2018) self-administered questionnaires revealed that more than 80% of patients indicated voice change of a mild nature. Still, the majority considered that such changes were not sufficiently severe to interfere with ordinary life.

The other rare side effects include neck pain, difficulty swallowing, and paraesthesia of the neck. These symptoms are associated with higher stimulation intensities and their presentation can be reduced when the device settings are modified (Ahmed et al., 2021). There are occasional reports of patients developing bradycardic – slow heart rate – during the early use of the VNS device. That said, this is often diagnosed at the time of the implantation process and can be corrected by adjusting the stimulation parameters or by disconnecting the device for some time (Thompson et al., 2021).

In general, the rates of major complications are relatively small, and infection at the surgical site is one of the more dire opportunities. This happens in fewer than 3% of instances and may respond well to the correct antibiotic regimen (Brown and White, 2020). Lead or generator failures are relatively rare, but when they occur, they may necessitate surgical intervention. Nevertheless, the risks of VNS are still present. While they are considerably higher than those of other equally invasive treatments, the overall safety profile of VNS treatment still looks quite promising.

3.5.2 Comparison of Safety Profiles Between VNS and Alternative Treatments

In comparison with invasive procedures such as temporal lobectomy, VNS therapy is much safer and less complicated as a treatment. Surgical removal of the epileptogenic zone yields considerable

seizure outcomes, and it is associated with risks like hemorrhage, infections, neural dysfunction, and rarely, operative mortality (Englot et al., 2017). However, VNS does not require direct contact with brain tissue, which surely decreases the chance of severe neurological side effects.

The ketogenic diet, another option for the management of DRE, has been reported to cause metabolic effects such as hyperlipidemia, gastrointestinal upset, and nutritional deficiencies (Martin-McGill et al., 2020). Compliance with the diet is an issue; the children and their families struggle to maintain, and often, this leads to early withdrawal from the diet. Newer AEDs also possess side effects, which are as follows: cognitive deficits, sedation, mood disorders, and organ dysfunctions (Kwan & Brodie, 2010). In contrast, the side effects of VNS are considerably less severe and thus more tolerable to sufferers who are either unable or unwilling to have surgical intervention or follow highly prescriptive diets (Taylor & Morris, 2022).

The long-term outcomes have found that the side effects that come with VNS are less severe, and over time; the patients have accepted the therapy (Wang & Liu, 2020). This renders VNS a long-term therapeutic approach to seizure control, especially when other management therapies are inefficient or have undesirable side effects.

3.5.3 Long-term Safety Data and Patient-Reported Outcomes

These findings reveal that VNS therapy is an effective method for decreasing the frequency of seizures, not causing any harm after a long-term application. A meta-analysis of trials with follow-ups of up to 5 years reveals that patients who have continued with VNS therapy still benefit, and outside of the peri-operative period, complications remain limited (Baker et al., 2017). Silva and Costa, in their cross-sectional study with longitudinal data collected from patients, reveal that patients have a stable condition in seizures for several years, in addition to enhanced mood and cognitive functioning. Such benefits will be valuable for patients with DRE as they have other complications like depression and anxiety.

According to patients' own experiences, it takes several weeks after the implantation of the device to decrease the intensity of side effects from stimulation, which appears to be generally acceptable for the majority of patients (Roberts & Allen, 2019). Increased social interaction, improved mood, and decreased seizure interference with daily life is typical, as patients mentioned (Carter & Roberts, 2019). Moreover, VNS therapy compliance outperforms most other non-pharmacological treatment interventions, as more than 85% of patients continue VNS treatment after two years (Harrison et al., 2021).

Another crucial feature of VNS therapy, which has to be mentioned, is its completely reversible character. In contrast to VNS, surgeries can be irreversible, and the VNS device can be deactivated or surgically implanted if the patient has adverse effects or does not improve as desired (Ahmed et al., 2021). This is particularly advantageous for VNS over other surgical operations, as patients are more comfortable, and there are no permanent alterations in the body.

VNS therapy appears to be well tolerated and safe in terms of side effects. It yields a higher tolerability compared to other treatment modalities, which is an important advantage given drug-resistant epilepsy. The side effects are few and usually mild to moderate. Thus, the treatment is non-invasive; there's long-term safety information to back up its use as a potent remedy to surgical and pharmacological interventions. That long-term VNS has produced further enhancements in these three parameters indicates that this therapy may offer a long-term strategy in DR epilepsy treatment.

4. Discussion

4.1 Interpretation of Key Findings

The synthesized studies within this systematic review evidence that vagus nerve stimulation (VNS) is a useful treatment modality in adults with DRE, especially when surgical options are ineligible. Altogether, VNS reduced the frequency of seizures, improved seizure severity, and kept patients' quality of life higher in the 20 studies that were reviewed. These findings were achieved by involving different patient samples, making the treatment modality of VNS relevant to patients with epilepsy from different backgrounds. Another important aspect emphasized in the review is the safety of VNS

as well as its tolerability, including comparably favorable side effect profiles to other therapeutic interventions.

The major finding arising from the present review is that VNS increases seizure frequency by 30-50% in patients diagnosed with DRE. Despite the fact that VNS may not produce very high levels of seizure freedom, which is often possible in the case of resective surgery, such as temporal lobectomy, VNS remains highly beneficial to patients who cannot be operated on or those who may avoid the latter (Toffaet al., 2020). Such a decrease in seizure frequency is beneficial from a clinical perspective because even minimal seizure control offers enhanced quality of life risks associated with uncontrolled seizures, including injuries, cognitive impairment, and social isolation.

Seizure severity and the patient-reported quality of life are the second major themes identified in this study. Some of the works reviewed, like that of Punia (2023), showed that VNS decreases seizure occurrence, as well as the severity, number, and duration of postictal symptoms and the time required for comprehensive recovery. Such a shift in seizure characteristics makes the lives of patients better, and often, patients who undergo VNS therapy experience improvement in their overall social interaction, reduced levels of anxiety, and improved cognitive function. The impact described on mood and behaviour, especially among children, again underscores the possibility of VNS in dealing with the psychosocial aspects arising from epilepsy (Aljeradat, 2024).

The effectiveness of VNS therapy is the other aspect analyzed by the review, and this will be examined further to examine its long-term effectiveness. Chronic effects of VNS are evident in outcomes as examined by Mao et al., (2022) and they show that these effects are long-term since the number and quality of lives of individuals who undergo the procedure continue to improve. This is different from pharmacotherapy, whereby patients taking antiepileptic drugs (AED) tolerance and side effects often result in reduced effectiveness over time (Wang, 2024). Given consistently high levels of participation,>80% of VNS therapy patients are likely to have positive attitudes towards the treatment options due to its less invasive form of intervention and minimal side effects association (Thompson et al., 2021).

4.2 Comparison with Existing Evidence on Other DRE Treatments

Analyzing similarities and differences between VNS and other treatments for DRE, the following should be noted: Medical treatment continues to be partially useful in dealing with epilepsy, and there's still no superior replacement of surgery as the common procedure, for instance, temporal lobectomy that offers the best outcome to people living with focal epilepsy with an easily identifiable seizure origin (Piazza et al., 2023). According to the different types of surgery, a seizure freedom rate of about 70-80% or more can be obtained for the selected group, which is much higher than that of the seizure reduction associated with VNS (Salem et al., 2023). Nevertheless, surgery as an invasive practice is not preferred by many patients due to the increased risk of neurological surgery side effects (Stumpo, 2021). However, VNS is much more minimally invasive and can be used in almost all epilepsy patients, even the non-surgical ones due to generalized or bilateral epilepsy.

The ketogenic diet is another non-medicinal approach that has been proven to be efficient in minimizing seizures, especially in children (Martin-McGill et al., 2020). However, maintaining a ketogenic diet is not so easy because ketogenic diets are classified as low-carb diets, and high protein and fat intake involves various metabolic side effects, including hyperlipidemia and gastrointestinal disorders (Furkatovna et al., 2024). However, VNS therapy has no complicated regime changes, and therefore, most patients can continue therapy without much strain. Literature included in this review, such as Toffa (2020), state that on a comparative level, VNS is consistent with better adherence rates than dietary interventions.

Medical management continues to be the mainstay in epilepsy management but is least effective in DRE as the efficacy of newly developed AEDs becomes flat (Rosal Lustosa, 2021). Other reviewed works of Sauer et al. (2024) show that when VNS was added to the existing AEDs, it helped the patients get extra seizure control and further enhancement of the quality of life, particularly where multiple drugs have failed. Refocusing VNS from this perspective helps to reveal the potential of this

method as an additional treatment option that can potentially improve the results of pharmacological treatments without adding new side effects (Colzato et al., 2023).

4.3 Implications of Findings for Clinical Practice

The implication of the results of this systematic review on the management of drug-resistant epilepsy in clinical practice can be drawn as follows. Firstly, VNS should be recommended for those DRE patients who have not responded to multiple AEDs and have no possibility of having a surgical removal of the lesion. The studies mean that VNS can be used as an additional treatment to pharmacological therapy, especially for patients who suffer from notable side effects provoked by the AEDs or cannot follow the diet requirements (Raspin et al., 2021). However, through the provision of an invasive-free treatment, VNS will be able to fill the gap created by other therapies.

Moreover, VNS is similar to other drugs with multiple gratifying long-term safety results, which is an advantage when used as a permanent treatment solution. Other effects include a change of voice, throat irritation, and sore throat, and they are mild because they reduce in severity as time goes by (Smith et al., 2020). The fact that it is possible to determine stimulation parameters individually can enhance the results and decrease the possible side effects (Thompson et al., 2021). This means the kind of stimulation applied can always be adjusted to give the best results, and since VNS therapy is reversible, patients have a favourable treatment plan.

In the particular case of children, VNS has an opportunity to provide a treatment paradigm not only for epileptic seizures but also for behavioral and cognitive development. This is important because epileptic children are prone to developmental problems and social issues affecting their development (Lähde, 2024). The effect of VNS on mood and the reduction of anxiety support the proposed use of VNS as an intervening treatment strategy that targets epilepsy from the neurological and psychosocial perspective (Roberts & Allen, 2019).

The review also points to the concept of patient delineation in the early stages, which is important for patients to undergo VNS therapy successfully. According to the observations, patients who have had at least a 50% reduction in seizure frequency during the stated time are in a position to benefit from the therapy for years (Wang & Liu, 2020). Hence, clinicians need to weigh the potential benefits of VNS therapy in those patients and consider early referrals to centers that implant this device because it can substantially enhance patients' quality of lifespan.

Moreover, based on the findings of this review, the next steps should involve the identification of the best criteria for selecting patients for VNS therapy. Knowledge of which patient characteristics (such as age, type of epilepsy, and additional disorders) are associated with better outcomes will improve treatment planning for the delivery of VNS (Taylor & Morris, 2022). There is also the call for more high-quality comparative trials involving randomized control that compare VNS therapy for OW and OB with other non-pharmacological interventions, such as responsive and dietary neuro-modulation.

4.4 Strengths and Limitations

This study has the advantage of systematically and exhaustively approaching the collection of data. Due to the inclusion of high-quality databases and while subjecting them to strict inclusion and exclusion criteria, this systematic review provides a strong summary of the literature regarding VNS for drug-resistant epilepsy. By using the PRISMA guidelines, the search of the studies was conducted systematically, and with the processes made clear, the study results were considered to be reliable. Furthermore, prayers in option and diversity of the features of different study types, including RCTs, cohort studies, and case-control studies, helped obtain comprehensive information on the effectiveness, risks, and late outcomes of VNS therapy.

Still, there are several sources of method bias. These encompass the following: A major limitation in the meta-analysis is the variability of the patient population, the study type, and measures used in the parent studies. This, in turn, makes it difficult to compare results and probably affects the ability to perform a meta-analysis where necessary. Even the differences in the stimulation settings parameters and follow-up duration used in different VNS protocols also hinder the generalization of the study.

Further, most of the published studies used patient questionnaires, and the results are subjective, which might affect the validity of the findings.

4.5 Future Directions

The authors of this systematic review identify several areas that should be pursued to enhance further the use of VNS in managing DRE. Two of them arise from a comparison of VNS with newer non-pharmacological interventions, namely, responsive neurostimulation (RNS) and transcranial magnetic stimulation (TMS). Some of these new therapies are promising. It would be useful to compare VNS with the current treatments in order to determine the best therapy schedules for patients with DRE. Further work should also be done on whether VNS is most effective when combined with another treatment, for example, dietary interventions or newer AEDs.

Two more significant directions for future investigations are enriching the understanding of the mechanisms through which VNS achieves its effects and improving the inclusion criteria, which would enhance the effectiveness of the treatment. Even though the effectiveness of VNS in seizure reduction and the increase in quality of life has been observed, a number of patients may have variable outcomes in terms of therapy. Establishing biomarkers or patient traits that would reveal positive outcomes to VNS may increase treatment efficacy and minimize the extra use of invasive interventions. The need to address research areas that will play a role in the selection of appropriate candidates for VNS therapy, including age, the type of epilepsy, genetic predisposition, and psychiatric disorders, will enhance results, increasing patients' benefits from VNS therapy.

Finally, studies of cost analysis are required more often, given that existing healthcare systems are becoming more concerned with productivity. VNS does require a large upfront investment to put in the device, but assuming the device is successful in reducing the frequency of seizures and hospital visits, and its utilization may be cost-beneficial in the long run. The subjective outcomes of VNS are often compared to those of other treatments to assess their economic effects, which, in return, will dictate the policies on treatment reimbursement.

5. Conclusion

Based on the findings of this systematic review, the levels of interventions that Vagus Nerve Stimulation (VNS) can offer in the treatment of drug-resistant epilepsy (DRE) are brought out. It should be noted that all of the 20 works revealed that VNS is an effective treatment option to decrease the number of seizures, the severity of seizures, and the quantity of patients' lives. In general, patients with VNS therapy reported between a 30 percent and 50 percent – and sometimes better – decrease in the number of seizures they had. In the line of treating epilepsy and seizure, VNS brought additional changes in the mood, cognitive ability, and social behavior of the patients' thus important aspects in the life of patients with chronic epilepsy. Such benefits show that VNS offers more than an anti-seizure function or role, as this technology additionally influences the psychosocial well-being of a patient.

VNS therapy has been used mostly for patients who cannot undergo other surgical interventions, such as resection, or who have not received satisfactory results from several AEDs. Here, VNS is a less invasive process compared to surgery and is not marked by a high-risk factor similar to surgery. The mild side effects, including altered voice and throat irritation, are well tolerated and reduce in severity as patients adapt to undergo the therapy. Thus, VNS shrugs off many drawbacks inherent to other types of treatment, including invasive procedures and notorious side effects of some medications applied for the disorder's pharmacological management.

This review also reveals the long-term prospect of VNS therapy. All available studies with follow-up periods of up to five years provide evidence that besides the short-term effect of VNS successfully used in reducing seizure frequency and improving the quality of life, and long-term effects are also seen. High adherence rates support the development of the theory attributable to the fact that patients find VNS to be a sustainable therapy without serious side effects. This is the case, especially since epilepsy is a chronic and may even be a lifelong disease that needs constant intervention. The ability and effectiveness of VNS in alleviating symptoms suggest that it may relieve the pressure that results from frequent hospitalizations and emergency treatments.

Future expectations of VNS as a treatment can only increase, particularly as device modifications become more maximized and focused stimulation parameters can be toggled. Further research should investigate what kind of patients are more amenable to VNS since the results indicated that the therapy has efficacy in selected cases. Furthermore, owing to the development of novel non-pharmacological treatments, including RNS and TMS, future incarnations of this article will depend on comparative analyses to compare the effectiveness and safety of these therapies.

Consequently, VNS is an important complementary measure to pharmacological treatment in patients with drug-resistant epilepsy. It is effective, well-tolerated, and has the advantage of long-term discrete management in patients whose conditions have not changed following conventional treatments. Analyzing VNS within further developing views on epilepsy treatment, its inclusion into individualized therapy regimens could appear as one of the main critical points that expands a patient's options for recovery. As for future developments, the further evolution of epilepsy treatment seems to be fostered by technological advancement, a patient-centered approach and further liberalized consideration of non-invasive methodologies before VNS treatment. With further optimization and extension of using VNS, we can provide improved seizure control, better quality of life for patients, and, in other words, a future for people suffering from this severe disorder.

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