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REVIEW

Vagus nerve stimulation outcome prediction: from simple parameters to advanced models

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ABSTRACT
Since its approval as an adjunct treatment for refractory partial epilepsy, the positive effects of vagus nerve stimulation (VNS) on seizure frequency and severity have been supported by many studies. Seizure reduction of more than 50 % can be expected in at least 50 % of patients. However, a complete post-VNS seizure freedom is rarely achieved and 25 % of patients do not benefit from VNS. Our study provides an overview of the potential predictors of VNS response, from the most simple and basic data to sophisticated EEG processing studies and functional imaging studying brain connectivity. The data support better outcomes in younger patients with early VNS implantation, in patients with posttraumatic epilepsy or tuberous sclerosis, and in patients without bilateral interictal epileptiform discharges. The variability of heart activity has also been studied with some promising results. Because the generally accepted hypothesis of the VNS mechanism is the modulation of synaptic activity in multiple cortical and subcortical regions of the brain, the studies of brain response to external stimulation and/or of brain connectivity were used for models predicting the effect of VNS in individual patients. Although the predictive value of these models is high, the required special equipment and sophisticated mathematical tools limit their routine use *(Ref. 58)*. Text in PDF *www.elis.sk*
KEY WORDS: epilepsy, vagus nerve stimulation, response predictor, EEG.

Introduction

Vagus nerve stimulation (VNS) was approved by the US Food and Drug Administration (FDA) in 1997 as an adjunct treatment for medically refractory epilepsy for individuals aged 12 and older with partial epilepsy. Before 2011, the positive effect of VNS on seizure frequency and severity was confirmed by three blinded, randomized controlled trials (Class I evidence) and two non-blinded, randomized controlled trials (Class II evidence) (1). In general, a greater than 50 % seizure reduction can be expected in at least 50 % of patients after two years of treatment with only mild side effects. However, a complete seizure freedom using VNS is rarely achieved and 25 % of patients do not benefit from VNS treatment (2, 3). The Engel classification which is used to evaluate epileptosurgical resection outcomes is therefore not routinely used for VNS patients. The patients are usually classified as responders, R (> 50 % seizure reduction), with the subgroup of seizure-free patients (CR – complete response), 90R (> 90 % seizure reduction), and non-responders, NR (< 50 % seizure reduction). In 2007, the McHugh classification using five classes of outcome was introduced (4).

The time pattern of seizure response for VNS patients varies. In general, the effect on seizure reduction increases with time after stimulation. In the first meta-analysis of VNS in epilepsy performed by Englot et al, the reduction of seizure frequency was 36 % at 3 to 12 months after surgery and 51 % at more than 1 year after surgery (1). Fluctuations of the VNS effect (patients classified as R changing to NR or vice versa) are only rarely reported, even in papers with long-term follow-up data for up to 17 years (5).

Because of the highly variable response to VNS, the potential predictors of individual patient response to VNS are an attractive topic for further investigation. Moreover, the study of any potential predictors can influence the analysis of efficacy of other neurostimulation treatment techniques, including deep brain stimulation (DBS) and responsive neurostimulation (RNS) (6).

The potential predictors of VNS response have been analyzed in prospective studies and in retrospective reviews of prospectively collected data from both pediatric and adult patients (3, 7). There are also retrospective studies based on data from patient registries managed and maintained by manufacturers of commercially available VNS systems (1, 8). In addition to these large studies,

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there have been multiple single-center clinical studies focusing on particular aspects of predicting VNS efficacy.

The aim of our study is to provide an overview of the current state of knowledge about potential predictors of VNS response, from the most simple and basic data such as age and duration of seizures to the results of sophisticated EEG processing studies and functional brain imaging, and to provide a prospect for further research in this field with a potential impact to be seen not exclusively in epileptology.

Patient age at implantation

Comprehensive papers based on data from VNS registries and systematic literature reviews support the assumption that a younger age at VNS implantation is a predictor of better outcomes in terms of seizure freedom (age at seizure onset < 12 years) (8–28) and seizure reduction (9). As an example of a single-center study confirming superior VNS efficacy in younger patients, Alexopoulos et al found that patient aged < 12 years at implantation (the initial FDA age limit) is associated with a better prognosis when considering median seizure frequency reduction (10). A paper by Colicchio et al reported that children and adolescents had better clinical outcomes than adult patients (11).

By contrast, some data do not support the premise that the response to VNS is better in younger patients. A Czech retrospective multicenter study observed lower efficacy rates of VNS in patients younger than 16 years (12). In Israel, a retrospective multicenter study comparing seizure reduction in patients aged < 22 years and ≥ 22 years indicated that the higher responder rate was found in older patients (13). In a VNS registry-based study studying the 12-month outcomes of 269 patients (aged 2 to 71 years, with no change in antiepileptic drugs during the study period) published by Labar et al in 2004, the mean seizure reduction in patients aged > 32 years was 64 %, i.e., higher than in patients < 32 years (50 %) (14). Although theoretically worse results with higher surgical risks could be expected in older patients with longer-lasting epilepsy, a multicenter study of 45 adults over 50 years old found that their response to VNS was similar to that of younger adults without increased morbidity (15). In summary, although the meta-analyses of literature data and the majority of VNS registry-based studies support better VNS outcomes in younger patients, the literature does not currently define any age limit associated with a worse prognosis for VNS.

Seizure duration

It can be expected that longer epilepsy duration may be associated with worse VNS outcomes because of the irreversible changes to the neuronal network caused by the ongoing seizures. This hypothesis is supported by an analysis of VNS patient registry data published in 2003 (405 patients) that found significantly higher percentages of patients with complete seizure remission and ≥ 90 % seizure reduction when a VNS system was implanted within 6 years of the seizure onset (16). A paper by Englot et al based on a VNS therapy patient outcome registry (5554 patients) indicated a trend toward a higher frequency of seizure freedom among patients with shorter epilepsy duration (threshold 10 years) prior to VNS implantation (8). According to a meta-analysis by Wang et al, the age at implantation and at seizure onset had no significant association with the good outcome of VNS, but shorter epilepsy duration may lead to a better seizure reduction outcome (17). Data neither confirming nor contradicting an association between shorter epilepsy duration and improved seizure outcome are less frequently reported. In a two-center study (Belgium – U.S.) the percentage of Engel I – III outcomes were slightly higher in patients with epilepsy duration ≥ 10 years (70 %) than in patients with epilepsy duration < 10 years (61 %), but the difference did not reach the level of statistical significance (18). Lagae et al also failed to confirm longer epilepsy duration as a negative prognostic factor in children and young adults (19). However, the results in summary favor the earlier use of VNS in refractory epilepsy patients.

Structural lesion as a cause of intractable epilepsy

Regarding the structural origin of epilepsy and neurological symptoms, Casazza et al classified the patients as "symptomatic" (e.g., perinatal injury, brain malformation, and low-grade tumor), "unknown etiology" (normal MRI, but neurological signs and symptoms), and "cryptogenic" (normal MRI, no neurological signs or symptoms) (20).

From a neurosurgical point of view, the possible relationship between causal structural pathology and the effect of VNS is very complex because the spectrum of causal structural pathologies requiring VNS that are not amenable for surgery includes single unresectable lesions, multifocal lesions, and multilobar and diffuse brain abnormalities. Not surprisingly, the literature data correlating VNS outcomes and lesional/non-lesional etiology of epilepsy are not definitively conclusive. Englot et al found a higher rate of seizure freedom in non-lesional patients (8). Arya et al found that the VNS responder rate in childhood epilepsy patients without MRI lesions was 80.8 %, compared to the 52.9 % responder rate in patients with MRI lesions (21). However, other studies have not confirmed the absence of structural brain lesion as a positive predictor of VNS outcome. A study by Colicchio et al including 135 drug-resistant epilepsy patients (57 cryptogenic, 78 symptomatic) concluded that the best VNS responders could be young lesional patients (11). Another study published by Colicchio et al in 2012 showed that lesional etiology was associated with better response to VNS (7). In a retrospective study, Montavont et al showed a nearly significant trend for better outcomes in partial epilepsies as symptoms of a focal lesion than in those with normal brain MRI ($p = 0.06$) (22). Arcos et al found no significant difference in VNS treatment outcome between patients with normal or abnormal MRI findings at the six-month follow-up visit. However, by the 12-month follow-up visit, 82.4 % of the patients with abnormal MRI findings were classified as responders, which was significantly higher than in patients with normal MRI (45 %) (23).

The multiplicity or poor delineation of lesions affecting multiple brain areas preventing resective surgery patients with tuberous sclerosis and malformations of cortical development require

particular attention. Despite the small number of patients included in published papers, the results of VNS in patients with tuberous sclerosis are encouraging. A multicenter study of children with tuberous sclerosis complex and medically refractory epilepsy had nine responders from ten tuberous sclerosis complex patients after VNS, and five had a 90 % or greater reduction in seizure frequency (24).

Very positive outcomes in post-VNS seizure reduction in pediatric patients with tuberous sclerosis (at least 50 % seizure reduction in 72 % of patients) together with significant improvement in adaptive behaviors, quality of life, and cognitive and neuropsychologic functioning were reported by Zamponi et al (25). Similarly, in a group of 12 patients with intractable epilepsy due to tuberous sclerosis, Elliot et al achieved a mean post-VNS seizure frequency reduction of 72 % (26). A meta-analysis by Englot et al, published after all these studies, concluded that tuberous sclerosis is a predictor of a positive VNS outcome (1).

The role of cortical malformation as a predictor of the positive VNS response is less clear. In the paper by Montavont et al, the finding of cortical development malformation was identified as one the few variables possibly predicting a seizure reduction of over 50 % (22). A study by Janszky et al found that the presence of malformation of cortical development is significantly associated with a seizure-free outcome after VNS (27).

Similarly, a multivariate analysis by Ghaemi et al found the presence of cortical dysgenesis (parietooccipital polymicrogyria, macrogyria) to be an independent predictor of seizure freedom in long-term follow-up care (28). In a review of articles dedicated to VNS for medically refractory epilepsy published before 2012 (including the papers mentioned above) Connor et al confirmed the presence of cortical malformation as a positive predictor of good response to VNS (29). Neuronal migration disorders were found to be negatively correlated with the VNS treatment outcome (3, 30).

Not surprisingly, the use of VNS in patients with intractable epilepsy associated with brain tumor is rarely reported. In the database of two epilepsy centers, 16 patients were found with VNS implanted for epilepsy associated with brain tumors. Seizure frequency decreased by 65.6 % in the patients with stable tumors and by 10.9 % in those with progressing tumors. Therefore, VNS can be recommended only in patients with intractable epilepsy caused by stable brain tumor (31). The same authors performed a study based on a VNS therapy patient outcome registry. The VNS system was implanted in 107 patients with epilepsy etiologically related to a brain tumor. The study resulted in a responder rate of 48 % at 3 months and 79 % at 24 months. There was no statistical difference in seizure reduction as compared with 326 case-control patients from the registry without brain tumors (32). However, the conclusion that VNS therapy is equally effective in patients who experience seizures secondary to brain tumors as in patients without brain tumor history should be made while taking into consideration the biological properties of the causal lesion with the possibility of malignant transformation of an initially benign lesion. Therefore, the need for adequate MRI follow-up care enabling early detection of tumor progression or upgrading should be considered before VNS implantation.

Patients with extensive posttraumatic changes and intractable epilepsy are poor candidates for curative resection. Therefore, VNS may be an attractive option for them. In a retrospective study based on a large prospectively collected patient registry, the posttraumatic epilepsy patients demonstrated a greater reduction in seizure frequency (fewer seizures by 73 % at 24 months) than patients with other etiology (fewer seizures by 57 % at 24 months) and a higher rate of VNS responders at 24 months of VNS therapy: 78 % in patients with posttraumatic epilepsy and 61 % among those with epilepsy of nontraumatic etiology (33). A meta-analysis by Xiong et al confirmed better outcomes of VNS in posttraumatic epilepsy patients (30). Therefore, the posttraumatic etiology of epilepsy can be considered a predictor of a positive VNS effect.

Data about the impact of epileptogenic lesions of another origin on the effect of VNS are limited. In their study of 53 prospectively long-term recorded patients, Colicchio et al mentioned tuberous sclerosis and post-ischemic lesions as favorable predictors of VNS treatment outcome (7).

Previous resective surgery

VNS is a possible palliative therapeutic option for patients after failed resective surgery. In an extensive retrospective study based on a VNS therapy outcome registry, Amar et al compared the outcomes of VNS in patients with a history of failed epilepsy surgery (921 patients with resection, callosotomy, or other cranial surgery for epilepsy) and patients without previous surgery (3,822 patients without surgery). The median reduction in seizure frequency after 24 months of VNS therapy was 50.5 % for the postsurgical group and 66.77 % for patients without prior surgery. The differences between the surgical and nonsurgical groups were statistically significant for both the resection and callosotomy subgroups (34). Another retrospective study compared the outcome of VNS in a group of 266 patients without previous resective epilepsy surgery and 110 patients after previous resective surgery (both children and adults). In contrast to the previous study, the mean seizure reduction was slightly higher in patients after intracranial epilepsy surgery (59.1 %) than in patients without previous craniotomy (56.5 %), but this difference was not statistically significant. No correlation between the type of intracranial epilepsy surgery (callosotomy or resection) and post-VNS seizure reduction was found (35). Although in the extensive study by Amar et al (34), the percentage of seizure reduction appears to be higher in patients without the history of previous intracranial surgery, the percentage of seizure reduction is still sufficient in patients with previous epilepsy surgery. Therefore, the history of previous failed resective surgery should not be considered a negative prognostic factor for VNS effect or even a contraindication for VNS implantation.

Type of epilepsy

The indication for VNS was initially approved by FDA for cases with partial-onset epilepsy, but the clinical applications of VNS have substantially expanded since then. Because the

resective surgery is generally not feasible in pharmacoresistant idiopathic and generalized forms of epilepsy, the possibility of seizure reduction with VNS therapy is particularly important for this group of patients.

There are data from extensive studies proving superior seizure control in patients with focal or partial form of epilepsy (3, 9). However, an investigational device exemption study in a limited group of 16 adult patients with pharmacoresistant generalized epilepsy syndromes showed an acceptable median seizure frequency reduction of 43.3 % (36).

According to the study by Englot et al that enrolled 5,554 patients with intractable epilepsy, predominantly generalized seizures are significantly associated with post-VNS seizure freedom when followed for 0 to 4 months and 4 to 12 months after the VNS therapy. However, this significant difference disappeared at 12 to 24 months and 24 to 48 months (8). A study by Wheeler et al comparing Engel I or II proved no statistically significant difference among a partial seizure group and primary or secondary generalized tonic-clonic seizure group (18).

The experience with pediatric patients regarding the seizure type and VNS outcome is less extensive than in adults (probably due to the initial age limit of 12 years). In a study on four distinct seizure types in pediatric patients (generalized, focal, myoclonic, and atonic), Sergaroglu et al observed that generalized tonic-clonic and atonic types had significantly more favorable outcomes with VNS than other seizure types did (37). However, according to a single-center retrospective study by Bodin et al, VNS tended to be more effective in children with non-idiopathic partial epilepsy than in those with non-idiopathic or idiopathic generalized epilepsy (38). In a study by Orosz et al, children with predominantly generalized seizures from genetic epilepsies like Dravet syndrome or Lennox-Gastaut syndrome also benefitted from VNS therapy, although the improvement was less marked than in the general population included in their study (39). However, Lagae et al did not prove a difference in outcomes between generalized and focal epilepsies in children and young adults (19).

To draw a conclusion from these studies, although some data suggest more favorable outcomes of VNS in partial or focal types of epilepsies than in primarily generalized seizures, the data do not provide a contraindication for VNS implantation for adult or pediatric patients with generalized seizures.

Regarding the lobar origin of the seizure, Casazza et al found that VNS was more effective in patients whose ictal discharge at onset involved the temporal region than in patients with ictal frontal, central, or diffuse discharges (20). A paper by Burakgazi et al demonstrated that 65 % of the patients with frontal lobe epilepsy and 15 % of the patients with temporal lobe epilepsy (TLE) had a satisfactory outcome (Engel I-III) (40).

However, the meta-analysis by Xiong et al has proved better outcomes of VNS in temporal epilepsy patients (30). Bitemporal epilepsy is a very important issue because resective surgery is not possible. Therefore, it is encouraging that the studies by Alsaadi et al and Kuba et al reported responder rates of 60 % and 62.5 % in patients with bilateral independent temporal lobe epilepsy (41, 42).

EEG findings and neurophysiological investigations

Detailed EEG analysis (including ictal and interictal recordings with video monitoring) is an absolutely mandatory part of the presurgical workup. The analyses of the potential relationship between the various EEG features and VNS responses that have been performed by many authors with differing results prevent definitive conclusions. Janszky et al found the absence of bilateral interictal epileptiform discharges (IEDs) as a predictor of a good VNS outcome (27). A multivariate analysis by Ghaemi et al showed that unilateral IEDs were significantly associated with seizure freedom at long-term follow-up visits (28). The meta-analysis by Xiong et al confirmed that focal IEDs were predictors of a more favorable VNS outcome as compared to generalized IEDs (30).

The quantitative analysis of EEG data may partially replace the visual interpretation; it can be considered a more objective and sensitive method than a simple visual analysis (depending on the individual neurophysiologist's expertise). In 2011, de Vos et al published data exploring interictal EEG features suggesting that a quantitative symmetry measure (with known clinical applications for the detection of focal ischemia and focal seizure activity), the pairwise derived Brain Symmetry Index (pdBSI), might predict good responders to VNS treatment. The pdBSI values for delta, theta, alpha, and beta bands were found to be higher in non-responders than in responders, and the average pdBSI of the theta and alpha bands could significantly discriminate between responders and non-responders (43). However, a validation study by Hilderink et al testing the pdBSI for relations with VNS outcome one year after surgery found no significant differences in the pdBSI of good responders, moderate responders, and non-responders (44).

Although the mechanism of action of VNS is fundamentally unknown, the generally accepted hypothesis is the modulation of synaptic activity and therefore excitability in widespread cortical and subcortical regions of the brain (e.g., the desynchronization of hippocampal and thalamocortical circuitry) during VNS (45, 46). Fraschini et al reported a significant correlation between VNS-induced global desynchronization in gamma bands and positive clinical outcomes in temporal lobe epilepsy patients (47). The changes in these rhythms as a reaction to external stimuli may provide information about the effect of external stimuli delivered via VNS on these circuits reflecting interindividual variability in (non-specific) susceptibility of EEG to be synchronized or desynchronized by external stimulation. Using standard computations of power spectral analyses of interictal EEG, Brázdil et al revealed significant differences between VNS responders and non-responders in alpha and gamma frequency bands and four different conditions (hyperventilation, eyes opening/closing, and resting periods) of standard clinical assessment. Whilst both patient groups (VNS responders and non-responders) demonstrated equivalent alpha desynchronization during eyes opening, they differed in alpha reactivity to photic stimulation and hyperventilation. Responders showed no decrease in alpha power during photic stimulation but an enormous increase during hyperventilation. This reactivity pattern stands in contrast to that observed in healthy individuals, in whom photic stimulation typically leads to alpha attenuation, and

standardized hyperventilation has been shown to decrease alpha power. Significant increases in gamma power during both photic stimulation and hyperventilation were observed more in responders than in non-responders (48). According to the results of a study by De Taeye et al, VNS induced a significant increase in the P3 event-related amplitude at the parietal midline electrode in VNS responders only; the authors concluded that modulation of the P3 amplitude should be further investigated as a noninvasive biomarker for the therapeutic efficacy of VNS in patients with refractory epilepsy (49). Cognitive event-related potential together with polysomnography and heart-rate variability (HRV) were studied in a prospective series of drug-resistant epilepsy patients planned for VNS. Prior to treatment with VNS, the amount of deep sleep (NREM 3), HRV high frequency power, and P3b amplitude were significantly different in responders as compared to non-responders after one year of VNS treatment. According to the authors, these non-invasive recordings may be used as VNS response predictors and are attributed to the changes in brain regions involved in the "vagal afferent network" (50).

Advanced imaging and functional techniques

Other authors attempted to predict VNS response using advanced techniques not routinely used in the presurgical workup. Generally, these techniques quantify the potential degree of brain connectivity using advanced functional mapping techniques supported by sophisticated mathematical apparatus (graph theory) and models. Although providing some promising results, such studies are single-center based and require special equipment not available for routine presurgical investigations with limited groups of patients. Using resting-state fMRI and multivariate generalized linear models adjusting for age and sedation status in a group of 21 children and young adults, Ibrahim et al found that enhanced connectivity of the thalami to the anterior cingulate cortex and left insula was associated with greater VNS efficacy. The model based on this study classified the response to VNS in an external cohort of 8 children with 88 % accuracy (51). A study by Babajani-Feremi et al investigated the resting-state magnetoencephalography (rs-MEG) network topology before VNS implantation as a potential predictor of VNS treatment efficacy. Using the graph theory applied to the rs-MEG data, they found a significant difference between VNS responders and non-responders. Surprisingly, the values of the graph measures in the controls were closer to those of responders than to those of non-responders. The model based on this theory achieved an accuracy of 87 % in classifying non-responders, responders, and controls (52). Mithani et al aimed to predict VNS response using both structural and functional connectome profiling (56 children, 38 in discovery and 18 in validation cohorts). They used diffusion tensor imaging to identify structural differences in white matter microstructure, which in turn informed the beamforming of the rs-MEG recordings. Treatment responders demonstrated greater fractional anisotropy in the left thalamocortical, limbic, and association fibers, as well as greater connectivity in a functional network encompassing the left thalamic, insular, and temporal nodes. In the external validation cohort, this model demonstrated an accuracy of 83.3 %, with a sensitivity of 85.7 % and specificity of 75.0 %. Although the authors provided the first multi-institutional multimodal connectome prediction algorithm for VNS, the complex equipment required will probably limit its wider clinical use (53).

Other potential predictors

Although efferent fibers form only 20 % of the vagus nerve trunk, the vagus nerve plays an important role in the homeostatic regulation of visceral functions (54). Heart activity using electrocardiogram (ECG) is routinely recorded during the video-EEG monitoring of potential epilepsy surgery candidates and therefore ECG data are readily available for analysis. In combination with the amount of deep sleep (NREM 3) and the P3b amplitude, the HRV high frequency power were significantly different between VNS responders and non-responders (50). The results published by Liu et al suggest that a sophisticated preoperative assessment of HRV using linear algorithms and multiscale entropy quantifying the complex regulatory dynamics of human biological signals can help predict VNS outcomes in patients with drug refractory epilepsy (55).

The efferent vagus nerve fibers modulate the immunological system response through the hypothalamic-pituitary-adrenal axis leading to the release of cortisol, vagal efferent fibers synapsing onto enteric neurons releasing acetylcholine at the synaptic junction with macrophages, and splenic sympathetic anti-inflammatory pathways (56, 57). It is therefore not surprising that immunological parameters have also been studied as a potential predictor of VNS efficacy. Aalbers et al conducted an exploratory study on VNS effects on cytokine levels in the plasma and cerebrospinal fluid of children with refractory epilepsy. The plasma levels of cytokines were compared between patients who received high- or low-output VNS stimulation for 20 weeks. All patients then received high-output stimulation for another 19 weeks. No significant changes in interictal interleukin-1β, interleukin-6, and interleukin-10 were found between the high- and low-output groups or between the last 19 weeks of high-output stimulation and baseline. However, baseline interleukin-6 predicted the clinical response. The theoretical background and preliminary data suggest potential future studies of the cytokine profile as a VNS efficacy predictor after the exclusion of other factors that may alter the immunological response (58).

Learning points

- Greater than 50% seizure reduction can be expected in at least 50% of patients after two years of vagus nerve stimulation with only mild side effects.
- A complete seizure freedom using VNS is rarely achieved and 25 % of patients do not benefit from VNS.
- There are no reliable predictors of the VNS effect, although better outcomes can be expected in younger patients treated early after the seizure onset, in patients with posttraumatic epilepsy or tuberous sclerosis complex and those with non-diffuse epileptic discharges.

– Models based on the studies of brain responses to external stimulation and of brain connectivity have a high predictive value, but the special equipment and mathematical tools limit their routine use.

Conclusions

Neither meta-analyses based on previous studies nor extensive studies using data from VNS registries and single-center publications have provided a reliable predictor of VNS outcomes in terms of seizure reduction. Some evidence supports the expectations of better outcomes in younger patients with VNS implanted early after the seizure onset and in patients with posttraumatic epilepsy or tuberous sclerosis complex and focal or multifocal epileptic discharges. Similarly, no data reliably predict poor responses to VNS, although some data indicate poorer outcomes, such as in older patients with longer seizure disorder duration and generalized or bilateral interictal epileptiform discharges. The effect of VNS on the visceral systems has also been studied as a potential predictor of VNS efficacy with some promising results in heart activity dynamics studies. Because of the suspected mechanism of VNS activity, the studies of brain responses to external stimulation and studies of brain connectivity have been used for models predicting the effect of VNS in an individual patient. However, although the predictive value of these models is high, the special equipment and sophisticated mathematical tools that they require limit their use with the probable exception of the model utilizing the changes in gamma power during both photic stimulation and hyperventilation that are routinely used during presurgical evaluation.

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